The Handbook of Stress Science

Biology, Psychology, and Health

Editors
Richard J. Contrada
Andrew Baum

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The Handbook of Stress Science: Biology, Psychology, and Health

Richard J. Contrada, PhD, is a Professor in the Department of Psychology at Rutgers, The State University of New Jersey. He obtained a PhD in Social/Personality Psychology at the Graduate Center of the City University of New York in 1985 and was a Postdoctoral Fellow at Uniformed Services University of the Health Sciences in Bethesda, Maryland, before joining the faculty at Rutgers in 1986. His work addresses psychosocial, behavioral, and psychophysiological aspects of physical disease, with a focus on cardiovascular disorders. He has a longstanding interest in the role of personality in physical health and his research on psychophysiologic mechanisms linking personality to cardiovascular disease has been supported by the National Institute of Mental Health. His investigations of psychosocial vulnerability and protective factors in adaptation to cardiac surgery have been funded by the Fetzer Institute and the National Institute on Aging. Work supported by the Charles A. Dana Foundation has examined proinflammatory cytokines as a basis for associations between depressive symptoms and coronary disease. He has published in *Health Psychology, Psychosomatic Medicine, Journal of Personality and Social Psychology, Psychophysiology, American Journal of Cardiology,* and *Journal of Psychosomatic Research.* He has also edited a book, *Self, Social Identity, and Physical Health: Interdisciplinary Explorations* (Oxford University Press, 1999). He has served as a member of the Health Behavior and Prevention Study Section of the NIMH and as Associate Editor of *Health Psychology.* He has also served on the editorial boards of the *Journal of Personality and Social Psychology, Journal of Applied Social Psychology, Journal of Behavioral Medicine, Annals of Behavioral Medicine, Stress and Health,* and *Psychosomatic Medicine*. He is a Fellow of APA, APS, and SBM, and has received the Rutgers University Award for Excellence in Graduate Teaching.

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To my parents, Pasquale and Theresa Contrada, for many years of support and encouragement.

–RJC

To the memory of Jerome E. Singer, a friend, colleague, and mentor. Jerry's intellect shone brightly and illuminated many dark corners, leading the way for others.

–RJC and *AB*

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In Memoriam

Thomas G. Pickering
(1940–2009)

Thomas G. Pickering, professor of medicine and director of the Center for Behavioral Cardiovascular Health at Columbia University, died May 14, 2009, after a valiant battle against cancer, during the time in which he was working on his contribution to this *Handbook*. Dr. Pickering's legacy was his national and international leadership in research and patient care in hypertension and the behavioral aspects of hypertension and heart disease. He published widely in the field and held many leadership positions, including serving as president of the Society of Behavioral Medicine, the Academy of Behavioral Medicine Research, and the American Society of Hypertension's eastern regional chapter. He coined the term "white-coat hypertension" to describe patients whose blood pressure is elevated in the doctor's office but normal otherwise, and he published the first editorial describing "masked hypertension," the opposite phenomenon. His commitment to behavioral medicine stemmed from his belief that much of cardiovascular disease arises from psychosocial factors and is potentially preventable or treatable by modifying these factors.

His record of scholarship and clinical expertise is accompanied by his remarkable mentorship of younger clinical investigators now working in the field around the world.

A native of England, Dr. Pickering received his MA degree from Trinity College of Cambridge University, his medical doctorate from Middlesex Hospital Medical School in London, and his D. Phil. degree from Linacre College of Oxford University. Before taking a position at Columbia, he had appointments at Mount Sinai Medical Center, Cornell and New York Hospital, and Rockefeller University.

Among the many awards he received are these recent ones: the Alvin P. Shapiro Award from the American Psychosomatic Society, in recognition of the importance and sophistication of his research, and the Franz Volhard Award and Lectureship from the International Society of Hypertension. The Volhard Award is given biennially to honor an individual whose research has garnered enduring interest. Dr. Pickering's father, Sir George Pickering, MD, received the award in 1974.

While recognizing Dr. Pickering's professional contributions, we do not overlook the personal impact he had on those who knew him. The editors and fellow contributors of this volume extend our sincerest condolences to his family—his wife, Janet, sons Robert and William, and their families—and to his many colleagues, students, and patients.

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Foreword

This is an important book about the scientific study of stress and human adaptation. It brings together both empirical data and theoretical developments that address the fundamental question of how psychosocial variables get inside the body to influence neurobiological processes that culminate in physical disease. This focus on stress and disease could be seen already in the *zeitgeist* of the biobehavioral sciences of the 1960s and 1970s. Building on the earlier biological stress perspectives centered on Cannon's (1932) "flight-or-fight" response and Selye's (1956) seminal description of a nonspecific physiological reaction to noxious stimulation, an influential book was published at the time containing empirical papers aimed at enhancing the permeability of multidisciplinary boundaries (Leiderman & Shapiro, 1964). The papers were an outgrowth of a symposium sponsored by the Office of Naval Research and Harvard Medical School. Its purpose was to bring together individuals conducting experimentation on social behavior that incorporated biological concepts and their measurement by whatever means were available, including plasma lipids, corticosteroids, muscle action potentials, and skin conductance.

The symposium reflected a conviction that much would be gained from interaction between biomedical, psychological, and sociological disciplines. It is self-evident that all these fields are concerned with living organisms, although each one emphasizes a different focus ranging from the neurobiological to the social nature of man. But, it was argued, each discipline cannot ignore the conceptual and empirical advances of the others. Just as complex behavior cannot be understood in purely biological terms, mental events cannot be understood without some recourse to the relevant biological processes within the organism. And, it is true also, that relevant social environmental factors must be incorporated into any serious effort to understand behavioral and physiological outcomes.

The interdisciplinary ferment of the 1960s and 1970s foreshadowed emergence of the scientific study of psychological stress and coping. This work is associated with names and concepts such as Richard Lazarus and cognitive appraisal (Lazarus & Folkman, 1984), Irving Janis and his analysis of decision-making under stress (Janis, 1984), Bruce McEwen and his notions of allostatic load and overload (1998; 2009), and Shelley Taylor with her "tend-and-befriend" model described in Chapter 8 of this volume. Indeed, these stress-and-coping paradigms have and will continue to represent major approaches to elucidating the complex interplay of biopsychosocial variables in the etiology and pathogenesis of a variety of chronic physical diseases. This book illustrates how Health Psychology and Behavioral Medicine are beneficiaries of this emphasis on stress and human adaptation.

Early foreshadowing of current research efforts in these areas was not confined to the Leiderman and Shapiro symposium. There were other forces extant in the 1960s and 1970s that led to conferences, investigator-initiated research, and advanced training programs dealing with the interface of the social world, mediating psychological processes, and biomedical outcomes. A comprehensive review of all of these factors is beyond the scope of this Foreword. However, four groups of what may be considered influential "vectors" warrant consideration here. First, there were active behavioral-science research and training programs in major medical centers across the country, particularly in departments of psychiatry and epidemiology. These programs received substantial financial support from both private foundations and federal agencies such as NIMH, NSF, and selected National Institutes of Health. Some of these efforts had profound effects on the nature of biomedical and social epidemiological research of the times (e.g., Geiger & Scotch, 1963).

Second, financial and other forms of support were given not only for research but also for interdisciplinary conferences and symposia. Along with the Leiderman-Shapiro proceedings, a noteworthy example is a series on the interface of biology and behavior, with successive themes emphasizing neurophysiology and emotion, genetics, and environmental influences (Glass, 1967, 1968a, 1968b). The conferences were held at The Rockefeller University and sponsored jointly with the Russell Sage Foundation. They brought together representatives from a broad array of disciplines, including

psychiatry, psychology, sociology, anthropology, ethology (animal behavior), genetics, nutrition, and what we now call the neurosciences. I was responsible for organizing the conferences and some of its themes are certainly evident in what follows in this *Handbook*. Exemplars include the chapters on stress and regulation of the hypothalamo–pituitary–adrenal axis, genetics and stress, social responses to stress, social status and stress, coping, and a number of others devoted to the association between stress and physical and mental outcomes.

The section on Research Methods, Tools, and Strategies in this *Handbook* reflects recent technological developments that are only dimly, if at all, evident in the pages of the *Biology and Behavior* series. Indeed, it can be argued that many of the achievements of stress research in the last two decades can be attributed to these advances in technology. An unfortunate counterpoint to this conclusion is that conceptual developments have not *always* kept pace with technological progress. On the other hand, there has been greater reliance on multilevel conceptualization and multidisciplinary efforts aimed at integrating within single models psychosocial factors and neurophysiological processes that culminate in disease end-points. This work—what are called process models—can be seen in several contributions to this *Handbook* and are discussed in summary form in Chapter 1. Note that models focusing on physiological mechanisms that mediate an association between psychosocial factors and disease have been around for several decades (Krantz & Glass, 1984). These older paradigms may be considered primitive by today's standards, but they do anticipate the current, more dynamic models.

This latter point is illustrated nicely by socioeconomic status (SES) and disease. There is an "... impressive literature [on] the pervasiveness of the SES-health gradient across diseases and populations" (Adler, Marmot, McEwen, & Stewart, 1999, Preface, p. xiv). But, SES is a demographic or "ecological" variable and it is necessary to determine the psychosocial processes that bring this aspect of the social environment down to the level of biological mechanisms. Put simply, an external social environment such as SES must be "... perceived by the individual in negative ways in order to have detrimental biological effects" (Miller, Chen, & Cole, 2009). This and related questions were addressed in a 1999 forum, the proceedings of which are contained in Adler et al. (1999). The forum was sponsored jointly by The MacArthur Foundation Research Network on Socioeconomic Status and Health and the New York Academy of Sciences. The overall message of the forum was the need for multilevel, interdisciplinary work aimed at unraveling the mechanisms whereby the SES gradient affects the health of the body. Conceptual work on SES and health over the last two decades constitutes a necessary corrective to static correlational models prevalent in the 1960s and 1970s. The efforts of this more dynamic perspective can be seen in the work reviewed in Chapter 14 of this volume, and in recent integrative efforts to link SES indicators, brain activity, and more distal health outcomes (e.g., Gianaros & Manuck, 2010). We are making steady progress.

A third early vector influencing current work on stress and disease involved activities of the Committee on Biological Bases of Social Behavior of the Social Science Research Council (SSRC). I served as Chair and my close colleague, the late Jerome E. Singer, was senior Staff Officer. Along with committee members such as Stanley Schachter, Peter Dews, Gardner Lindzey, and Gerry McClearn, we submitted a number of grant proposals to the Training Branch of NIMH. The proposals were for successive summer institutes designed to train social psychologists and other social scientists in the genetic basis of behavior, medical physiology and immunology, psychophysiology, and neurobiology. The stress concept, although not well developed at the time, was an evident theme in many of these institutes. Our goal was to train social scientists who would combine psychosocial and biological concepts and methods in their future research. It is noteworthy, therefore, that some of the authors in this volume are graduates, or students of graduates of these early training programs.

Observational research on primates in their natural habitats constitutes a fourth vector that stimulated a biopsychosocial approach to stress and health. It is, perhaps, less obvious than the other three, but the close integration of psychosocial and biological factors is illustrated in research on human evolution. This large body of research is beyond comprehensive discussion in this Foreword. Suffice it to note that empirical support was found for the view that social organization functions as a biological adaptation both in individual development and in social interactions among nonhuman organisms, including primates (e.g., Calhoun, 1973; Hamburg, 1963). Living in groups confers selective advantages, including protection against predators, meeting nutritional requirements, and preparing the young to cope with subsequent environmental stresses, including disease. This line of thought was represented in the work of several laboratories at Rockefeller University. Under their auspices, university-wide lectures were given by animal behavior researchers from around the country. Many leading social psychologists attended these lectures and later pursued human research on behavioral responses to stressful features of the physical environment. Physical space arrangements, crowding, urban noise, and extreme temperature were among the more active topics pursued at the time.

Consider noise as a case in point. Jerry Singer and I developed a program of research on behavioral effects and aftereffects of stressors characteristic of large urban centers. Laboratory analogues of urban

noise constituted a dominant theme in our work. The basic premise was that although people adapt to noise, they pay a price for their efforts to cope with unwanted sounds and this occurs especially when noise is *perceived* as uncontrollable. These costs of adaptation are revealed in subsequent behavior and, I might note, bear a more than superficial resemblance to what McEwen (1998; 2009) has described as allostatic overload. The experimental evidence did, indeed, support the idea that the effect of an environmental event is mediated by perceiving negative features of the event, in this case its uncontrollability (Glass & Singer, 1972). The results gave rise to speculations about substructures such as the sympathetic adrenomedullary and hypothalamic–pituitary–adrenocortical systems from which biological responses to the environment might spring. This led, in turn, to increased attention to the possible relationships among stress, coping, and physiological processes that may culminate in disease, including cardiovascular disease (Krantz & Glass, 1984).

I have discussed four factors in the latter part of the 20th century that produced what might be called a "resultant vector" toward systematic research on stress and its possible links with physical illness. We see, in this constellation of forces, the origins of modern Health Psychology and Behavioral Medicine. It is, in effect, an early attempt to integrate psychosocial constructs with measures of biological processes in an effort to unravel the complexities involved in understanding and predicting "hard" disease outcomes. The lynchpin of this effort is the multilevel research we see today. At the risk of appearing overly optimistic, even prescient, I would suggest that the next few decades will be a stage for exciting programs of research whose focus on stress and coping should elucidate biological pathways whereby environmental events become implicated in the production of organic disease. The promise of this future work can be seen in the pages of this *Handbook*.

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Preface

The study of stress addresses fundamental processes of human adaptation and is essential for understanding the ways in which psychological processes can influence physical health and well-being. At the same time, like most areas of science, the stress field has not been without its critics. Problems and pitfalls in the study of stress have frequently been discussed in the published literature. However, reflecting on the status of stress science also puts us in mind of occasions on which public speakers saw fit to make mocking reference to difficulties with the stress concept. One took place in the 1980s at a behavioral medicine conference at a large state university. Introducing the topic of stress, one of the meeting organizers began with an allusion to the broad and sometimes too permeable boundaries that are set by key definitions, stating that "Everything that happens in life is stressful, and everything that you do is coping." The second was at a national scientific meeting that took place at about the same time. One staunch critic of the stress concept had fun with the problem of circular definitions by describing a study in which the animal was "subjected to a stress" (i.e., a noxious stimulus) and, in turn, "responded with a stress" (i.e., a heart rate elevation).

Although definitional issues and other conceptual difficulties remain, we believe it is very clear that the field of stress is alive and well, and can be expected to form a focus of research in Health Psychology and Behavioral Medicine for the foreseeable future. At the same time, scientific progress cannot be taken for granted, and requires systematic critical examination of generally accepted conceptual frameworks, empirical generalizations, and methodological tools. We believe that this *Handbook* will satisfy the need for a reference volume that examines the state of the science on biological and psychological factors in stress as they relate to outcomes of interest to health researchers. It should serve as a valuable resource for researchers in the field, from post docs to senior investigators, as well as for graduate students and advanced undergraduates. It should also provide very helpful material for social, personality, and developmental psychologists, as well as for clinical psychologists, physicians, and other practitioners who work with patients with physical health problems. Educators will find that the *Handbook* is an excellent source of required and supplementary readings for graduate seminars, as well as upper-level undergraduate courses, in many areas of psychology, as well as in sociology, anthropology, nursing, and other disciplines.

To describe a Handbook such as this as a group project is a major understatement. Of the many individuals who had a hand in this endeavor, we would first like to acknowledge Philip Laughlin. Because this *Handbook* originated in conversations he initiated with us, it is as much his brainchild as it is ours. Phil's general guidance, specific suggestions, and periodic "checking in" on our progress, especially in the early going, were crucial in giving the project direction and impetus.

Of course, we are extremely grateful for the outstanding contributions of the authors. In many cases, the only input they had from us was a general topic area. In all cases, the end result is an essential component of the overall picture of the field. Collectively, the efforts of these prominent and influential scientists have produced an important, incisive statement of status of the field of stress and health, and a projection of where that field is going. We thank them for their work in this regard, as well as for their prompt and thoughtful responsiveness to feedback.

We are especially indebted to several authors whose efforts exceeded normal expectations because they wrote under particularly difficult circumstances, and to authors and additional friends, colleagues, and former students who advised us about potential chapter topics and contributors, including: Carol Aneshensel, Matthew Burg, Chuck Carver, Bruce Compas, Karina Davidson, Len Epstein, Garrett Gatchel, Susan Gore, Tara Gruenewald, Ellen Idler, Tom Kamarck, Ron Kessler, Neal Krause, Kara Lorduy, Andrew Miller, Scott Monroe, Ben Natelson, Karen Rook, Teresa Seeman, Tanya Spruill, Tracey Shors, Bert Uchino, Debra Umberson, and Terry Wilson.

When Phil Laughlin left Springer to pursue a new career opportunity, we worked for a while with the able assistance of Jennifer Perillo, who then handed things off to Nancy Hale. Nancy took over the project and saw it through the final stages of production. Her guidance,

gentle and yet firm, was a perfect match for the task at hand.

Last, but not least, we would like to thank David Glass and the late Jerry Singer. Although they did not collaborate with us directly on this *Handbook*, the lasting impression that they made on us can be seen in all of our work. David Glass served formally as graduate advisor to one of us (RJC) but has been a mentor to us both. And we both had the pleasure of working in the Department of Medical Psychology that Jerry Singer created and chaired at the Uniformed Services University of the Health Sciences. Although Jerry left us much too soon, the rich and supportive social and intellectual environment that he created and maintained at USUHS will always be a special time and place in our lives.

Richard J. Contrada
Andrew Baum

The Handbook of Stress Science: Biology, Psychology, and Health

1 Stress, Adaptation, and Health

Richard J. Contrada

Stress is the topic of extensive and diverse literatures in social, behavioral, and life sciences. The broad scope and multidisciplinary usage of the term *stress* are among the considerations that have led some to suggest that it can usefully serve only as a general rubric for a set of loosely related research areas, and that it is ill-suited as a label for any single concept with any one particular technical definition. Others, by contrast, have offered quite narrow, discipline-specific definitions of stress. Still others, pointing to problems with definitions and other sources of dissatisfaction with stress research, have argued that the stress concept should be abandoned. Among those favoring retention of *stress* as a meaningful scientific concept, one often finds a position, intermediate to the very broad and very narrow views, in which there is an attempt to specify the essence of *stress* that remains constant across varied applications of the term. In one example of the latter approach, stress is defined as "a process in which *environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place persons at risk for disease*" (Cohen, Kessler, & Gordon, 1997, p. 3, emphasis in original).

Middle-ground definitions of stress such as that of Cohen et al. (1997) contain several key elements. One of these is the inclusion of environmental, psychological, and biological phenomena, which incorporates three distinct traditions that can be traced back through the history of stress research. A second is a focus on process, which contrasts with some earlier views in which *stress* is a more static construct, referring, for example, to a stimulus or a response. A third aspect of this definition, the idea of an imbalance between environmental demands and adaptive capacity, suggests a person–situation interaction that causes a departure from homeostasis and activates compensatory psychological and biological activity. Fourth, although stress has been studied in relation to many different kinds of consequences, this definition recognizes that much interest in stress among scientists and lay persons alike lies in its potential role in the development and control of health problems, particularly those involving physical disease.

Environmental, psychological, and biological traditions, and approaches in which these paradigms have been effectively integrated, have provided a strong foundation for an active, productive, and cumulative field of health-related stress science. The importance of stress concepts and associated research methodologies is nowhere more salient than it is in the fields of health psychology and behavioral medicine. Many social and psychological variables of interest as possible risk or protective factors in the development of physical disease are themselves conceptualized as forms, aspects, or consequences of stress, or are seen as stress moderators that exert their health effects by amplifying or dampening stress-related processes. Moreover, the central nervous system, neuroendocrine, and autonomic changes that have been identified as components of the biological stress response have been linked to alterations in cardiovascular, immunological, and other physiological systems whose dysregulation has been implicated in a wide variety of physical health problems. Additionally, there is growing recognition that stress is associated with behavioral processes, including eating, drug use, and illness management, that form indirect pathways to disease outcomes. It also appears that cognitive and behavioral interventions can reduce stress and thereby improve physical health.

Just as stress science has informed our understanding of health problems, the study of physical health and disease has been a useful arena in which to develop, test, and refine conceptions of stress. Stress is an essential topic within the larger set of basic sciences that are aimed at uncovering the fundamental principles of human psychology and biology. To characterize the negative health consequences of stress, and the processes through which they develop, is to describe the operating features of the evolved machinery of the human mind, brain, and body, and to begin to understand how that machinery interacts with the physical and sociocultural environment. Beyond that, the identification of a role for stress in problems of physical health and disease underscores the practical importance of both basic and applied stress research. It is therefore the premise of this *Handbook* that much is to be gained by taking stock of conceptual developments, empirical findings, clinical applications, and investigative strategies and tools that have accumulated over the past few decades of stress research, a time period that has seen a burgeoning of health-related stress science.

The purpose of this chapter is to set the stage for the chapters that follow. It begins by discussing some of the definitional problems alluded to above. It then describes a set of themes and developments that characterize the field of health-related stress research as it has unfolded over the past few decades. This is followed by a discussion of some of the main challenges that are faced by researchers seeking to further our knowledge of the role of stress in the development and control of physical disease. Next, the structure of the *Handbook* is outlined, and some of its limitations are enumerated. A concluding comment conveys our expectations for the use and impact of this volume and for the further scientific study of stress.

DEFINING STRESS

Debates about how to define stress are long-standing and highly nuanced. Fortunately, they have had little apparent effect, if any, in inhibiting progress in the field. Although a detailed discussion of the issues will not be attempted here, an overview of selected highlights may be worthwhile. Below we briefly discuss the problems of *circularity*, *fuzziness*, and *probabilistic causation*.

CIRCULARITY

It is difficult to imagine the field arriving at a broad consensus in favor of a stimulus-based definition in which *stress* corresponds solely to a particular set of specific kinds of environmental events or conditions. But, if that were to occur, *stress* (or *stressors*) might be defined as a list with elements such as bereavement, war, terrorism, and the like. One problem with this scenario is the likelihood of definitional overinclusiveness, that is, there may be individuals who experience bereavement or war but do not show the hypothesized effects of stressor exposure. This would run counter to connotations of the term *stressor* in which a measureable psychological and biological impact is expected and, definitions aside, it would diminish the predictive value of such a stress concept. At the same time, it is likely that such a definition would also be too restrictive, omitting events and conditions that are often, though not always, *stressful*, such as a divorce or a demanding job. Based on common usage, one naturally looks to the consequences of events/conditions that purportedly operate as stressors for evidence that this is indeed the case. This leads to dissatisfaction because it goes beyond the bounds of a stimulus definition, entailing as it does a consideration of stress responses, and because it asserts causal effects of stressors, an empirical matter, as true by definition.

Similar problems arise from response-based definitions of stress. Alterations in endocrine and autonomic activity might form parts of such a definition, but if those physiological changes are produced by engaging in sexual activity or viewing a tennis match, the point of the definition will be seen to have been lost by many stress researchers. Excluding some stress response episodes from the definition, or distinguishing between *good* and *bad* forms of stress based on the nature of the eliciting stimuli, would, again, involve circularity, since a response-based definition should not entail stimulus considerations or presume hypothesized causes. Thus, stimulus-focused conceptions of stress appear inadequate, as do response-focused ones, with attention to both stimulus and response needed in order to maintain contact with many phenomena of interest, to exclude irrelevant topics, and to generate accurate predictions. This issue was apparently of concern to Hans Seyle, whose work had an enormous impact in popularizing the study of stress. He originally defined stress in terms of stimuli, before shifting to a response-based definition with his concept of a *general adaptation syndrome* (Selye, 1956). The issue also figured into John Mason's subsequent critique of the revised, response-based approach (Mason, 1975a, 1975b).

FUZZINESS

A certain amount of imprecision is to be expected in defining constructs, especially in the early going and when those constructs are burdened with the role of representing complex social, psychological, and biological phenomena. Thus, formulations that avoid the limitations of stimulus- and response-focused approaches, by defining stress in terms of processes (i.e., whereby certain kinds of stimuli lead to certain kinds of responses), will leave something to be desired as regards precision and specificity, until those processes are clearly and thoroughly characterized. In a way, the problem may appear to become worse, rather than better, as progress is made.

For example, difficulties in specifying general rules regarding the effects of *stressful* stimuli on *stress* responses were addressed in a theoretical synthesis described by Richard S. Lazarus. In what is nearly universally regarded as a major psychological contribution to understanding stress, Lazarus argued that the concepts of cognitive appraisal and coping are required in order to explain how exposure to certain kinds of (stressful) events and conditions leads to certain kinds of (stress) responses, and to account for individual differences in those responses (Lazarus & Folkman, 1984). Although it is hard to deny that the appraisal and coping concepts have proved at least somewhat useful, they also have their limitations. One is that, as defined, it is difficult to tease them apart, either conceptually or operationally. That is, it is hard to say where the cognitive–evaluative (appraisal) process that initiates stress terminates, and where the coping activity whereby the person manages the perceived stressor and its effects, and which invariably has a

cognitive component, begins. Consequently, it is difficult to obtain a measure that reflects cognitive appraisal but is independent of coping. Other problems arise in distinguishing among stressful stimuli, other social–contextual factors, and personal dispositions, and in separating appraisal and coping from other responses to stressors. Thus, although both appraisal and coping constructs appear necessary, and are widely accepted, they are certainly not without their critics, for reasons that include (though by no means are limited to) issues of fuzziness and conceptual and measurement-level overlap (e.g., Coyne & Racioppo, 2000; Dohrenwend & Shrout, 1985).

PROBABILISTIC CAUSATION

It has been suggested that definitional problems with the stress concept have contributed to its inability to provide a basis for acquiring adequate empirical support for a priori statements as to what kinds of stimuli will provoke stress responses and which bodily systems will respond (e.g., Engel, 1998). However, this criticism may be countered, as it is in many areas of inquiry, by recognizing that elements of the processes involved in stress show probabilistic, rather than deterministic causal relationships with one another. Much of the progress that has been made in the stress field has resulted from extending the stress-coping framework by incorporating additional constructs to improve predictive precision. Thus, stressors are not inherently stressful, they are events and conditions that are *potentially* stressful (i.e., that *may* produce predicted responses) depending upon cognitive appraisal and coping processes. The outcomes of those appraisal and coping processes, in turn, depend upon personal attributes and social–contextual factors that operate as resources or vulnerabilities, either dampening or amplifying the stress response (at least in part) through their effects on appraisal and coping. Better understanding of appraisal and coping, further identification of resource/vulnerability factors, and more detailed characterizations of the processes of interplay linking appraisal and coping to resources and vulnerabilities, have increased the precision of predictions regarding the occurrence and outcomes of stress.

THEMES AND DEVELOPMENTS

Overall, research concerning stress and health has shown increased differentiation over the past few decades, more closely approximating the complexity of the phenomena it seeks to understand. This can be seen in a number of different developments. In the next few sections, we highlight several of these, which include increased emphasis of *cognition, multilevel analysis*, greater attention to *patterning in stress phenomena,* more sophisticated *measurement models,* more *dynamic process models,* and increased specificity in modeling *disease-promoting mechanisms.*

COGNITION

Lazarus's first studies of the appraisal process (e.g., Lazarus & Alfert, 1964), and criticisms of Selye's (1956) stress model in which Mason emphasized the role of perceptual processes as the initiating event in stress (Mason, 1975a, 1975b), were among the early observations that foreshadowed contemporary views in which the role of cognition is central to understanding the provocation of psychological stress, coping, and other adaptive responses that ensue. Also important in this regard was Glass and Singer's (1972) programmatic examination of the role of perceived predictability and controllability in the behavioral and physiological impact of urban stressors, and Leventhal's theoretical work concerning the influences of cognitive representations of health threats on the management of chronic disease (Leventhal, Meyer, & Nerenz, 1980). Notwithstanding the importance of stress processes that arise from noncognitive sources (e.g., systemic stress responses stimulated by activity of proinflammatory cytokines), a cognitive perspective now dominates in research concerning the initiation of stress.

It follows that a cognitive perspective also guides a considerable amount of work focused on coping and other forms of adaptation to stressors. Thus, the selection and execution of coping responses are viewed as processes that are shaped by cognitive appraisal. For example, a stressor that is perceived to be potentially controllable will more likely instigate active, problem-focused coping activity than one that appears uncontrollable and therefore unlikely to be responsive to such efforts. Moreover, many specific forms of coping activity themselves involve cognitive processes, such as attention, interpretation/reinterpretation, meaning making, and cognitive approach and avoidance (Carver, chapter 17).

The impact of major moderators of the stress-coping process is also frequently construed in cognitive terms. For example, effects of social support often depend upon how social resources are *perceived* (e.g., Sarason, Sarason, Potter, & Antoni, 1985) and, among personality factors influencing the stress-coping process, much attention has been given to those that involve *expectancies*, such as dispositional optimism (e.g., Scheier, Carver, & Bridges, 1994) and locus of control (e.g., Bollini, Walker, Hamann, & Kestler, 2004); *attributions*, such as explanatory style (e.g., Jackson, Sellers, & Peterson, 2002); *information-related preferences*, such as monitoring-blunting (e.g., Hoffner, 1993); and *beliefs*, such as cynicism and mistrust (e.g., Williams, Smith, Gunn, & Uchino, chapter 18). In stress-reduction research, *cognitive–behavioral* interventions have produced positive effects on both psychological and biological outcomes in patients with various chronic medical conditions (see chapters in this volume by Baum, Trevino, & Dougall; Nezu, Nezu, & Xanthopoulos; and Perez, Cruess, & Kalichman).

MULTILEVEL ANALYSIS

Stress research has progressed to a point where it stretches *from cells to society*, to use what is perhaps a hokey but nonetheless appropriate catch phrase. A psychological level of analysis that focuses on the individual person has been extended *downward* to basic processes at the cellular and molecular levels, as well as *upward* to the levels of the dyad, group, organization, and larger society (Norman, DeVries, Cacioppo, & Berntson, chapter 43). This can be seen as a product of the capacity for psychology to serve as a *hub* science in relation to neighboring fields of inquiry (Cacioppo, 2007). It also reflects the increasing permeability of traditional disciplinary boundaries that has characterized the health sciences in the past few decades (Leiderman & Shapiro, 1964; Schwartz & Weiss, 1978).

One sense in which interactions of factors at different levels of analysis have long been a focus of stress research is the emphasis noted above on the cognitive elicitation of biological stress responses. In contemporary, health-focused stress research, this form of *psychophysiological* cross-level analysis has been greatly extended, reaching both upward and downward to still higher and lower levels of analysis. This follows from the identification of biological stress responses with a category of disease-promoting mechanisms though which social, psychological, and behavioral factors influence the etiology and pathogenesis of physical disorders, which ultimately involve alteration of the structure and functioning of bodily systems, organs, and cells. Thus, for example, one can trace the influence of global human activity (international trade) and associated historical events (enslavement and transport of Africans to the United States) on the emergence of sociocultural factors (institutional racism) that have led, in turn, to social psychological phenomena (individual-level prejudice, stereotyping, and discrimination) whose psychological impact (race-related stress) may promote cardiovascular diseases involving damage to the heart that can be observed under a microscope (myocardial hypertrophy).

In addition to efforts aimed at tracing the flow of events *downward* from macrolevel social–environmental forces through midlevel psychological factors to microlevel disease processes, developments in stress science over the past few decades have involved other forms of multilevel analysis. As in many areas of psychological research, the understanding of stress-related phenomena has been enhanced in work that has sought to integrate neurobiological analysis with analysis of cognitive, social, and affective processes. Salient examples include characterization of the biology of threat perception, emotional memory, and conditioning (LeDoux, 1996); the genetic (McCaffery, chapter 6) and central nervous system processes (Dallman & Hellhammer, and Gianaros & O'Connor, chapters 2 and 39) underlying initiation of peripheral physiological stress responses; influences of oxytocin and opioid mechanisms on nurturing and affiliative behaviors promoted by stress and their possible role in promoting social support processes (Taylor & Master, chapter 8); immunological influences on emotional behavior (Hash-Converse & Kusnecov, chapter 5); and the neurobiology of health-related personality factors (Williams et al., chapter 18).

PATTERNING

The foundational contributions to the stress field of Walter B. Cannon (1929) and Hans Selye (1956) involved the discovery of biological response patterns, namely *fight-or-flight* and the *general adaptation syndrome*. In the time since, and especially in the last few decades, additional stress response pattern constructs have been introduced. In some cases, these refer to individual differences and/or cross-situational variations in the activity of a physiological response system; one example is the observation that cardiovascular adjustments to behavioral stressors may involve a largely myocardial response, a largely vascular response, or a mixture of the two (Burg & Pickering, chapter 3). In other cases, patterns have been described in terms of responses that are integrated across multiple systems. Examples include the *tend-and-befriend* response (Taylor & Master, chapter 8), characterized both in terms of patterns of nurturing and affiliative behaviors that underlie health-promoting effects of social support processes (Uchino & Birmingham, chapter 9) and their neural and neuroendocrine underpinnings. Another is *sickness behavior*, defined with reference to a syndrome of behaviors including anhedonia, aphagia, and fatigue and underlying immune system processes including central nervous system effects of proinflammatory cytokines (Hash-Converse & Kusnecov, chapter 5).

Patterning has also figured into developments in thinking about psychological eliciting and response processes in stress. Advances in theory regarding the role of appraisal in psychological stress have been made by drawing upon emotion research, thereby extending earlier conceptions in which stressful appraisals were limited to threat, harm/loss, and challenge. Stress may be better understood as arising from a larger set of more complex appraisal patterns, such as have been described in accounts of qualitatively distinct basic emotions such as fear, anger, and sadness (e.g., Lazarus, 1991; Smith & Kirby, chapter 15). Similarly, distinctions between different patterns of coping activity, initially confined to that between its problem-focused and emotion-focused forms, have been the subject of efforts to provide a more complete and nuanced coping framework (Carver, chapter 17). These include the identification of coping patterns that appear most likely to be accompanied by health-damaging physiological activity, such as vigorous efforts to master potentially uncontrollable stressors (Glass, 1977), and coping patterns that are directly damaging to health, such as the use of nicotine, alcohol, and other substances (Grunberg, Berger, & Hamilton, chapter 22). Similarly, research on adaptation to

threatening medical diagnoses and treatments has identified coping patterns of potentially broad relevance to multiple forms of stress, such as in the work of Taylor (1983) on processes of adjustment in cancer patients that entail a search for meaning, attempts to regain mastery, and efforts to restore self-esteem. Self-management of chronic medical conditions also can be seen as a pattern of coping activity that is guided by illness-related belief patterns and directed toward a health-related stressor (Garrido, Hash-Converse, Leventhal, & Leventhal, chapter 35).

MEASUREMENT MODELS

Newly identified forms of patterning in stress elicitation and response processes have major implications for measurement tools. Studies involving the assessment of a single dimension of stressor exposure and a single dimension of stress response are increasingly giving over to studies that make use of multidimensional assessments of both stressor and stress response. For example, in research on stressful life events, instruments have been developed that differentiate major life stressors, stressful events that occur on a daily basis, and the unfolding of stressful encounters during the course of a given day (see chapters in this volume by Anderson, Wethington, & Kamarck; Almeida, Stawski, & Cichy; and Kamarck, Shiffman, & Wethington). In addition, the relevant assessment tools and associated statistical techniques make it possible to tease apart multiple features of the stressor, of cognitive and affective responses to the stressor, and of coping behaviors. Moreover, they also provide a means of relating these stress process components to psychosocial risk and vulnerability factors that characterize the individuals confronting the stressor, and the social context in which this occurs, often in a way that integrates both between- and within-person levels of analysis.

Assessment of psychosocial moderators of stress processes also has been guided by more sophisticated measurement models. For example, the measurement of exchanges within social networks now distinguishes between beneficial and detrimental forms of each of support, companionship, and control (Rook, August, & Sorkin, chapter 10). Social support is further differentiated into multiple forms, including those referring to the types of support that may be available, and to the types that are received, and relationships with social network members are characterized in terms of separable dimensions of negativity and positivity. The latter development draws attention to the problem of ambivalent social ties, which may pose even more serious difficulties than those arising from simple negativity (Uchino & Birmingham, chapter 9). Greater attention to the independence of positive and negative psychological phenomena is also seen in the assessment of emotional responses that accompany stress, where, for example, there have been efforts to model the conditions under which these dimensions remain largely uncorrelated and define a two-dimensional space, and when they collapse into a single, bipolar dimension (Finan, Zautra, & Wershba, chapter 16).

At a biological level, there appears to be an ever-growing array of structures and processes that are activated by stress. From the central nervous system circuits that mediate stressor appraisal and initiate peripheral physiological manifestations of stress (Dallman & Hellhammer, and Gianaros & O'Connor, chapters 2 and 39), to the neural hormones and peptides involved in social behavioral responses to stressors (Taylor & Master, chapter 8), to the immune/inflammatory (Dhabhar, and Hash-Converse & Kusnecov, chapters 4 and 5), genetic (McCaffery, chapter 6), and molecular (Baum, Lorduy, & Jenkins, chapter 7) effects and moderators of stressor exposure, theoretical and technical advances have had a major impact in expanding the set of measurable biological parameters that are accessible to stress researchers.

In addition to newly emerged biological stress indices, there have been significant improvements in the assessment of more traditional ones. For example, classic stress hormones, such as cortisol and the catecholamines, epinephrine and norepinephrine, are amenable to increasingly precise measurements based on an expanded set of sources (e.g., blood, urine, saliva) that suit different research questions and satisfy various practical considerations (Lundberg, this volume). In addition, examination of temporal patterning has enhanced the breadth and resolving power of measurements involving both traditional stress hormones (Lundberg, chapter 38) and cardiovascular parameters (Christie, Jennings, & Egizio, chapter 37).

DYNAMIC PROCESS MODELS

Greater use of multilevel analysis and growing numbers of elicitation and response patterning concepts have revealed some limitations in traditional views of stress processes. As a consequence, work in the past few decades has made use of increasingly more complex and sophisticated theoretical modeling. In many instances these models are also more dynamic in the sense of emphasizing processes of change, multidirectional influences, and systems-level as opposed to variable-focused conceptualizations.

One salient example may be found in discussions of basic principles of stress physiology (Berntson & Cacioppo, 2007; Norman et al., chapter 43). Contemporary views of this topic have been strongly influenced by the concept of *homeostasis*, a term coined by Cannon (1929) to capture and extend Claude Bernard's observations regarding the processes whereby constancy is maintained in the internal environment (*mileau intérior*) of organisms in response to its threatened disruption. More recently, alternative concepts have been suggested as a means of updating Cannon's view to give more explicit recognition to the complexities and dynamism of homeostatic regulation. For example, Sterling and Eyer (1988) introduced the term

allostasis to incorporate the notion that physiological regulation is guided by changing, rather than fixed, set-points, and to capture the idea that higher neural centers may regulate a wide range of systems to achieve control of a particular function. This view of allostasis or *stability through change* has been extended by McEwen and Wingfield (2003, 2010), who describe processes whereby exposure to stressors may create *allostatic load* (the cumulative cost to the body of allostasis) and eventually lead to *allostatic overload* (a state in which serious pathophysiology can occur). Others have proposed somewhat different frameworks in attempting to formulate more dynamic models of stress physiology (e.g., Berntson & Cacioppo, 2007; Norman et al., chapter 43; Romero, Dickens, & Cyr, 2009).

More dynamic models also have been found to be useful in accounting for social and psychological aspects of stress. Increasingly, personality and social relationship factors thought to influence stress processes have been conceptualized in ways that allow for multiple forms of interplay between stressor, social context, and personality attribute (Betensky, Glass, & Contrada, in press; Williams et al., chapter 18). Bidirectional influences are also seen in frameworks for understanding stress in particular contexts, such as the workplace (Pandey, Quick, Rossi, Nelson, & Martin, chapter 11) and other organizational settings (Weinberg & Cooper, chapter 12). Similarly, race- and ethnicity-related maltreatment has been modeled in terms that explicitly address interactions between institutional and environmental factors and individual-level discrimination (Brondolo, Brady, Libby, & Pencille, chapter 13).

DISEASE-PROMOTING MECHANISMS

Although Cannon did not refer to *stress* frequently in his writings, he did express the belief that stress would eventually become an important concept in understanding and treating medical problems (Cannon, 1928). Selye (1956) impressed upon the stress field the idea that *wear and tear* produced by repeated activation of the general adaptation syndrome was a contributing factor in the development of physical disease. The emergence of the fields of health psychology and behavioral medicine was associated with general recognition of the role of stress in mechanisms through which psychological and behavioral factors influence physical health outcomes (Krantz, Glass, Contrada, & Miller, 1981). At about the same time, evidence linking the Type A pattern to coronary heart disease (CHD) became a major impetus for research evaluating the hypothesis that stress-induced elevations in cardiovascular activity and underlying hormonal and autonomic changes contribute to the initiation and progression of coronary atherosclerosis and the precipitation of clinical CHD (Krantz & Manuck, 1984). One important product of this research was the development of a paradigm that integrated *epidemiological* findings regarding the relationship of Type A behavior to CHD with a *stress-coping* framework containing an explicit *mechanistic* component (Glass, 1977). In that framework, Type A behavior represents a pattern of coping with potentially uncontrollable stressors that is accompanied by elevations in circulating catecholamine levels and cardiovascular activity, markers for processes that may culminate in CHD outcomes.

In the years since, increasingly detailed models of the relationship between biological stress responses and negative health outcomes have been advanced. The birth and maturation of the field of psychoneuroimmunology reflect steadily accumulating knowledge regarding the complex relationships between stress and immune function (Dhabhar, chapter 4), and these relationships may be involved in pathways linking stress to infectious diseases (Pedersen, Bovbjerg, & Zachariae, chapter 31), cancers (Baum, Trevino, & Dougall, chapter 30), and CHD (Bekkouche, Holmes, Whittaker, & Krantz, chapter 28). In addition to recent findings concerning stress-related immune and inflammatory processes, mechanism-focused research on CHD has in other ways extended well beyond measures of acute changes in blood pressure and heart rate, to include, for example, assessments of vascular activity, endothelial dysfunction, and blood platelet aggregation (Burg & Pickering, and Bekkouche et al., chapters 3 and 28). Still another development of note in the cardiovascular area is the incorporation into stress research paradigms of intermediate and subclinical disease markers, such as cardiometabolic syndrome (Brooks, McCabe, & Schneiderman, chapter 29), and nonfatal clinical markers, such as stress-induced myocardial ischemia (Bekkouche et al., chapter 28). In this regard, Bekkouche et al. outline a model that links specific pathogenic stress responses to a series of time points in the natural history of CHD, from effects of stress on traditional CHD risk factors such as resting blood pressure and lipid levels in healthy individuals, to the provocation of malignant cardiac arrhythmias in coronary patients exposed to stressors. Finally, the search for specificity in the identification and characterization of stress-related biological mechanisms culminating in physical disease may be undergoing a transformative expansion in its extension to cellular and molecular processes, including those involving effects of oxidative stress on DNA damage and repair that have possible implications for carcinogenesis (Baum, Lorduy, & Jenkins, chapter 7), and changes in endothelial function that may be involved in the pathogenesis of CHD (Burg & Pickering, chapter 3).

Although the study of stress traditionally has emphasized its direct biological effects as a pathway to disease, the role of stress in psychological and behavioral processes that promote physical health problems is receiving increased attention. These include substance use, eating patterns, and a sedentary lifestyle, which may promote chronic diseases in healthy individuals (see chapters in this volume by Grunberg et al.; O'Connor & Conner;

and Edenfield & Blumenthal). They also include perceptual, cognitive, and behavioral processes involved in the patient's efforts to understand and manage chronic medical conditions (Garrido et al., chapter 35). Thus, although direct psychophysiological effects of stress, behavioral effects of stress, and reactions to illness are usefully distinguished as three general forms of disease-promoting mechanisms (Krantz et al., 1981), and while health-related behaviors are often treated as potential confounds in research linking stress to disease outcomes, interactions and areas of overlap among these three sets of mechanisms have become increasingly evident and, appropriately, have come to form the subject of more integrative examination in research on stress and health.

CHALLENGES

Although there has been significant progress in health-related stress research, enormous challenges remain. Concerns about definitions of the term *stress* are not entirely without substance. Even casual perusal of this *Handbook* will reveal nontrivial variations in how authors prefer to conceptualize stress, distinguished in some cases by a preference for either a primarily environmental, psychological, or biological formulation. It also will raise questions about the unique and common elements of *psychological stress, psychosocial stress*, *interpersonal stress*, *systemic stress*, *restraint stress*, *rotation stress*, *cognitive stress*, and *emotional stress*, to list just some of the many *stress* phrases that stress researchers find necessary. The demand for unity or at least a greater degree of conceptual cohesiveness has its counterpart at the level of measurement. It is nearly inconceivable that a single measure or measurement battery will ever be devised to make possible an assessment of stress that would be equally useful for the wide variety of research questions and clinical applications in which stress appears to play a central role. In many ways, a full picture of the biological stress response is only beginning to take shape, and much the same can be said of its environmental and psychological antecedents, on the one hand, and the pathways through which stress promotes mental and physical health problems, on the other. Similarly, the operation of social and personal risk and protective factors that appear to moderate stress processes are much more often described in terms of statistical interactions or boxes and arrows rather than with regard to substantive processes of interaction. Psychological interventions can reduce stress and in some cases have exerted a positive impact on health outcomes, but it remains to be seen whether stress reduction can make a significant contribution in controlling the major sources of morbidity and mortality and their associated direct and indirect economic costs. As the chapters in this volume attest, major advances have been made in response to these and other challenges, but much more needs to be done.

ORGANIZATION OF THE *HANDBOOK*

This *Handbook* is composed of five sections. Section I reviews current knowledge regarding the major biological structures and systems that are involved in the stress response. A chapter on central, neuroendocrine, and autonomic mediation of stress-related physiological and behavioral activity is followed by treatments of the interplay of those initiating processes with cardiovascular and immunological processes. These updates on traditional topics of stress biology are accompanied by discussions of more recently emerging literatures concerning immunological and genetic modulation of stress responses and effects of stress that are observable at the molecular level.

Section II covers social–contextual contributions to stress and to processes of adaptation to stress. It begins with a discussion of the tendency of humans to form relationships and provide one another with support in response to life stress as an evolved biological adaptation traceable to mammalian evolution. This is followed by psychological and sociological treatments of the structure and function of social relationships as they relate to stress and support processes. A series of chapters then discuss stress and its consequences in the context of the workplace, organizations, race and ethnicity, and the socioeconomic spectrum.

Section III is concerned with psychological factors in stress. It begins with a theoretical review and update of the concept of cognitive appraisal as it relates to stress and emotion, with particular reference to the potential for appraisal constructs to integrate and extend these two fields of study. Research on emotion is then subjected to further discussion as a way of expanding the more traditional psychological stress perspective. The next chapter is on coping, another concept that is fundamental to psychological perspectives on stress. Stress and coping are then discussed in relation to personality, gender, and adult development.

Section IV provides reviews of the evidence linking stress to health-related behaviors and mental and physical health outcomes. Eating and drug use are discussed as behaviors that are to some extent driven by stress, and physical exercise is considered as a behavioral means of reducing stress and its health effects. Stress is then examined as a factor in pregnancy and childbirth outcomes, and in relation to depression and childhood and adolescent mental health problems. The remaining chapters focus on physical health outcomes. First, traumatic stress is examined as a contributor to a variety of physical health problems. Successive chapters then focus on specific medical conditions: cardiovascular diseases, cardiometabolic syndrome, the cancers, infectious diseases, and HIV/AIDS. Subsequent chapters consider the relationship between stress and pain, interventions for reducing stress in chronically ill patients, and the role of stress in the management of chronic illnesses.

Section V covers research methods, tools, and strategies. It begins with a review of the principles and

techniques of laboratory experimentation in stress research. Following are chapters that detail methods for the use of cardiovascular and neuroendocrine measures. The next chapter discusses the recent introduction of brain imaging to stress research. Three chapters then provide reviews and updates on tools for the self-report assessment of environmental stress. The final chapter discusses multilevel analysis as an overarching strategy for research on stress and health.

SOME LIMITATIONS

This *Handbook* does not provide comprehensive coverage of the field of stress science, nor was it intended to. Its size and scope did expand as we enumerated topics and enlisted authors, and this enabled us to cover more territory. Nonetheless, the resulting set of chapters is representative, but not exhaustive, in covering the major areas of stress research that are concerned with psychological and biological processes whereby stressful environmental events and conditions promote health problems. It is clearly more than an arbitrary sampling of those topics but, at the same time, it is a less than encyclopedic collection.

Even within its intended scope, there are several topics that might have been represented by adding chapters but, because of limited space and various other practical reasons, this could not be done. Among these are additional biological systems (e.g., respiration, digestion), life functions (e.g., sleep), and physical conditions (e.g., rheumatoid arthritis, irritable bowel syndrome) that may be influenced by stress. A review of basic psychological literatures concerning the effects of stress on memory and learning would have provided useful foundation for coverage of appraisal, coping, and emotion. Additional sociocultural dimensions of stress of significant interest include religion, spirituality, and acculturation. Within the mental health domain, we confined coverage of the many major forms of psychopathology in which stress appears to play a role to conditions (e.g., depression, trauma) that have attracted considerable interest for their possible physical health effects. In many cases, topics addressed within chapters that we did include easily could have formed the basis for multiple chapters (e.g., on specific individual problem drugs or different cardiovascular disorders). Similarly, the many different techniques that have been developed as means of reducing stress warrant handbook-sized coverage on their own.

CONCLUSIONS AND OUTLOOK

Nonetheless, within the confines of a large but manageable set of chapters, we believe that this *Handbook* captures the major contours and essential features of a clearly identifiable and important area of research. That research is concerned with understanding the role of stress in physical health and disease. Each of the individual chapters in this volume stands as a significant contribution in its own right. Taken together, the full set of chapters captures the excitement and promise, as well as the challenges, of a vibrant and productive field of inquiry. Accordingly, we believe this book will serve as a valuable resource for many years to come. Over time, the value of stress science will be judged by the progress that is made in the further accumulation and practical application of knowledge about the nature of stress, its causes, and its consequences for human health. We hope and expect that this *Handbook* will inspire current and future stress scientists to make the discoveries that will bring about such progress.

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2 Regulation of the Hypothalamo–Pituitary–Adrenal Axis, Chronic Stress, and Energy: The Role of Brain Networks

Mary F. Dallman and Dirk Hellhammer

INTRODUCTION

Large changes in our appreciation of stress networks have occurred in recent years because of advances from basic animal work, the growing impetus of genetic studies, and brain imaging in humans and nonhuman primates. It has become apparent that the entire brain is involved in responding to stressors. Moreover, the importance of epigenetic processes has begun to illuminate how early experience can modify adult behaviors, including those that are related to stress. It is an exciting time, and this chapter will set the scene, based on our new understanding of the brain networks involved in responses to stressors. Literature from animal and human work will be put into a framework, and the application of this understanding to treat troubled humans will be described.

A major premise of this chapter is that the glucocorticoids (GC), which are secreted in response to stressors, are more generally essential to the normal brain and body functions that allow life to persist under unfavorable circumstances. The GC not only exert various metabolic effects that support life, but also are required for the sustained activation of chronic central stress-response networks that serve to shift behavioral, autonomic, and endocrine activities toward surviving stressors and gaining more energy stores. Maintenance of energy stores above a critical level is essential for sustaining life, and the hypothalamo–pituitary–adrenal (HPA) axis is a key player in assuring that this occurs.

WHAT ARE THE STRESS NETWORKS?

Stress networks are a set of highly connected and conserved brain structures that are activated when real or imagined threats to the individual are perceived by vertebrate organisms, from fish to humans (Arborelius, Owens, Plotsky, & Nemeroff, 1999; Brown & Fisher, 1985; Chrousos & Gold, 1992; Crespi & Denver, 2005; Gold & Chrousos, 2002; Holsboer & Ising, 2008; Overli et al., 2004; Urry et al., 2006; Yao, Stenzel-Poore, & Denver, 2007). Activity in these networks, initiated by amygdalar corticotropin-releasing factor (CRF), serves to bias normal responses in the direction of heightened alertness toward salient stimuli and more self-protective behaviors. Sensory perceptions (pain), anxiety and other emotions, learning, and memory are all affected. Additionally, the limbic stress networks impinge on and modulate basic activities regulated by the hypothalamus and upper mesencephalon, such as feeding and aggressive, sexual, social, and maternal behaviors. The networks activate greater than usual responses of the sympathetic nervous system (SNS) and the HPA to a variety of new stimuli (Brown & Fisher, 1985; Chrousos & Gold, 1992; Cooper & Rothwell, 1991; Dallman et al., 1987; Henry, 1986; Rothwell, 1989; Rozanski, Blumenthal, Davidson, Saab, & Kubzansky, 2005) Heightened activity in the stress networks produces an overall feeling state of anxiety, or of alarm. Organisms respond to this state (with or without conscious perception of it) with behaviors that reduce activity in the stress networks (Pecoraro et al., 2006). Motivation to pursue salient stimuli that provoke action (and thus some relief) increases when the networks are transiently or persistently activated by acute, or chronic, unavoidable stressors. Perhaps the elevated motivation provided by chronic stressors can account, in part, for worsening problems seen today such as increased obesity and drug abuse (Artiga et al., 2007; Carr, 2002; Gluck, Geliebter, Hung, & Yahav, 2004; Kreek, Borg, & Schluger, 2002; Kreek & Koob, 1998; Laessle & Schulz, 2009; Lo Sauro, Ravaldi, Cabras, Faravelli, & Ricca, 2008; Loth, van den Berg, Eisenberg, & Neumark-Sztainer, 2008; Mitchell et al., 1999; Shalev, Highfield, Yap, & Shaham, 2000; Zorrilla, Tache, & Koob, 2003).

Appropriate activation of stress networks has been essential for the maintenance of life throughout evolutionary time in vertebrates. Simple nervous systems first evolved to provide immediate motor responses to important sensory stimuli in the environment, such as the awareness of food, touch of possible threat, and sexual pheromones. As time went on and multicellular organisms developed more complex subsystems, it became increasingly important to have more centralized control and regulation of disparate functions such as respiration and cardiovascular, renal, and muscular activity. Similarly, the capacity for behavioral pursuit of needs was

selected, establishing motivational states, such as hunger, social interaction, and sexual receptivity, and emotions developed, including pleasure, fear, anger, and anxiety. The result has been increasing complexity of brains. Brains have developed from simple ganglia to the hindbrain, which regulates simple behaviors and responses to external stimuli. Next came development of the midbrain, which coordinates these hindbrain behaviors, then the diencephalon and limbic brains that regulate arousal, drives, and emotions, and that integrate these with activity in the midbrain and hindbrain. Finally, the cortical brain and especially the neocortex developed, particularly in primates, whales, and elephants. The neocortex serves to modulate activity in all of the foregoing structures, and is the seat of consciousness. However, it is critical to note that as these new structures evolved, all of the preceding structures and organization were maintained, and that the latter are acted on (reciprocally) by each of the parts of the brain that emerged later in time, as recognized so strongly by Paul MacLean (MacLean, 1949; Ploog, 2003).

SELF AND FEELING—THE EMOTIONAL NERVOUS SYSTEM (FIGURE 2.1)

The organization and interactions of the body and nervous system reflect a high degree of complexity and

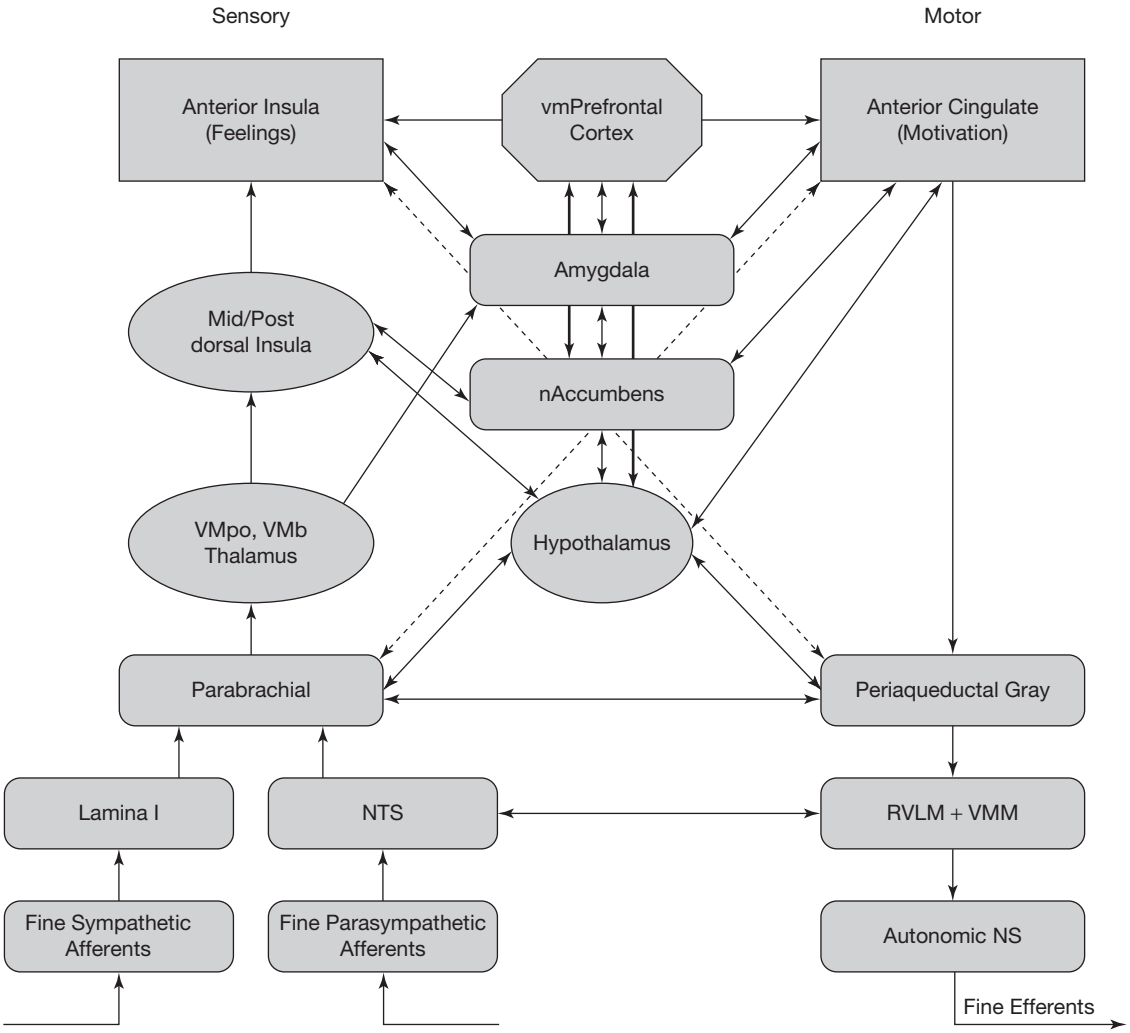

Figure 2.1 ■ The emotional nervous system. This schematic is adapted from a review (Craig, A. D. [2002]. How do you feel? Interoception: The sense of the physiological condition of the body. *Nature Reviews. Neuroscience, 3,* 655–666) with modifications to show additional structures that have been found to be key to modulating responses to challenge in many vertebrate species. Arrows represent some of the interactions between cell groups; note that there are interactions at each level of the brain as well as rostral and caudal interactions. Lamina I, lamina I in the dorsal horn of the spinal cord, pain pathway; NTS, nucleus of the tractus solitarius in the brainstem medulla; RVLM, rostroventrolateral medulla; VMM, ventromedial medulla; VMpo and VMb, ventromedial thalamic structures.

multidirectional communication. For example, while the primary senses of touch, smell, vision, audition, and taste capture environmental stimuli, there is also a massive set of internal senses, with receptors that funnel their impulses to the brain. These include temperature and pain receptors, stretch receptors that innervate the capsules of every joint, receptors in internal organs and blood vessels, chemoreceptors that sense oxygen and carbon dioxide content, and cytokine-, glucose-, fat-, and hormone-sensing receptors in the gut, liver, and elsewhere (Berthoud, 2000; Saper, 2002). Thus the brain has access to all that is happening, both inside and outside of the body. In humans and other mammals there is a network of fine, nonmyelinated fibers that enters the spinal cord and synapses in the dorsal horn. From there, axons cross the cord and ascend in the spinothalamic pathway to innervate both the nucleus of the tractus solitarius in the medulla and the parabrachial nuclei in the mesencephalon. Both of these sites also have direct access to the limbic system and hypothalamus, as well as, through a thalamic relay, certain cortical structures. Spinal pathways provide this information to the insular cortex through the same central neural network in rats (Saper, 1982). Together, the integration of inputs from the exteroceptive and interoceptive senses provide limbic cortical knowledge of "how things are." The orbitofrontal, ventromedial prefrontal, and anterior cingulate cortices form the cortical outputs of the system.

The motor output from cortex that responds to the limbic sensory brain input is mediated by the hypothalamus, periaqueductal gray, autonomic premotor neurons in the rostral ventrolateral medulla, and ventromedial medulla and autonomic motor neurons in the autonomic nervous system (ANS) (see Figure 2.1). Major integration of intero- and exteroceptive signals occurs in the parabrachial nuclei, the hypothalamus, and the posterior insular cortex (Craig, 2002; Damasio et al., 2000). Receiving modulating emotional and motivational information from the amygdala and the nucleus accumbens in the middle insular cortex, the signals may be copied into the anterior insular cortex to provide the ongoing template of awareness (Craig, 2009; Pollatos, Gramann, & Schandry, 2007). This construct of emotional awareness and feeling, provided primarily by studies using the techniques of positron emission tomography (PET) and functional magnetic resonance imaging (fMRI), encompasses thoughts about consciousness of both William James (James, 1890), based on introspection and observation, and those of Antonio Damasio (Damasio, 1994; Damasio, 1999; Damasio et al., 2000), based on both brain imaging studies (Damasio et al., 2000) and observations of the effects of destructive brain lesions. Only given cursory attention, below is the burgeoning evidence about the role(s) of the dorso- and ventrolateral cortices, which also respond to interoceptive and exteroceptive information and exert voluntary control over the emotional brain (Kringelbach, 2004; Saleem, Kondo, & Price, 2008). However, a recent meta-analysis of a large number of imaging studies has shown a key role for the prefrontal cortex (PFC) in emotion, and has suggested that six networks, including those in Figure 2.1, are involved (Kober et al., 2008). Sites in frontal cortex can acutely reduce motor outputs from, and regulate the urgency of, inputs from interoceptive and emotional signals (for further information, see Gross, 2007; also see Drabant, McRae, Manuck, Hariri, & Gross, 2008; Goldin, McRae, Ramel, & Gross, 2008; Root et al., 2009).

HUNGER

Consider the example of hunger. Hunger is among the most powerful of the primary feelings and drives. That is no wonder, since there is an absolute need for sufficient calories to keep us alive to be fit to proceed with other evolutionarily essential activities, such as procreation. Although the best maneuver found to increase longevity has been marked caloric restriction (Longo & Finch, 2003), this reduces reproductive efficiency, and, perhaps, the quality of life. An early fMRI study of hunger compared a 36-hour fast to satiation (50% of resting energy expenditure). After the fast, the feeling brain sites enumerated above (including insular and anterior cingulate cortex [ACC] as well as hypothalamus) were activated (Tataranni et al., 1999). Comparing sites activated by satiation with those during the fast, prefrontal cortical activity was increased and the activity in both insular and orbitofrontal cortical was reduced in strong relationship with the feeding-induced change in insulin (Tataranni et al., 1999). This shows that the emotional brain is highly engaged with hunger. Furthermore, it can be a great pleasure to eat highly palatable calories (Kelley, Baldo, & Pratt, 2005), and this fact (realized through nonessential feeding) is abused by many individuals under conditions of ongoing stress (Gibson, 2006).

This chapter (Peters et al., 2004, 2007) presents the hypothesis, elaborated below, that the central stress system is embedded in the network that regulates energy balance, and that the SNS and HPA axis both represent components of this large system that help it to ensure the adequacy of metabolic energy stores and their acute mobilization. First we will discuss the anatomy and characteristics of the outputs of the HPA axis and ANS, and the hypothalamic/brainstem system (periaqueductal gray) that initiates behavioral responses. Next we will discuss the anatomy and functions of the CRF-stress response system, and the effects of chronic stressors. We will then discuss the relationship of various feeding regimens to the major outputs as well as to the chronic stress network. In the second part of this chapter, this framework will be applied to individuals with problems through the use of a system that uses measurement of output variables and history to help these people with diagnosis and suggested treatments of their problems. Overall, this examination of stress, hunger, energy balance, and associated processes and forms of dysfunction is intended to provide an illustration of the potential utility and heuristic value of organizing stress research according to the notion of stress networks.

CHARACTERISTICS OF THE HPA AXIS

The HPA axis is consisted of CRF-synthesizing and -secreting neurons in the paraventricular nuclei (PVN) of the hypothalamus, corticotropin (ACTH) synthesizing and secreting cells (corticotropes) in the anterior pituitary, and GC synthesizing and secreting cells in zona fasciculata of the adrenal gland. CRF- and ACTH-secreting cells have stored hormone that can be secreted rapidly upon stimulation. By contrast, in the adrenal, GC-secreting cells must both synthesize and secrete hormone on demand from ACTH, and thus there is a lag of minutes between increases in plasma ACTH and the responsive increases in GC. Furthermore, the GC-secreting (primarily cortisol in humans, corticosterone in rats) adrenal has a limited maximal response to ACTH, which saturates in the lower quartile of the ACTH response range. However, when ACTH is above the maximal adrenal corticosteroid response, the adrenal integrates the ACTH signal, via a linear increase in the second messenger, cyclic adenosine monophosphate (cAMP), and sustains secretion for a longer time (Keller-Wood, Shinsako, & Dallman, 1983). This fact may explain the observation that often plasma GC concentrations are still high when ACTH is no longer elevated after a stressor has occurred.

In addition to ACTH driving the adrenal, there is a sympathetic neural pathway from the hypothalamus to the adrenal cortex that serves to increase the responsivity of the adrenal to ACTH (Kaneko, Kaneko, Shinsako, & Dallman, 1981). The increased neural activity normally occurs daily at the circadian peak (see below) but may also occur with stressors (Buijs et al., 1999; Jasper & Engeland, 1994; Perreau-Lenz, Pevet, Buijs, & Kalsbeek, 2004). Thus, the apparent sensitivity of the adrenal to ACTH can vary in response to sympathetic stimulation of the gland.

Secreted GC are bound in the circulation to corticosteroid-binding globulin (CBG) or transcortin, and it is only the unbound fraction, usually only 1% to 10% of the total (Dallman et al., 1989), that is available to act on target brain and peripheral tissues. It is the free steroid that can diffuse through capillaries to enter cells and bind with corticosteroid receptors. CBG is produced by the liver and is sensitive to GC, so that when GC concentrations increase from exogenous treatment or prolonged stressor exposure, CBG concentrations fall; by contrast, in adrenalectomized animals, CBG concentrations are high. Moreover, CBG production is stimulated by estradiol, in part explaining the higher total plasma GC concentrations in female rats and pregnant women.

GC are removed from the circulation primarily by forming reduced metabolites and by esterification in the liver. Thus their clearance is affected by changes in liver blood flow. When this is high, for example, during relaxation after meals, GC are cleared faster, and when it is low, as occurs when blood flow is shunted to the muscles during running, clearance is slower. The active form of the steroid requires a Δ^{4-}3-ketone in the A-ring and hydroxyl groups at positions 11 and 21 of the molecule. In liver, and to some extent, in other tissues, the A-ring is reduced, and the 11-hydroxyl group may be oxidized. Water solubility is enhanced, thereby aiding excretion via the kidneys by producing glucuronide or sulfate esters of the molecule. Oxidation of the 11-hydroxyl group changes cortisol to the inactive cortisone, which circulates in considerable quantities. Other tissues, in particular fat, also contain enzymes that can oxidize or reduce cortisol. Of considerable current interest are the enzymes 11β-hydroxysteroid dehydrogenase (11β-HSD) types 1 and 2. The former catalyzes the reduction of cortisone to cortisol, and the latter catalyzes the oxidation from cortisol to cortisone. Both are theoretically important. The fact that cortisone is reduced in considerable amounts by the body allows treatment of patients with inactive (and inexpensive) cortisone, rather than the active cortisol. 11β-HSD type 2 expressed in brain and placenta oxidizes cortisol, thus reducing cellular exposure to GC of mineralocorticoid receptors (MR) in brain, or exposure of the fetus to the active GC (Benediktsson, Lindsay, Noble, Seckl, & Edwards, 1993; Edwards, Benediktsson, Lindsay, & Seckl, 1996; Lindsay, Lindsay, Waddell, & Seckl, 1996). There is also good evidence that the active steroid, cortisol, is generated from cortisone in mesenteric fat, and that cortisol concentrations are higher in the hepatic than mesenteric vein, possibly inducing the metabolic syndrome in some people (Basu et al., 2004; Benediktsson et al., 1993; Brunner et al., 2002; Seckl & Walker, 2004).

WHAT ARE SOME METABOLIC EFFECTS OF THE GC?

In the presence of low insulin concentrations, the GC are markedly catabolic on tissues high in protein and fat, whereas they are anabolic in liver and cause synthesis of enzymes involved in gluconeogenesis. Thus, they increase the supply of amino acids and free fatty acids gained from breakdown in the periphery for enhanced glucose production by liver, and serve a key role in providing the essential glucose which supports neuronal activity. Probably because of the increased glucose production by liver, insulin concentrations also increase pari passu with increases in GC. These effects are evident after only 18 hours of a high dose of dexamethasone in the drinking water given to rats, as shown in Figure 2.2. However, with increasing duration of exposure to abnormally elevated GC (such as occurs with chronic stressors), together with ad lib sucrose ingestion and increased insulin secretion, there is an unexpected loss of body weight accompanied by increased intra-abdominal fat stores, with no effect on subcutaneous stores, over a range of GC concentrations (see Figure 2.3). In vitro, GC act on preadipocytes together with insulin to cause differentiation to mature adipocytes and also to increase lipoprotein lipase in the blood vessels supplying adipocytes. This allows increased access of both glucose (through elevated insulin) and free

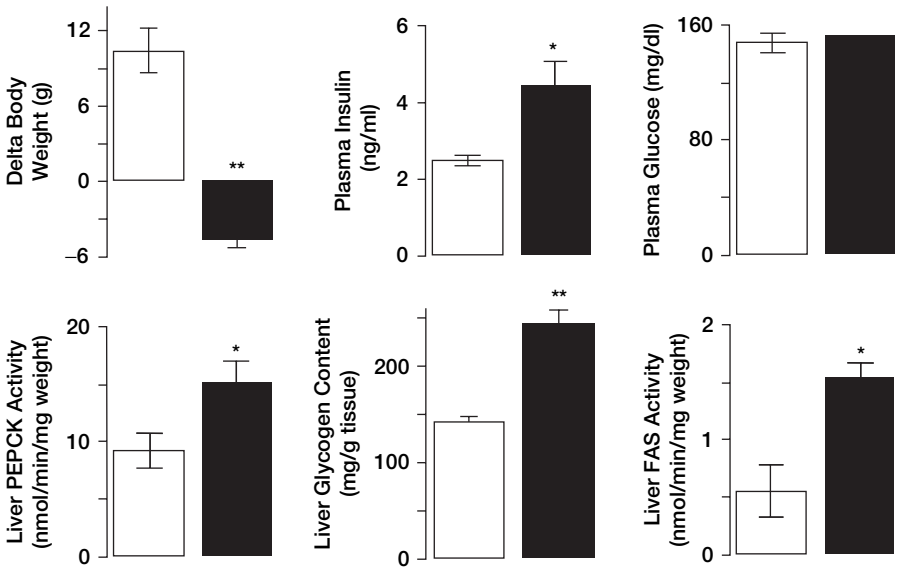

Figure 2.2 ■ Some metabolic effects of elevated glucocorticoid concentrations. Male rats were provided with dexamethasone in their drinking water overnight; they ingested an average of 200 μg/kg steroid. The rats lost body weight, and plasma insulin concentrations increased with normal glucose; the anabolic actions of glucocorticoid treatment in liver are represented by increased activity of phosphoenolpyruvate (PEPCK), the rate limiting enzyme for gluconeogenesis, increased glycogen deposition, and increased fatty acid synthase (FAS) activity. Unpublished data from James P. Warne, 2005.

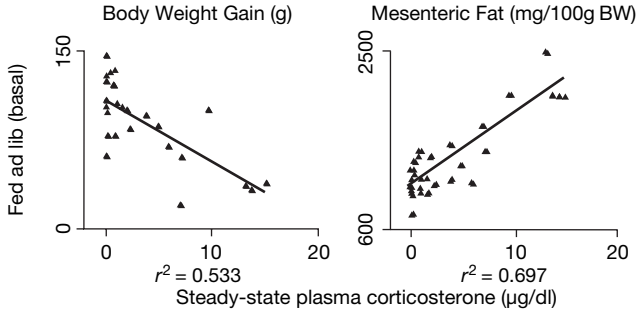

Figure 2.3 ■ Glucocorticoids decrease body weight (BW) while increasing mesenteric fat weight. Adrenalectomized rats were treated using pellets of corticosterone for 7 days with various amounts that ranged from none to those that produced steady-state plasma corticosterone concentrations that approximated the daily circadian maximum (Bell, M. E., Bhatnagar, S., Liang, J., Soriano, L., Nagy, T. R., & Dallman, M. F. [2000]. Voluntary sucrose ingestion, like corticosterone replacement, prevents the metabolic deficits of adrenalectomy. *Journal of Neuroendocrinology, 12*, 461–470).

fatty acids to the adipocytes (Hauner, Schmid, & Pfeiffer, 1987; Macfarlane, Forbes, & Walker, 2008; McCarty, 2001; Mantha & Deshaies, 2000). When intra-abdominal fat stores are mobilized, the free fatty acids and glycerol are immediately transported to liver where their energy can be utilized for gluconeogenesis.

HPA RESPONSES

Under undisturbed basal conditions, secretion in the HPA axis is episodic and circadian, with marked increases in plasma cortisol occurring during the hours before onset of daily activity (Krieger, Allen, Rizzo, & Krieger, 1971). Figure 2.4 shows free corticosterone concentrations (uncorrected for recovery) measured by dialysis in the hippocampus of freely moving rats for 5 consecutive days (Linthorst & Reul, 2008). Lights off, when rats become active, occurred at 20:00h. Notice the very low concentrations of free corticosterone in brain; concentrations of the steroid in plasma are ~1 μg/dl at the nadir of the rhythm, and >15 μg/dl at its peak, just before lights out. These ~10–100× differences between circulating concentrations of GC and those in hippocampus represent the effect of CBG binding that maintains the hormone in plasma (Dallman et al., 1987). The anticipatory circadian peak, driven by the light-sensitive endogenous clock in the suprachiasmatic nuclei (SCN), occurs in both diurnally and nocturnally active species (Pecoraro, et al., 2006). However, if food intake is reduced and restricted to only part of the light period in nocturnally active rodents, the rhythm is then taken over by a food-entrained oscillator (FEO) that is probably located in the dorsomedial hypothalamus (Gooley, Schomer, & Saper, 2006; Pecoraro et al., 2006) This oscillator causes peak GC to occur just before feeding, and it is the GC rhythm that establishes rhythmic metabolic activity in the liver (Diaz-Munoz, Vasques-Martinez, Aguilar-Roblero, & Escobar, C., 2000; Le Minh, Damiola, Tronche, Schutz, & Schibler, 2001; Lemberger et al., 1996; Oishi et al., 2005). The magnitude of peak cortisol in humans is clearly linked to glucose requirements occurring toward the end of normal sleep periods (Benedict et al., in press; van Cauter, Polonsky, & Scheen, 1997). After waking, there is, in most people, a further cortisol awakening response (CAR) that peaks 30–45 minutes later, and appears to reflect the current load of stressors on the individual (Fries, Dettenborn, & Kirschbaum, 2009; Schlotz, Hellhammer, Schulz, & Stone, 2004). People with bilateral hippocampal damage have a normal circadian rhythm in cortisol, but do not have a CAR (Buchanan, Kern, Allen, Tranel, & Kirschbaum, 2004), suggesting that with loss of short-term memory,

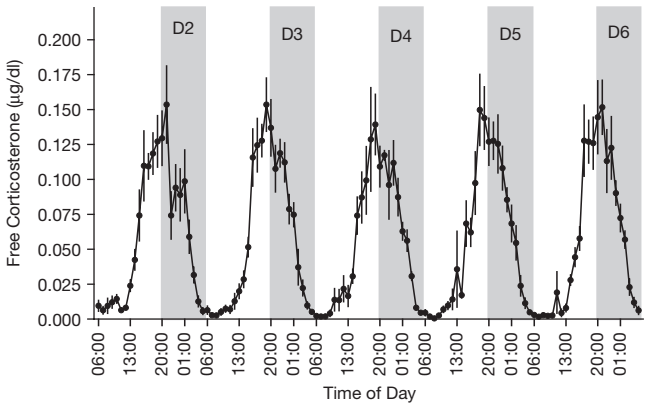

Figure 2.4 ■ Circadian rhythm in free corticosterone concentrations in the hippocampus. Rats were prepared with a guide cannula in the hippocampus; after 8 days' recovery from surgery a dialysis probe was implanted. Starting 2 days later, dialysate was collected throughout a period of 5 days. Corticosterone was measured in the dialysate. The values reported are not corrected for recovery, which averaged about 40%. Although corticosterone concentrations in hippocampus are very low compared to plasma, the values faithfully reflect the circadian rhythm in basal HPA function (Linthorst, A. C. E., & Reul, J. M. [2008]. Stress and the brain: Solving the puzzle using microdialysis. Pharmacology, biochemistry, and behavior. *Microdialysis: Recent Developments*, *90*, 163–173), with the very kind permission of Astrid Linthorst).

the stressors no longer affect the CAR. Either physically or psychologically threatening acute stressors, presented at any time of day, result in CRF, ACTH, and GC secretion above basal values (Dallman et al., 1987; Pecoraro et al., 2006). The effects of chronic stressors will be addressed below.

FEEDBACK REGULATION OF THE HPA AXIS FROM THE PERIPHERY

GC FEEDBACK

GC have been used for treatment of many diseases in people, with concomitant inhibition of function in the HPA axis (Miller & Tyrrell, 1995). In addition, in animal and human studies, a marked increase in CRF and ACTH secretion occurs when GC are abnormally low or lacking (Keller-Wood & Dallman, 1984). GC replacement in adrenalectomized rats reveals dose-related inhibition of CRF in the PVN and pituitary ACTH (Akana, Cascio, Shinsako, & Dallman, 1985; Watts & Sanchez-Watts, 1995) across the physiological range. Thus, GC feedback control of the HPA axis is a widely recognized and clinically important physiological phenomenon. GC receptors (GR) are found in pituitary corticotrope cells as well as in the hypothalamic PVN and throughout the rest of the brain (Fuxe et al., 1985; Gustafsson et al., 1987; Swaab, Bao, & Lucassen, 2005). GC feedback occurs both in the brain and at the pituitary gland (Keller-Wood & Dallman, 1984), although, with sufficient CRF drive, the pituitary feedback can be overcome (Schlaghecke, Kornely, Santen, & Ridderskamp, 1992). Dexamethasone, a synthetic GC, is frequently used to test steroid feedback efficacy in people. It does not bind to CBG, and is essentially entirely free to act in both the pituitary and the brain. It is likely that, compared with cortisol, relatively more of its action is on pituitary than on brain, because pituitary ACTH cells contain CBG, which binds much of the endogenous GC and keeps it away from the GR in corticotropes (Koch, Lutz-Bucher, Briaud, & Miahle, 1979).

There are two receptors in the brain that bind GC. The high-affinity mineralocorticoid (MR), or type 1 corticosteroid receptor, binds both aldosterone and the GC, and the GR, or lower affinity, type II corticosteroid receptor also binds GC (Reul, van den Bosch, & de Kloet, 1987). Evidence in both humans and rodents shows that both MR and GR are involved in feedback inhibition of activity in the HPA axis (Dallman et al., 1989; Dodt, Kern, Fehm, & Born, 1993). GC feedback inhibits both basal and stressor-induced ACTH secretion in direct proportion to the dose of steroid administered (Keller-Wood, Shinsako, & Dallman, 1984). Elevating circulating GC over the low range in the intact rat increases trough but diminishes peak corticosterone levels so that the daily mean of corticosterone is maintained (Akana et al., 1992). This and other studies (Levin, Shinsako, & Dallman, 1988; McHugh & Smith, 1967) show clear evidence for GC feedback in neuronal networks afferent to CRF neurons in PVN in rats and nonhuman primates. However, there are some brain pathways afferent to the PVN that are GC-insensitive and thus stimulate CRF neurons when GC levels are high, causing HPA responses that are less sensitive to GC feedback in both rats and people (Dallman et al., 1987; Wilkinson, Engeland, Shinsako, & Dallman, 1981).

Noted above was the use of dexamethasone in studying or modulating GC feedback. In people, low doses of dexamethasone are used to test GC feedback control of the HPA axis (de Kloet et al., 2006; Kudielka, Schmidt-Reinwald, Hellhammer, & Kirschbaum, 1999). Increased central drive to the HPA axis is evident by a decrease in the usual feedback efficacy of the steroid, whereas less than normal central drive is shown by greater inhibition of the HPA axis. There are also fast, intermediate, and slow time domains of feedback inhibition by GC in the HPA axis (Keller-Wood & Dallman, 1984). Fast feedback, although not very powerful, is important in limiting the duration of HPA axis activity after a stressor has occurred (Raff, Flemma, & Findling, 1988), thus containing the amount of GC to which the individual is exposed. The intermediate feedback domain (2–24 hours) dampens brain and pituitary responses to subsequent stressors, probably primarily through protein–protein interactions of the GC–GR complex with other translational factors. The slow feedback may be mediated through both protein–protein and direct genomic actions of the GC–GR

complex (Bamberger, Schulte, & Chrousos, 1996). In the absence of chronic stress (see below), GC feedback serves as a classic long loop endocrine feedback mechanism, maintaining the forward elements of the system under control through GC actions on brain and pituitary.

METABOLIC FEEDBACK

In addition to this classic neuroendocrine feedback regulation provided by the adrenal GC response to HPA activation, there is another feedback loop in the HPA axis that is driven by some signal of the level of calorie storage. This is most clearly seen when adrenalectomized rats are given 30% sucrose to drink ad lib (Bell et al., 2000). Drinking palatable sucrose prevents the normal effects of bilateral adrenalectomy and removal of the GC on energy balance. Adrenalectomized rats also prefer sucrose to equally sweet saccharin (Laugero, Bell, Bhatnagar, Soriano, & Dallman, 2001). The usual effects of adrenalectomy on increasing hypothalamic CRF and pituitary ACTH secretion under basal conditions do not occur (Laugero et al., 2001; Laugero, Gomez, Siao, & Dallman, 2002). Moreover, there is a negative relationship between the mesenteric fat mass and hypothalamic CRF expression (Dallman et al., 2003), such that adrenalectomized rats with large abdominal fat stores have low hypothalamic CRF. CRF mRNA in the central nucleus of the amygdala (CeA), which is decreased in adrenalectomized rats without sucrose, is restored to normal in adrenalectomized rats drinking sucrose. These results suggest strongly that it is the well-known peripheral actions of GC on energy storage, in addition to, or instead of, their effects on brain, which normalize feedback in the HPA axis under nonstress conditions. Adrenalectomized rats without GC ingest about 40% as much as intact rats of both calorically important sucrose (Bell et al., 2000) and fat (la Fleur, Akana, Manalo, & Dallman, 2004) (but do not drink noncaloric, but equally sweet saccharin [Bhatnagar et al., 2000]).

Both GC and metabolic well-being reduce the motor CRF output of the HPA axis, supporting the hypothesis that this neuroendocrine system is embedded in a larger system that regulates energy balance. We now turn to these larger systems.

CHARACTERISTICS OF THE ANS

MOTOR SYMPATHETIC AND PARASYMPATHETIC DIVISIONS

The sympathetic (ergotrophic) nervous system and the parasympathetic (trophotropic) nervous system (PNS) innervate the organs, glands, and vessels of the body, and often the two branches work in an opposing manner. Generally, the SNS activates the organism and releases stored energy, and the PNS relaxes the organism and stores energy (see extensive discussion below). The transmitter of the SNS is norepinephrine (NE), secreted from postganglionic neurons with cell bodies located in vertebral, paravertebral, and abdominal ganglia, and with efferent axons innervating blood vessels, organs, glands, and muscles. By contrast, the PNS secretes acetylcholine from ganglia that are buried in the organs and glands that it innervates. Another distinction that has been made between the two branches of the ANS was that activation of the PNS and acetylcholine secretion were highly specific to a given organ, but that the SNS outflow of NE was general and nonselective (Sherrington, 1898). It is now clear that there is very fine, tissue-by-tissue control of function by the sympathetic system as well (Saper, 2002). Recently, it has become apparent that upon vigorous electrical stimulation or intense stressors, motor neurons of the SNS may secrete neuropeptide Y (NPY) as well as NE. Acting through NPY receptors on vascular and adipose tissue, secreted NPY may serve to push cardiovascular and adipose function toward pathophysiology (Kuo et al., 2007, 2008; Ruohonen et al., 2000; Zukowska, Pons, Lee, & Li, 2003).

Central Autonomic Network (Saper, 2002)

As outlined in Figure 2.1, interoceptive afferent signals that encode pain, temperature, stretch, and chemical sensations enter the spinal cord, ascend in the spinothalamic and spinoreticular tracts of the cord, and synapse on neurons in the medullary nucleus of the solitary tract (NTS) and the parabrachial nuclei (PBN). At this level, there is direct connection with the autonomic motor output neurons in the ventrolateral medulla, allowing for autonomic reflex responses to visceral inputs and pain. From these two sites, input from the visceral and pain afferents signal the insula and other parts of cortex through synapses in the visceral sensory thalamus, the ventromedial nucleus, and other midline nuclei. Neurons in both the NTS and the PBN also innervate other medullary, pontine, hypothalamic, and forebrain sites directly. At every level of this interoceptive system, there are direct connections between the afferent and efferent components of the ANS (Saper, 2002). Motor outputs to the ANS are patterned and organized in the hypothalamus, with activation occurring from much of the forebrain as well as from hindbrain (Saper, 2002; Swanson, 1987, 2000, 2007). Patterned outputs occur that include integrated behavioral, hormonal, and autonomic responses. Major outputs from the hypothalamus include responses to challenge. Metabolic, thermoregulatory, defensive, defeat, and sexual responses are all organized and patterned in the hypothalamus, and much of the output is mediated by activity in the dorsomedial nucleus (DMN) (Morilak et al., 2005). In addition to the HPA-regulating CRF neurons, there is also a direct motor contribution to the ANS from the PVN (Swanson & Sawchenko, 1980). Skeletal motor (behavioral), as well as autonomic outputs, are, for the most part, achieved through hypothalamic (limbic and cortical) activation of

the periaqueductal gray (Adamec, 2001; Carrive, Bandler, & Dampney, 1989; Subramanian, Balnave, & Holstege, 2008). Outputs from these cell groups synapse in the sacral spinal cord and dorsal motor nucleus of the vagus and hypoglossal nerves to regulate parasympathetic outflow. SNS outflow is regulated by premotor neurons in the lateral horn of the spinal cord. The two nervous systems work simultaneously in many instances, and the balance of this activity on the heart is frequently determined by measurement of heart rate variability (Berntson, Norman, Hawkley, & Cacioppo, 2008).

Clearly, the central cell groups that regulate ANS, behavioral, and endocrine function are highly interconnected at all levels, and it is typical that the higher the site investigated by electrical stimulation or lesions, the more flexible are the response patterns elicited. Many parts of the limbic and cortical brain feed into the hypothalamic visceromotor pattern generators and the neuroendocrine and autonomic hypothalamus (Alheid, de Olmos, & Beltramo, 1995; Canteras, Simerly, & Swanson, 1995; Dong, Petrovich, & Swanson, 2000; Dong, Petrovich, Watts, & Swanson, 2001; Gray, 1991; Herman et al., 2003; Kelley, Baldo, Pratt, & Will, 2005; Pennartz, Groenewegen, & Lopes da Silva, 1994; Petrovich, Risold, & Swanson, 1996; Swanson, 2000; Thompson, & Swanson, 1998) providing further enhanced capability for the bewildering flexibility and specificity of individual responses to stimuli. Generally, there are choices to be made in the motor responses to challenge, for example, fight or flight, and whether either or neither occurs depends on the net activity of most of the conscious brain. Challenges also call on stored memories, habits, and the current state of the emotional brain to formulate the responses of the organism.

THE CHRONIC STRESS RESPONSE NETWORK

Minor stressors are brief, momentary challenges that either are of limited duration, can be escaped from through changing behavior, or result in rapid death. By contrast, chronic stressors are sustained or repeated, or of very high intensity, and cannot immediately be escaped from, or coped with, by using the behavioral repertoire at hand. Throughout time, it is likely that many chronic stressors were imposed by natural or social catastrophes (e.g., flood, hurricane, fire, earthquake, drought, crowding, and territorial aggression) that removed the usual sources of food or water from the immediate environment. These events required that people and animals be motivated to seek food and water elsewhere, perhaps at considerable distances from their ongoing living space. To endure the essential journey to find food and water sources, it is critical that there are sufficient endogenous calorie stores to call upon. Travel, by foot or wing (Kitaysky, Kitaiskaia, Wingfield, & Piatt, 2001; McEwen & Wingfield, 2003), is energetically very expensive, and requires a consistent and constant supply of energy to both plan and execute. In this case, highly focused and coordinated activity in the HPA, ANS, and behavioral networks are essential to maintain life. Altered function in the emotional brain to drive this activity is essential for a successful response, and hunger is a powerful motivator. Psychologists and neuroscientists use hunger/thirst and food/liquid reward to have research animals tell them how much they want something and how they perceive sensory signals. In the 1970s it became clear from rat studies that such restricted feeding also shifts the circadian rhythm in GC to peak before the expected time of feeding (Gray, Bergfors, Levin, & Levine, 1978). These stressors clearly still exist today in human societies, together with the additional chronic stressors that have emerged with the vagaries of societal organization and population pressures in the face of limited resources. An additional and very important factor is the profound stressor of early and serious maltreatment of a child, which, through epigenetic events, may bias the adult toward a permanent enhancement of function in the chronic stress network in rats and humans (Anisman, Zaharia, Meaney, & Merali, 1998; Caldji et al., 1998; Caldji, Diorio, & Meaney, 2000; Champagne et al., 2008; McGowan et al., 2003; Meaney, Aitken, Viau, Sharma, & Sarrieau, 1989; Meaney et al., 1994). The notion of "being stressed-out" is now integrated into the popular vocabulary, and is applied to the effect of living conditions (e.g., low socioeconomic status, urban blight, high population density), and of occupational factors (e.g., workplace hazards, job insecurity, task overload), as well as of individual tragedies and conditions (e.g., bereavement, divorce).

THE CRF-MEDIATED STRESS-RESPONSE NETWORKS

In addition to the HPA motor neurons in the PVN, CRF-synthesizing neurons and CRF receptors are found throughout the brain (Reul & Holsboer, 2002; Sawchenko, Imaki, Potter, Kovacs, & Vale, 1993). There are clusters of CRF neurons in the midbrain (Barrington's nucleus) as well as in the CeA, and in the extended nucleus of the amygdala, the bed nucleus of the stria terminalis (BST). Furthermore, there are many cortical interneurons that contain CRF, as well as neurons that may express CRF under conditions of chronic stress (Watts, 1996). When CRF is injected into the brain ventricles, monoaminergic (serotonin, dopamine [DA], and NE) cell groups are excited, and the recipient animal behaves as though it were massively stressed. Behaviorally, increased freezing, anxiety, and aggression occur in association with increases in activity by the SNS as well as HPA outflow (Brown & Fisher, 1985, 1983; Brown et al., 1982; Carpenter et al., 2007; Dallman et al., 2006; Matsuzaki, Takamatsu, & Moroji, 1989; Spina et al., 2000). This shows a patterned, integrated response to the injected CRF. Although acute stressors stimulate CRF secretion from the CeA (Cook, 2004; Merali, McIntosh, Kent, Michaud,

& Anisman, 1998), we will focus on the effects of chronic stress on the CRF cell group in the CeA, about which most is known and understood. Chronic stressors may stimulate both CRF synthesis and secretion from the CeA (Dallman et al., 2006).

However, and of key importance, GR action in the CeA is *required* for chronic stressors to increase CRF synthesis and secretion (Cook, 2002; Dallman et al., 2006; Kolber et al., 2008; Schulkin, Morgan, & Rosen, 2005). Although systemic GC infusions inhibit CRF expression in the PVN in a dose-related fashion, they positively regulate CRF in the CeA (Pisarska, Mulchahey, Sheriff, Geracioti, & Kasckow, 2001; Watts & Sanchez-Watts, 1995). The role of GC in the CeA in stimulating activity in coherent stress-response networks has been shown most compellingly by Muglia's lab, using knockout (KO) mice. The forebrain GR KO mouse, made using a CaM kinase II construct, has no GR in hippocampus, or in other cortical structures, although it does retain GR in the CeA and PVN. This mouse, and several other brain GR KO mice (excluding GR KO in the CeA), has remarkably mild behavioral deficits (Howell & Muglia, 2006). However, when CaM Kinase II GR KO were virally engineered to KO GR in the CeA of the forebrain KO mice as well as in normal mice with forebrain GR, full blown responses to stressors were observed (Kolber et al., 2008). CRF neurons in the CeA innervate much of the brain, including hippocampus, PFC, nucleus accumbens, and the three monoaminergic (Curtis, Bello, Connolly, & Valentino, 2002) cell groups in the midbrain and hindbrain. Stimulated CeA neurons have been shown to result in diffusion of CRF from the CeA to the basolateral amygdala (BLA) where the neurons are heavily invested with CRF receptors (Roozendaal, Brunson, Holloway, McGaugh, & Baram, 2002). Thus, these neurons are poised to recruit activity in key brain systems that alter memory, decision-making, motivation, arousal, alertness, aggression, and feeding behaviors. The output of the CeA CRF-containing neurons also extends to regulation of sympathetic neural activity and neuroendocrine activity (Alheid et al., 1995; Schulkin et al., 2005).

GC and chronic stressors both acutely (Mitra & Sapolsky, 2008) and chronically increase the size and architectural complexity of amygdaloid dendrites, in both rats and humans (Blair, Schafe, Bauer, Rodrigues, & LeDoux, 2001; Radley & Morrison, 2005; McEwen, 2000, 2008; Vyas, Bernal, & Chattarji, 2003; Vyas, Mitra, Shankaranarayana Rao, & Chattarji, 2002). Chronic stressors and GC in rats have been shown to increase dendritic branching and synaptic spines in the amygdala and ACC, while a concomitant decrease in neuronal complexity occurs in the hippocampus and PFC (McEwen & Magarinos, 2001; Pecoraro et al., 2006; Radley & Morrison, 2005; Radley et al., 2005; Vyas et al., 2003; Vyas et al., 2002; Watanabe, Gould, & McEwen, 1992; Wellman, 2001). However, these changes may be pathway-selective, since it has recently been shown that the inputs from PFC to inhibitory neurons in amygdala do not show the stressor-induced structural effects observed in neighboring PFC neurons (Shansky, Hamo, Hof, McEwen, & Morrison, 2009).

In people, after acute laboratory stressors, as well as during chronic conditions that elevate GC, such as depression (Musselman, Betan, Larsen, & Phillips, 2003; Musselman, Evans, & Nemeroff, 1998), drug addiction (Breiter et al., 1997; Volkow & Li, 2005), type II diabetes (Oltmanns et al., 2006), and many other diseases, fMRI and PET studies nearly unanimously show greater amygdalar activation than normal (Abercrombie et al., 1998; Abler, Erk, Herwig, & Walter, 2007; Aleman & Kahn, 2005; Altshuler et al., 2005; Anand et al., 2005; Anders, Lotze, Erb, Grodd, & Birbaumer, 2004; Blumberg et al., 2005). Generally, increased activation of the amygdala is accompanied by increased activation in the ACC and by decreased activation in the PFC, which regulates the activity of both structures.

A LABORATORY CHRONIC STRESS RESPONSE: INTERMITTENT MORPHINE TREATMENT IN RATS DURING TREATMENT AND AFTER WITHDRAWAL (FIGURE 2.5)

Acute injections of morphine provoke increased HPA and sympathetic activity and, when it is injected in male rats on a q.12 hourly schedule for 4–16 days, is a marked chronic stressor in addition to being addicting Houshyar, Cooper, & Woods, 2001; Houshyar, Galigniana, Pratt, & Woods, 2001; Houshyar, Gomez, Manalo, Bhargava, & Dallman, 2003; Houshyar, Manalo, & Dallman, 2004). This is probably because morphine is cleared rapidly and rats are in withdrawal for much of the 12-hour period between injections. The consequences of this chronic stressor are decreased chow intake with no body weight gain, hyperthermia, persistently elevated hypothalamic CRF, plasma ACTH, and corticosterone, as well as hyperresponsivity to a new stressor at the end of treatment (see Figure 2.5, top). This is at a time before the major withdrawal symptoms occur 24–36 hours later. CRF mRNA is increased in PVN and Barrington's nucleus, and in the BST, but it is unchanged, or reduced, in the CeA.

Eight days after the last dose of morphine a markedly different picture is observed. Food intake and the rate of body weight gain and temperature regulation have recovered. Basal activity in the HPA axis is low, as are ACTH and corticosterone responses to a new stressor (see Figure 2.5, bottom); nonetheless, CRF mRNA in PVN is still hyperresponsive to the stressor despite, or perhaps because of, the marked inhibition of systemic hormones. At this point, CRF mRNA in Barrington's nucleus is still increased, and it is now increased in CeA, but has returned to normal in the BST. Thus, this chronic stressor in rats shows the anticipated increases in HPA and SNS activity during the period of its administration. It results in elevated CRF in brainstem and BST of the extended amygdala, but not in the CeA. Relief from the stressor results in normalization of several variables, but shows a marked reduction in

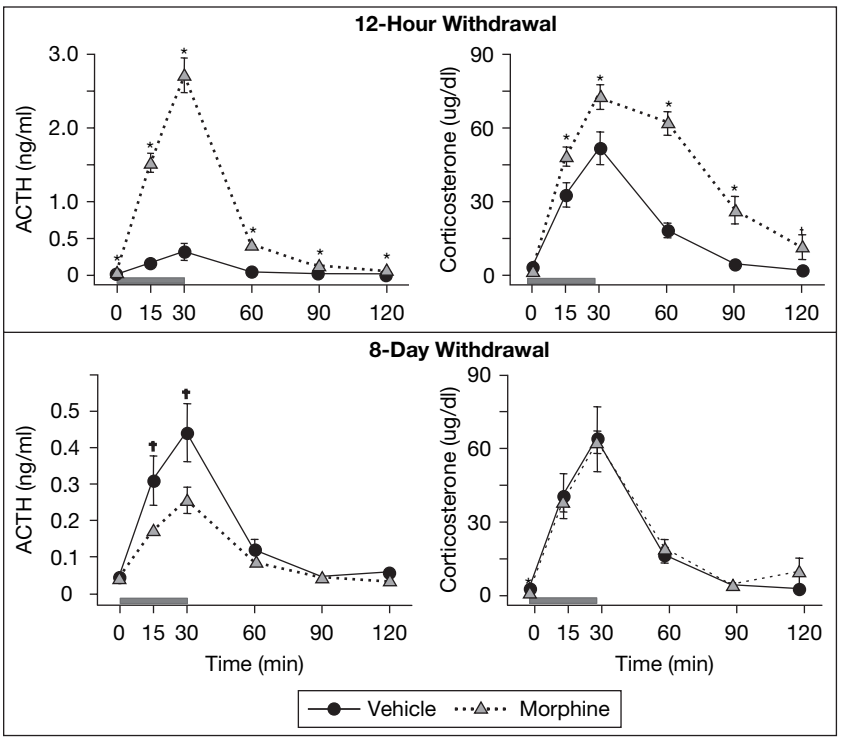

Figure 2.5 ■ Responses to a novel stressor are facilitated at the end of a chronic stressor, and are inhibited 8 days after the end of the stressor. Rats were treated q12h with escalating doses of morphine for the first 8 days, and treated with vehicle thereafter. Restraint for 30 minutes was applied 12 hours after the final dose of morphine (top) and 8 days after the end of morphine treatment (bottom). At the end of morphine administration, body weight was significantly decreased; 8 days later, body weight was normal (From Houshyar et al., 2003).

ACTH and corticosterone secretion in the face of elevated CRF in the PVN and increased CRF mRNA in the CeA. Observationally, the rats appear to be most anxious during the postmorphine period. They huddle in their cages and although they are not aggressive, they object vociferously when picked up. This behavior is compatible with the effects of either corticosterone or CRF placed into the amygdala (Schulkin et al., 2005), and the CRF-induced fear- and anxiety-like behaviors, and memory consolidation, are blocked by GC-dependent treatment with CRFR1 antagonists (Hubbard, Nakashima, Lee, & Takahashi, 2007; Roozendaal, Schelling, & McGaugh, 2008; Sandi et al., 2008). These interesting responses observed at the end of the morphine regimen are consistently reported (Dallman, 1993).

Also of interest are responses that are consistently observed 1–2 weeks after the *end* of the stressor (Astrid VallËs & Antonio, 2003; Buwalda et al., 1999; van Dijken et al., 1993). These poststressor responses resemble, to some extent, the findings in veterans with posttraumatic stress disorder (Baker et al., 1999; Liberzon, Abelson, Flagel, Raz, & Young, 1999). After intense or chronic stressors, there appears first to be a period of HPA hyperresponsiveness followed by prolonged ACTH and GC hyporesponsiveness with normal, or elevated neuroendocrine and CeA CRF and, in humans, SNS hyperresponsiveness. An analogous biphasic on–off response of the stress network appears to occur in people under several conditions. A recent review (Berlin, 2009) of the literature on the endocrinological and metabolic effects of quitting smoking points out the persistent HPA response to smoking cigarettes and the under-responsiveness that follows for at least a month after quitting, together with considerable weight gain. Hyporesponsiveness in the HPA axis is also observed after withdrawal from morphine addiction in people maintained on methadone (Kreek et al., 1984) and in people after an intense stressor (Yehuda, 2001).

SUMMARY

In laboratory studies it is clear that stressor-induced GC secretion acts at the CeA to cause increased secretion and synthesis of neuronal CRF. Heightened activity of CRF neurons in the CeA produces the behavioral, autonomic, and neuroendocrine effects observed during acute and chronic stressors in rodents, sheep, and nonhuman primates. In people, CRF antagonists have shown some efficacy against manifestations of depression (Holsboer & Ising, 2008), as have GR antagonists (Holsboer, 2001), which would be expected to inhibit elevations in amygdalar CRF (but see Kling, Coleman, & Schulkin, 2009). Although it is early, there is considerable new evidence that implies that GC stimulation of neuronal CRF secretion and synthesis is a key initiator of the central stress-response network. While the CRF network innervates and acts at very many sites in the brain, to affect many sets of responses, we will focus exclusively on its effects on the three monoaminergic cell groups in the midbrain that each globally innervates the forebrain.

MONOAMINERGIC SYSTEMS AND CHRONIC STRESS

The monoaminergic systems in the ventral tegmental nucleus (VTA, DA), the locus coeruleus (LC, NE), and the dorsal raphe nuclei (DRN, serotonin; 5HT) all contain CRF receptors and fan out into the brain to innervate most of the forebrain structures we have considered (Korzan, Summers, & Summers, 2000; Loullis & Hellhammer, 1986; Overli et al., 2007). Because major depression often follows a precipitating stressor, the changes that occur in major depression may reveal changes in all monoaminergic cell groups that occur with chronic stress (Belmaker & Agam, 2008). It now seems clear that there are some genetic disorders within the monoaminergic pathways that predispose people to depression (Jabbi, Korf, Ormel, Kema, & den Boer, 2008). With stressors, secretion of all three monoamines in brain is increased. After acute challenge, content may be decreased but, with chronic stress, synthesis usually increases and content may be normal although monoamine turnover is increased (Anisman, Merali, & Hayley, 2008; Hellhammer, Rea, Bell, Belkien, & Ludwig, M., 1984).

DA secretion in the mesolimbic pathway (from the VTA onto the shell of the nucleus accumbens; nAcc) is a key to motivation, or the salience of stimuli (Berridge, 2004; Berridge & Robinson, 1998). However, increased activity in the shell of the nAcc does not allow the conclusion that its activity provides pleasure. Under normal vivarium housing conditions, stimulation of the rostral portion of the shell elicits hedonic responses, such as drinking sucrose, whereas stimulation of the caudal part of the cell group elicits fear-like responses (Reynolds & Berridge, 2001, 2003). Responses of nAcc neurons to stimulation are sensitive to both the internal and the external environment. A change in internal conditions, sodium depletion, caused positive-like shifts in the neuronal firing rate in nAcc after normally aversive hypertonic saline was placed on the tongue, although the response to sucrose was always positive (Tindell, Smith, Pecina, Berridge, & Aldridge, 2006). Moreover, the usual rostral–caudal pleasure-to-fear gradient in nAcc can be shifted to nearly all pleasure, or nearly all fear, by altering conditions in the room in which the animals live, from a dark and very quiet environment, to a bright and noisy one (Reynolds & Berridge, 2008).

Palatable foods (Kelley, Baldo, & Pratt, 2005), access to the opposite (receptive) sex, and fighting, as well as drug availability, all stimulate DA secretion over the nAcc (Berridge & Robinson, 2003; Kelley & Berridge, 2002). Two recent reviews point out that, based on their effects on DA secretion, both drugs and sucrose (palatable foods) may be addictive (Avena, Rada, & Hoebel, 2008a, 2008b; Volkow, Wang, Fowler, & Telang, 2008). Because most addictive drugs stimulate activity in the HPA axis, many studies of the role of GC on activity in the mesolimbic pathway have been done with a focus on drug addiction or stress-induced drug relapse (see Koob & Kreek, 2007; Piazza et al., 1993). GC are essential for adequate DA secretion in the shell of the nAcc. In their absence, little DA secretion occurs upon stimulation, and when the GC are replaced, DA secretion, specifically in the shell of the nAcc, returns to normal (Barrot et al., 2000, 2001). Moreover, a recent report shows that virally damping the expression of GR in neurons innervated by DA axons in nAcc increases DA secretion (Ambroggi et al., 2009). The PFC appears to inhibit both stress-induced GC secretion and DA in the nAcc (Brake et al., 2000). In people, the interaction between GC and DA appears to apply as well (Volkow & Wise, 2005). The intensity of a pleasurable response to amphetamine and the DA response in the basal striatum were directly related to circulating cortisol concentrations (Wand et al., 2007). The VTA dopaminergic neurons contain CRF receptors, and DA secretion is increased by CRF (Bonci & Borgland, in press; Lu, Liu, Huang, & Zhang, 2003; Wanat, Hopf, Stuber, Phillips, & Bonci, 2008; Wang et al., 2005). Moreover, CRF injected into the shell of the nAcc causes increased behavioral arousal and motor activity (Holahan, Kalin, & Kelley, 1997), and also results in increased cue-triggered responding of rats for sucrose reward (Pecina, Schulkin, & Berridge, 2006). Thus, in the DA motivation/reward network, both stress-induced GC and CRF promote its activity, but what emotion (fear, pleasure) is elicited depends on the internal and external conditions of the animal at the moment.

Norepinephrine secretion from the LC results in arousal, alerting, and attention to salient stimuli, enhancing situation-appropriate behavior, emotional responses, and memory recall (Aston-Jones & Cohen, 2005; Berridge, 2008; Sara, 2009; Foote, Berridge, Adams, & Pineda, 1991; Liddell et al., 2005; Sterpenich et al., 2006). Stressors excite the LC, and chronic stressors increase its activity, as well as that of DA, in response to a new stressor (Abercrombie & Jacobs, 1987; Finlay, Zigmond, & Abercrombie, 1995). Again, both GC and CRF promote activity in LC NE neurons (Pavcovich & Valentino, 1997; Valentino, Foote, & Aston-Jones, 1983). The source of at least some of the excitatory CRF input to NE neurons in LC is from the amygdala (Van Bockstaele, Bajic, Proudfit, & Valentino, 2001; Van Bockstaele, Colago, & Valentino, 1998). GC and CRF facilitate activity in the LC network to forebrain, subserving arousal and other responses to stressors. Moreover, if they are to be consolidated, emotional memories require NE, GC, and CRF inputs to the amygdala, and GC action at the hippocampus (Roozendaal, B., 2002; Roozendaal, Castello, Vedana, Barsegyan, & McGaugh, 2008; Roozendaal, Okuda, Van der Zee, & McGaugh, 2006; Roozendaal, Schelling, & McGaugh, 2008).

Serotonin secretion from the DRN results in modulation of ongoing behaviors. Azmitia summarizes the role of serotonin in brain as integrating external and internal signals and maintaining the integrity of the neural target cells for these signals in an optimally responsive state

(Azmitia, 1999, 2001). Adrenalectomy and GC treatments decrease and increase, respectively, 5HT expression in serotonin neurons of the raphe (Azmitia & McEwen, 1969, 1974), although it is not clear whether these effects of altering GC are mediated by CRF neuronal activity. Both stress and CRF infusions into the dorsal raphe region modulate neuronal activity and serotonin output in the forebrain, as well as behaviors, in complex ways that appear to be determined by which cells or which CRF receptors are activated (Price, Curtis, Kirby, Valentino, & Lucki, 1998). Unlike most of the other monoaminergic cell groups, the dorsal raphe has more CRF2 than CRF1 receptors, and many of the effects of CRF on serotonin secretion appear to be mediated by CRFR2. For instance, a CRF receptor antagonist infused into the dorsal raphe before an initial swim stress blocks the enhanced serotonin secretion in the lateral septum that generally accompanies this stimulus, but an antagonist, similarly provided 24 hours later, enhances serotonin secretion in the lateral septum (Price, Kirby, Valentino, & Lucki, 2002), actions that are believed to shift swimming behavior from an active to what is probably a more appropriate passive mode (Valentino & Commons, 2005). Reduced brain serotonin, as would result from starvation, is strongly associated with aggressive behaviors (Wallner & Machatschke, in press).

FEEDING AND METABOLISM

Tataranni has suggested that dysfunction in the insula and other sites in the emotional brain (Figure 2.1) may produce both hyperphagia and anorexia in people (Tataranni et al., 1999). In patients with prefrontal dementia, atrophy in the prefrontal lobe that specifically includes the insula accompanies an inability to curb food intake during a meal, despite "knowing" that sufficient food has been eaten (Woolley et al., 2007). Sensory associations with high-caloric food also stimulate activity in the insula (Gordon et al., 2000; Nagai, Kishi, & Kato, 2007). The insula and rest of the emotional brain is a key network that is sensitive to food (Wang et al., 2004). On the whole, people, primarily women, with eating disorders that fulfill psychiatric criteria for anorexia and bulimia nervosa, seem to have extreme, cognitively driven inhibition of the emotional brain. Moreover, a partial reason why other eating disorders may be more common in females than in males is that, normally, women do not cognitively inhibit activity in brain sites associated with the drive to eat as men do (Wang et al., 2009). When instructed to suppress hunger responses to their favorite foods, men did inhibit activity in amygdala, insula, hippocampus, and orbitofrontal cortex, and reported less hunger and less desire for their favorite food, whereas women instructed to suppress hunger did not inhibit activity in those areas, and reported less hunger, but not less desire for their favorite food (Wang et al., 2009).

STARVATION

In both rats and humans, starvation prompts rapid and sustained increases in HPA activity and decreases in secretion of reproductive hormones as well as other anterior pituitary hormones, probably as a consequence of the GC response (Bergendahl, Vance, Iranmanesh, Thorner, & Veldhuis, 1996; Dallman et al., 1999; Samuels & Kramer, 1996; Samuels & McDaniel, 1997). With lack of food and the elevation in GC and SNS-mediated inhibition of insulin secretion, weight loss occurs (Fichter & Pirke, 1984, 1986), but circulating glucose remains at nearly normal levels until the duration of starvation has stripped nonessential body stores. Then, the animal, or person dies. Initially the level of physical activity increases, possibly representing motivated search behavior (rats will work hard for the possibility of calories) but, subsequently, as stores are depleted, activity subsides and the animal becomes lethargic (Richter, 1927). Again, calories that can be mobilized are essential for survival behavior.

Anorexia nervosa is a disease of voluntary starvation that occurs primarily in females at the time of puberty. Imaging studies have shown specific reduction in volume of the ACC, the proposed motor output of the emotional brain (Figure 2.1), which may (McCormick et al., 2008), or may not (Muhlau et al., 2007) recover with weight gain to normal. There is also a consistent reduction in blood flow in limbic structures in young anorexic patients (Lask et al., 2005). Thus, brain structures that are heavily involved in the emotional/self brain network are also involved with the neural changes that occur in anorexia nervosa. The disease represents a life-threatening reduction in metabolic stores, and a response to it occurs in all components of the HPA axis (Boyar et al., 1977; Gold et al., 1986; Kling et al., 1993; Licinio, Wong, & Gold, 1996) that is highly appropriate to the metabolic stressor. It is noteworthy that elevated cortisol, together with the small amount of insulin secreted, helps to protect abdominal fat stores, rather than subcutaneous fat, thus saving a source of immediate energy supply to liver (Mayo-Smith et al., 1989; Zamboni et al., 1997). Circulating hormones related to hunger and fat depot mass are reliably increased (ghrelin) and decreased (leptin) as would be anticipated from the energy status of individuals with anorexia nervosa and bulimia nervosa (Monteleone, Castaldo, & Maj, 2008). Additionally, however, as Lo Sauro et al. (2008) point out in their review of eating disorders, "both hormonal alterations in the HPA axis and life stress are factors that are commonly seen at the outset or during the maintenance of eating disorders" (pp. 97–98 therein).

VOLUNTARILY LOW-NORMAL BODY WEIGHT

A new and interesting model for restricted caloric intake has been provided recently for rats (Kasanen et al., 2009). The animals can eat all they are willing to, ad lib, but the food is not easy to get at. The consequence of this

is that most of the rats "voluntarily" lose ~15% of their body weight, and maintain this reduced weight for weeks. Consequently, the animals appear to have normal circadian eating patterns, and maintain growth parallel to ad lib-fed controls, but remain underweight. It is interesting that even with this externally unforced weight differential, plasma GC are persistently elevated in these "dieting" animals (Kasanen et al., 2009), suggesting that even this moderate degree of underweight in adult male lab rats, containing plenty of fat stores, acts as a stressor. No studies other than observational and blood collection under basal conditions have been reported yet, but it would be surprising if they did not show facilitated HPA and SNS responses to an acute stressor, and the changes in brain that are characteristic of chronic stress. However, it is possible that their circadian rhythms remain entrained to the master clock in the SCN of the hypothalamus, rather than engaging the FEO in the hypothalamic DMN. These animals may be a good model for the human "restricted" eater and successful dieter, who maintains slightly lower weight than the freely feeding "set point" by conscious choice, top-down mechanisms, probably by using the inhibitory PFC to override the wants of the emotional brain (DelParigi et al., 2006). Human restricted eaters of normal body weight have higher resting cortisol concentrations, higher body fat, and resistance of the HPA axis to dexamethasone suppression (Rutters, Nieuwenhuizen, Lemmens, Born, & Westerterp-Plantenga, 2009). Moreover, when challenged by a controlled lab stressor, the "restricted" eater has a facilitated HPA response and subsequently eats more high sugar/fat foods than nonrestrained eaters (Gluck et al., 2004; Epel, Lapidus, McEwen, & Brownell, 2001; Epel et al., 2004). Food restriction has been shown to increase the probability of drug seeking through changes in the dopaminergic reward system (Carr, 2007), making it likely that there is heightening of other rewards as well, with restriction that is not life threatening.

BULIMIA NERVOSA

Bulimic patients strongly restrict caloric intake, but they then lose control and binge on excessive amounts of food at least twice a week. After bingeing, they purge, using various mechanisms to counteract the effects of the excessive caloric intake on body weight. In one study, mood was quantified using the brief psychiatric rating scale immediately before and after the binge/purge cycle, and it appeared that the cycle reduced anxiety in most of the small number of patients (Kaye, Gewirtsman, George, Weiss, & Jimerson, 1989). Depressed activity in both emotional brain sites and in the executive PFC occur in task-related fMRI studies of bulimic patients (Marsh et al., 2009). When shown images of palatable food after an overnight fast, all women responded with increased activation in the insula, orbitofrontal cortex, and ACC. However, normal-weight individuals with bulimia showed higher orbitofrontal cortical responses to pictures of highly palatable, calorically dense foods than did controls, and reported more sensitivity to reward on the BAS/BIS scale (Schienle, Schafer, Hermann, & Vaitl, 2009), suggesting that they were trying, ineffectually, to inhibit the feeding response.

Function in the HPA axis in patients with bulimia nervosa appears to depend on the body weight that is maintained during a period without active purging. Similar to anorexic patients, underweight bulimic patients under-respond with startle (a centrally engendered but SNS-mediated response) to pleasurable food images, but respond normally if they are of normal weight (Friederich et al., 2006). Hormone concentrations were measured in a small sample of normal-weight bulimic patients before and after bingeing and after purging; controls were asked to eat a large meal at the same time of day (Kaye, Gwirtsman, & George, 1989). Initial cortisol concentrations were twice as high in the bulimic patients as controls, but both groups responded to the large meal with similar peak cortisol concentrations; however, in the hours after the meal, the bulimic patients maintained elevated cortisol concentrations, compared to control. Of considerable interest, plasma insulin concentrations were also elevated after the onset of eating in the bulimic patients, compared to the controls, and essentially paralleled the results for cortisol (Kaye, Gwirtsman, & George, 1989). The combined hypersecretion of cortisol and of insulin during periods of bingeing and purging nicely explains the observation that when heavily purging bulimics of normal body mass index (BMI) were studied, they had increased adrenal gland mass, implying GC overactivity, and that they also had an absolute increase of visceral abdominal fat, compared to people with normal eating habits and similar BMI (Ludescher et al., 2009). The increased visceral fat mass would be an expected consequence of elevated cortisol and insulin concentrations at the time of the binge–purge episodes. Perhaps the threatened or actual loss of potential metabolic stores may activate the HPA axis during active bingeing/purging, again, as in anorexia nervosa, resulting in increased stores of metabolically available visceral fat. However, in a small group of eight women after at least 3 weeks remission from bulimia nervosa, activity in the HPA axis was decreased compared to normal (Birketvedt et al., 2006). This reduction in HPA activity after remission from binge–purge cycles may be analogous to the reduction in HPA function seen after a single, severe stressor, or to morphine withdrawal in rats, withdrawn addicts, or severely stressed individuals (see earlier).

TIME-RESTRICTED FEEDING

In rodents allowed chow for 2–4 hours/day, body weight is usually reduced by ~15% and, once they have learned that there is only a limited time in which to eat, intake plateaus and the weight differential remains constant. When food is provided during the light period of the cycle, the

reduced body weight engages the FEO, and temperature and corticosterone levels peak just before the onset of feeding. Additionally, there is a bout of anticipatory activity with onset several hours before they are to be fed (Honma, Honma, & Hiroshige, 1983, 1984; Honma, von Goetz, & Aschoff, 1983; Krieger, 1974; Krieger, Hauser, & Krey, 1977). Observant Muslims, who eat only after sun-down during the month of Ramadan, also appear to entrain their cortisol rhythms to food (Bogdan, Bouchareb, & Touitou, 2001). This paradigm has been used to good effect in rats by Amir's lab to find out what is happening in the brain. Using either Fos or a clock gene, Per2, Amir's group has shown that, in rats fed ad lib, rhythms in the BST, dentate gyrus of the hippocampus (DG), and both CeA and BLA follow the SCN-clock light–dark transition rhythm (the rhythms in BLA and DG are 180º out of phase with the rhythms in SCN, CeA, and BST). Adrenalectomy abolishes the Per2 rhythm in CeA and BST, but not in the BLA or DG (Amir et al., 2005; Lamont, Robinson, Stewart, & Amir, 2005; Waddington-Lamont, Robinson, Stewart, & Amir, 2005). The Per2 rhythms in the oval nucleus of the BST and the CeA (both CRF containing), but not in the other structures, depend on corticosterone (Amir, Lamont, Robinson, & Stewart, 2004; Segall, Perrin, Walker, Stewart, & Amir, 2006). Moreover, in rats that have been held under constant, arrhythmic conditions and have lost the normal Per2 rhythm in the SCN, restricted feeding also restores a rhythm in the master clock (Lamont, Diaz, Barry-Shaw, Stewart, & Amir, 2005). Restricted feeding induces a Per2 rhythm in the hypothalamic DMN (Verwey, Khoja, Stewart, & Amir, 2008) and causes the Per2 rhythms in all of the limbic sites to shift to follow the time of feeding, rather than the light cycle. In this case, GC are not required for expression of the rhythms in BST and CeA (Segall, Verwey, & Amir, 2008). Together the results clearly suggest that the Per2 rhythms depend strongly on the metabolic state of the animal. Under ad lib feeding conditions, the rhythm in metabolically active corticosterone provides the necessary rhythmic information to the CeA and BST. However with restricted feeding, when circulating GC are elevated above normal, the FEO in the hypothalamic DMN seems capable of programming the Per2 rhythm in the limbic sites that particularly regulate behavioral, autonomic, and neuroendocrine outflows, ensuring an integrated response to the restricted schedule.

FOOD CHOICE AND GC

For rats, 30% sucrose and lard are both palatable foods and, if given a choice, they will compose ~50–60% of their total daily calories from either or both of those foods and ~40–50% from chow (Bell et al., 2000; la Fleur et al., 2004; Pecoraro, Reyes, Gomez, Bhargava, & Dallman, 2004). However, in adrenalectomized rats, fewer calories of sucrose or fat are eaten, and there is a dose-related increase in ingestion of palatable calories as GC levels are increased, although chow intake is not affected (Dallman et al., 2004). Moreover, when adrenalectomized rats are also made diabetic, chow intake increases in proportion to the dose of GC. Insulin, infused into diabetic rats with high circulating GC, then increases fat intake in a dose-related manner (la Fleur et al., 2004). On the opposite side of the same coin, intact rats given a high-fat diet (56% fat) and treated with a GR antagonist, RU486, reduced their palatable food intake to that seen in groups eating low-fat diet, and returned to the body weight of the low-fat group. In the low-fat chow-eating group, RU486 had no effect on chow intake or body weight, although treated rats in both diet groups lost fat mass (Okada, York, & Bray, 1992). People treated with high doses of the synthetic GC, prednisone, also do not eat more calories when fed a controlled maintenance diet. However, when they are allowed to eat various foods ad lib, CG-treated people eat significantly more calories as carbohydrate and protein than a placebo-treated group (Tataranni et al., 1996). In another study of the effects of GC on feeding, more food from a mixed meal was ingested and recall of foods consumed indicated greater carbohydrate intake while on the GC treatment (Udden et al., 2003). Thus, GC stimulate caloric intake under conditions in which there is choice of palatable foods, but not otherwise. Because eating both sugar and fat stimulates DA neuronal activity in the VTA and DA output in the shell of the nAcc (Levine, Kotz, & Gosnell, 2003), it seems certain that the mesolimbic network is involved in the GC-dependent response to palatable foods.

STRESSOR-INDUCED INTAKE OF PALATABLE FOODS

The immediate response to a stressor is often to decrease caloric intake. However, during a stressor, even if total calorie ingestion is reduced, when there is a choice between bland and palatable foods, the proportion of the total that is represented by palatable foods is increased both acutely (Foster et al., 2009; see Figure 2.6, right), and chronically (Artiga et al., 2007; Gibson, 2006; la Fleur, Houshyar, Roy, & Dallman, 2005; Pecoraro, Reyes, Gomez, Bhargava, & Dallman, 2004; Pecoraro et al., 2006). Interestingly, tail-pinch stress in rats caused animals to gain excess weight with time in one study in which the rats were allowed highly palatable sweetened, condensed milk (Rowland & Antelman, 1976), but not in another, when the rats were given chow (Levine & Morley, 1981). Tail pinch stimulates DA secretion in the nucleus accumbens that is indirectly regulated by NE-sensitive mechanisms in the PFC (NicNiocaill & Gratton, 2007). Moreover, intracerebroventricular CRF antagonist blocked food intake in response to acute tail pinch, as did DA-receptor antagonists (Samarghandian, Ohata, Yamauchi, & Shibasaki, 2003). Finally, in chronically stressed rats, novel tail pinch increased DA output over the nucleus accumbens, but presentation of highly palatable food did not,

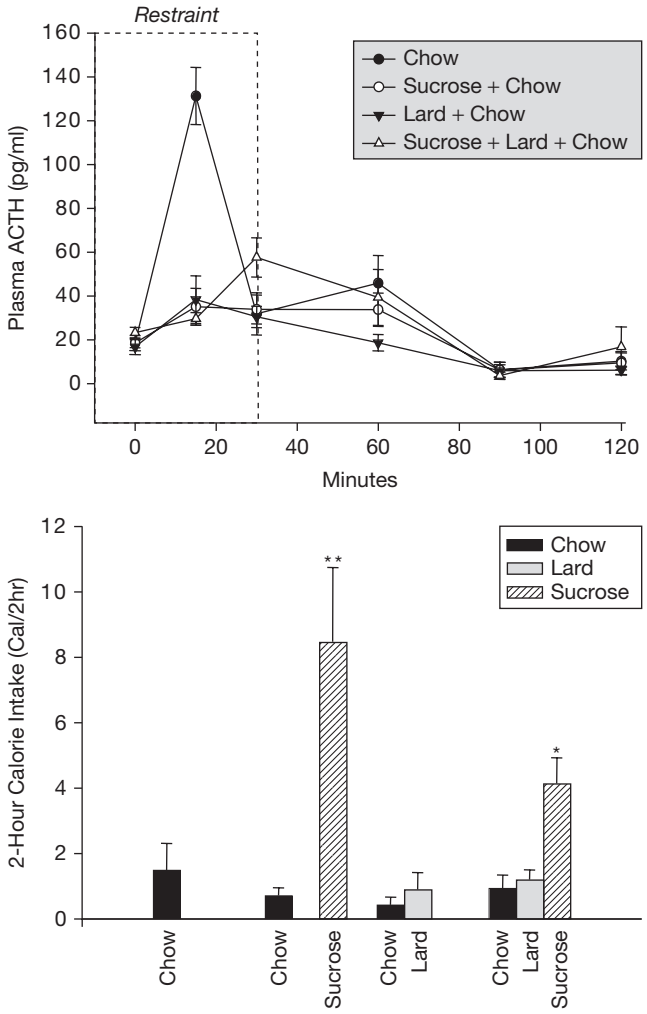

Figure 2.6 ■ Ingesting sucrose and lard for a week reduces acute HPA responses to restraint, and increased sucrose intake follows the stressor. Groups of rats were allowed ad lib access to chow, chow plus 30% sucrose, chow plus lard, or chow plus sucrose and lard for 7 days before applying 30 minutes restraint stress. ACTH responses were damped in all groups allowed palatable foods, compared to the chow-only group (top panel). Two hours after the onset of restraint, foods were returned and intake was measured during the next 2 hours (bottom panel). Rats with sucrose available drank it after the stress (From Foster, M. T., Warne, J. P., Ginsberg, A. B., Horneman, H. F., Pecoraro, N. C., Akana, S. F., et al. [2009]. Palatable foods, stress, and energy stores sculpt corticotropin-releasing factor, adrenocorticotropin, and corticosterone concentrations after restraint. *Endocrinology, 150,* 2325–2333).

compared to control animals (Di Chiara, Loddo, & Tanda, 1999). Together, these studies using the stressor of tail pinch suggest that increased feeding during the stressor requires highly palatable foods that act through the dopaminergic reward system in the nucleus accumbens. It is probable that the GC response to tail pinch augments the DA response, possibly through stimulation of limbic CRF secretion. However, after a chronic stressor, although tail pinch stimulates greater DA secretion over the nucleus accumbens, the sight and smell of palatable food alone is no longer stimulatory. This may result from altered regulation of accumbal DA secretion by the activity of the PFC (Brake et al., 2000).

People also chose to eat highly palatable foods both after perceived acute stressors (Epel et al., 2001; Newman, O'Connor, & Conner, 2007), even when they were presatiated (Rutters, Nieuwenhuizen, Lemmens, Born, & Westerterp-Plantenga, 2008), and after a longer period of more persistent stress (Gibson, 2006; Greeno & Wing, 1994). They appear to deliberately and wittingly use eating palatable foods and drinking beer, wine, and spirits as coping mechanisms (Laitinen, Ek, & Sovio, 2002). In laboratory studies, it has been shown that only those who acutely respond with increased cortisol to a laboratory stressor (Trier Social Stress Test [TSST]) respond to the stressor or "hassles" with eating more sweet, fatty, or salty foods (Epel et al., 2001; Epel et al., 2000; Newman et al., 2007). This suggests that, as in rats, the rise in GC in response to the stimulus increased the salience of these pleasurable foods. In Newman et al. (2007), after basic psychological testing and the acute lab stressor, female subjects kept diaries recording the daily score for hassles and snacking during the next 2 weeks. There was a significant positive relationship between the intensity of hassles and snacking in the high, but not low, cortisol-reactor group. Snacking in the low reactor group was related to mood, increasing with negative, and decreasing with positive affect. Moreover, there were significant relationships between eating styles, with restraint, emotional eating, and disinhibition important in both groups, and in both studies (Epel et al., 2001; Newman et al., 2007). However, the degree to which restraint, emotion, or disinhibition is required for stress-induced feeding is still debated (Yeomans & Coughlan, in press; Goldfield & Lumb, 2009).

RESTRICTED ACCESS TO SWEET-FAT FOODS IN RATS

Rats fed highly palatable foods for only a few hours a day, or fed the foods for a period of time and then weaned from them, will binge on the foods when they are returned and they are stressed (Berner, Avena, & Hoebel, 2008; Hagen, Chandler, Wauford, Rybak, & Oswald, 2003; Hagen et al., 2002). Moreover when these animals are exposed to the palatable foods intermittently for a sufficient period, they become fat. It is clear that when they binge on sucrose, DA is secreted in the nucleus accumbens, and more DA is secreted when the animals are restricted in the amount of chow they are allowed to eat (Avena, Bocarsly, Rada, Kim, & Hoebel, 2008; Avena, Long, & Hoebel, 2005; Avena, Rada, & Hoebel, 2008a, 2008b; Bello, Sweigart, Lakoski, Norgren, & Hajnal, 2003; Rada, Avena, & Hoebel, 2005). This seems like an extraordinarily good model to use to study diseases such as night-eating syndrome (NES) and binge-eating disorder (BED) in people.

NES/BED

These disorders occur in both normal-weight and overweight people. In both instances, there is a sense that stress precipitates the bingeing behavior (Birketvedt et al., 1999; Gluck, 2006; Gluck et al., 2004). When very obese NES and BED individuals were compared with very obese controls without eating disorders, people with NES, BED, or the combination scored high on trait and state anxiety, behavioral disinhibition, and eating self-efficacy for negative affect (Napolitano, Head, Babyak, & Blumenthal, 2001).

People with NES usually do not eat breakfast, eat little lunch, and eat more than 50% of their daily calories after dinner, with increased carbohydrate and fat intake at this time (Birketvedt et al., 1999; Stunkard, Grace, & Wolff, 1955). Although the early description was of NES in the obese, people with NES can be either obese, as initially described, or younger and of normal body weight; both groups crave food when awake during the night, need to eat to fall back to sleep after waking, and have little control over night eating (Lundgren, Allison, O'Reardon, & Stunkard, 2008; Marshall, Allison, O'Reardon, Birketvedt, & Stunkard, 2004). A recent study, based on the finding that there is a therapeutic response to sertraline, a selective serotonin reuptake blocker, showed that people with NES had significantly greater uptake of a serotonin transporter into their midbrain than did normal controls, implicating the serotonin system as a factor in NES (Lundgren et al., 2008).

People with NES have been reported to have elevated activity in the HPA axis (Birketvedt, Sundsfjord, & Florholmen, 2002; Birketvedt et al., 1999), a cortisol rhythm of damped amplitude resulting from decreased peak and increased trough values (Goel et al., 2009), or no difference from appropriate controls (Allison et al., 2005). It is unclear what variables determined the different results. However, further exploration of the HPA response to an acute stressor might be warranted as was done with BED (below), to further determine HPA status in people with NES.

After exposure to pictures of high-caloric foods, overweight healthy controls, overweight BED patients, normal-weight controls, and normal-weight patients with bulimia all increased activity (as indicated by fMRI) in the emotional cortices: insula, orbitofrontal cortex, and ACC (Schienle et al., 2009). However, overweight BED patients experienced enhanced reward sensitivity and greater activation in the orbitofrontal cortex than any other group, whereas bulimic patients exhibited greater arousal, insula, and anterior cingulate activation than the other groups (Schienle et al., 2009). Neither group of patients reacted differently to disgusting pictures than did controls (Schienle et al., 2009).

Obese women with and without BED were studied on 1 day without a stressor and on another when they were given a lab stressor (TSST); on both days they were provided a bowl of chocolate pudding, and rates and amounts of eating and total intake were measured. Both the rate and acceleration of eating were increased in people with BED after the stressor, although total intake was not affected (Laessle & Schulz, 2009). Differences in eating behavior are observed in the lab between BED and non-BED people; when they were asked to binge, there was a reliable doubling in calorie intake in people with BED, however, when negative affect was induced in other lab studies, there was no difference in caloric intake between the groups (Walsh & Boudreau, 2003). It seems possible that the lab stressor, or the palatable foods offered, may have been inadequate to trigger stress-induced eating; no measures of stressor-induced changes in cortisol were reported.

Nonetheless, BED is difficult to distinguish from normal in terms of HPA axis function. Evening cortisol concentrations in obese people are usually quite low, and correlate inversely with BMI in women without BED (Coutinho, Moreira, Spagnol, & Appolinario, 2007). However, this study found that in women with BED (21 of 47), there was a positive relationship between the score on the binge-eating scale and evening salivary cortisol concentration, suggesting to the authors that potential binges during the day may have affected evening cortisol levels (Coutinho et al., 2007). Another study showed increases in fasting cortisol, cortisol response, and hunger following a cold-pressor test in obese BED patients compared with obese controls (Gluck, 2006). However, the differences in the HPA axis responses to the stressor between those with BED and controls were, again, very slight. On the other hand, there was a positive and strong relationship between waist–hip ratio and the cortisol response to the stressor in those with BED, but not in the controls (Gluck, 2006). It seems possible that in very obese people with BED, the considerable metabolic stores that they carry (like rats made fat on palatable diets) protects their HPA axis from over-responding to stressors, despite their increased levels of state and trait anxiety.

In summary, although it is clear that the eating disorders anorexia nervosa and bulimia nervosa are both associated with marked abnormalities in HPA function, it is not at all clear that the other eating disorders, NES and BED, disrupt activity in the HPA axis. However, this slight or wobbly association with disorders and HPA axis activity may result from the fact that most patients with NES and BED diagnoses usually carry plentiful stores of metabolic energy.

SELF-MEDICATION

In studies on rats, it seems abundantly clear that when the animals have been allowed to adapt to choice diets of chow, sucrose, and/or lard, the magnitude of the central HPA response to both acute (Foster et al., 2009; Kinzig, Hargrave, & Honors, 2008; la Fleur, Houshyar, Roy, & Dallman, 2005) and repeated (Pecoraro, Reyes, Gomez, Bhargava, & Dallman, 2004) restraint is markedly reduced

(e.g., Figure 2.6, left). This result was expected, in that rats with choice have larger metabolic energy reserves and have far less need for increased caloric intake to combat threats, and it may be the abundant metabolic feedback signal, discussed above, that damps stress responses. Behavioral freezing to the context in which they had experienced shock a day earlier did not occur in rats that drank glucose over the night after the shock and did not lose weight (Minor & Saade, 1997). However, the calories ingested are pleasurable and stimulate DA secretion in nAcc, which in turn may act to inhibit activity in the central stress-response network. The absolute calories ingested as low-fat chow are usually decreased (Kinzig et al., 2008; Pecoraro, Reyes, Gomez, Bhargava, & Dallman, 2004). This is similar to what was found by Gibson when asking about types of food ingested by about the 30% of students who had not gained weight during a difficult 3-month period that was perceived as stressful (Gibson, 2006). Intake of "healthful" foods (vegetables, fish, and fruits) was decreased, whereas the proportional intake of sweet and savory foods was increased (Gibson, 2006). Elevated corticosterone levels have been shown to augment CRF secretion immediately after air-puff startle stress over both the CeA and the PFC, while blocking corticosterone responses to the stressor (Merali, Anisman, James, Kent, & Schulkin, 2008). Of course, the consequence of social stress-induced eating of palatable calories in rodents is abdominal obesity (Bartolomucci et al., 2009; Bell et al., 2002), which may also be so in humans (Brunner, Chandola, & Marmot, 2007; Nishitani, Sakakibara, & Akiyama, 2009). This may be an evolutionarily valuable system that ensures sufficient energy stores for behavioral escape from stressors, despite the fact that it is maladaptive in many currently overnourished societies.

Thus, both acute and chronic stressors, probably through GC secretion and the effects of the GC s on both central stress networks and peripheral metabolism, serve to engage various aspects of feeding behavior and energy storage. With stressors, this behavior favors eating highly palatable foods although the intake of healthy foods may actually be depressed. This seems to be a consequence of coping responses in the challenged individual, and the stress networks serve to ensure, if possible, adequate supplies of stored calories, so that thinking about how to cope, and, eventually, actual escape from the stressor(s), can be carried out in an energetically fit individual.

TRANSLATION

This chapter has addressed and integrated numerous research studies, illustrating the contributions of basic research studies on stress and stress-related disorders. It seems that the time is now ripe to translate some of this knowledge to the "bedside." Practically, such translational approaches should focus on outpatients, since the great majority of patients with depression, anxiety disorders, somatoform disorders, adjustment disorders, and the like, are seen exclusively by the general physician or family doctor.

In the past 10 years, we developed "Neuropattern," the first translational tool in stress medicine (Hellhammer & Hellhammer, 2008). Neuropattern is a diagnostic instrument that can be applied by patients and physician to detect dysregulation in the stress-response network. The physician provides anamnestic and some physiological data, while the patient takes other measures at home, generating, for example, psychological, symptomatic, and biological data. Among the biological data are electrocardiogram measures for analyses of heart rate variability, and salivary cortisol measures before and after a dexamethasone challenge test. All data are analyzed in a central laboratory, which generates a written report for the physician, including a disease model, from which personalized recommendations for pharmacological and psychological treatments are derived. Neuropattern additionally offers individualized internet modules to inform patients about the disease model and to teach them what they can do themselves to improve their medical conditions.

So far, Neuropattern has already been applied to a couple of thousand patients and probands, and will now be incorporated stepwise into clinical routine. Evidently, we are now able to utilize knowledge about the stress-response networks and use it translationally. The enormous amount of data being collected in patients will surely stimulate further basic and translational research, and hopefully facilitate improvement of diagnostic and therapeutic treatment options in stress medicine in the near future.

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3 The Cardiovascular System

Matthew M. Burg and Thomas G. Pickering

INTRODUCTION

The cardiovascular (CV) system serves to maintain the supply of oxygen and other nutrients to, and the removal of waste products from, all the cells in the body. It achieves this by *perfusing* with blood all body organs according to the metabolic needs of these organs. Furthermore, as the metabolic needs of specific organs are always changing, control and regulation of the CV system must be accomplished in a way that provides for rapid and continuous adaptation to these changes so as to maintain a sufficient level of perfusion to organs throughout the body to preserve function, while increasing perfusion in those organs and tissues that require an increase to mount whatever response is required by environmental conditions. Hence, the blood supply to bodily tissues needs to be closely regulated and adjusted to match regional needs. This regulation is exceedingly complex and includes a wide array of processes that ensure sufficient systemic and local perfusion pressures as blood is continuously pumped by the heart through the vascular system to the various organs, and perhaps most notably to the lungs, where carbon dioxide is exchanged for oxygen, and to the kidneys, where waste products are excreted.

The CV system has become, perhaps, the most widely studied physiological system in behavioral medicine, largely due to its crucial role in the proper function of all other systems and the manner in which it responds to emotion- and stress-related stimuli in the service of somatic and behavioral responses to these stimuli. Furthermore, pathology in this system is responsible for the largest health care burden in the western industrialized world (Rosamond et al., 2008). Hence, the CV system has played a central role in behavioral medicine research. Measurement of CV function in both the psychophysiology laboratory and the natural environment has grown considerably since the inception of the field described generally as "cardiovascular behavioral medicine," which can be traced through any review of extant literature to the last quarter of the 20th century. More recent advances in computer, communication, and biological technologies have provided for ever more precise and continuous measurement of moment to moment changes in CV function, and of the myriad array of processes underlying, and consequent to, CV regulation. The expanding body of data resulting from these advances continues to confirm a link between stress and emotional factors on the one hand and cardiovascular disease (CVD) on the other, while providing ever greater insights concerning the pathophysiology underlying this link.

We begin this chapter with a description of the main components of the CV system. We then turn to a discussion of the effect of psychological stress on CV activity. This discussion emphasizes key processes in CV regulation, including endothelial function, hemodynamic patterning in blood pressure (BP) regulation, hypothalamic pituitary adrenocortical influences, and the significance of vasoactive peptides, proinflammatory cytokines, and reactive oxygen species (ROS) for the structural and functional integrity of the vascular system.

THE CV SYSTEM

The CV system comprises the heart and the conduit vascular system that routes blood from the heart to the full range of bodily organs and tissues (the arterial and capillary components) as well as returns blood from these organs and tissues to the heart (the venous system).

THE HEART

This organ may best be thought of as a pump, though a complex one both in structure and regulation, with two sides—a left side and right side pump—that work in concert, each with an antechamber (the atrium) and main pumping chamber (the ventricle), and valves that ensure a single direction of blood flow, from the body into the atria, then to the ventricles, and then back out to the body. Although essentially a muscle, myocardial muscle fibers are unique in their composition. The walls of the heart are comprised of intertwined muscle fibers that generally spiral along the outer walls from the base of the heart to the apex and back again along the inner walls. Furthermore, a thick band of muscle fibers surround the left ventricle, thereby supporting the greater pumping work for which this chamber is responsible. Indeed,

this unique structural element provides for a pumping action defined by its force and the speed with which it attains peak velocity. The force and speed with which these fibers contract is in part determined by their length, which is maximized when the associated heart chamber is filled with blood—the more blood there is in the chamber, the greater the length of the fibers and, hence, the stronger and faster the contraction.

The left side of the heart or high pressure system, receives oxygenated blood from the lungs and pumps that blood through the aorta—the largest artery in the vascular system—and then through a continuously branching arterial system to the tissues and organs of the body, thereby providing the sustenance needed to support their function. As the arteries branch, arterial diameter decreases to the point of becoming microvascular, capillary beds. The size and permeability of capillaries provide for the passage of single blood cells and the exchange of oxygen and other nutrients with body tissues. The higher pumping pressure of the heart's left side matches the wider distribution of blood associated with the array of organs and tissues dependent on it for proper perfusion.

The right side of the heart receives deoxygenated blood from body tissues and organs through the venous return system that, in a reverse manner, mirrors in size the arterial system. The right side of the heart directs this blood to the lungs, where carbon dioxide and associated metabolic byproducts are exchanged for oxygen, again through capillary beds. The pulmonary vasculature provides low resistance with pressures of approximately one fifth that of the left side, or systemic circulation (Rushmer, 1970). The oxygenated blood is returned to the left side of the heart, and the cycle is repeated, with a normal heart contracting on average 70 times per minute and more than 30 million times per year, for the life of the individual.

The rate, force, and timing of myocardial contraction are determined by self-regulatory elements, direct inputs from the autonomic nervous system, and ancillary circulatory elements, which together determine cardiac output (CO), the volume of blood in liters ejected by the left ventricle per unit of time (see Figure 3.1). Self-regulatory elements include the very nature of myocardial cells, which are similar to skeletal muscles in their striation and contractile properties, but which are unique in that they are excited by the spread of excitation from contiguous cells. The structural arrangement of myocardial cells further supports this cross cell excitation, with an almost instantaneous contraction of all cells of a chamber. Fibrous rings between atria and ventricles ensure that these excitation effects are maintained within chambers, thereby providing for a pulsatile movement of blood from atria to ventricles. The heart also includes two key electrophysiological systems: (1) the sinoatrial (SA) node or cardiac pacemaker, which is located in the right atrial wall near the entry point of the veins returning deoxygenated blood from the body, and which spontaneously originates successive

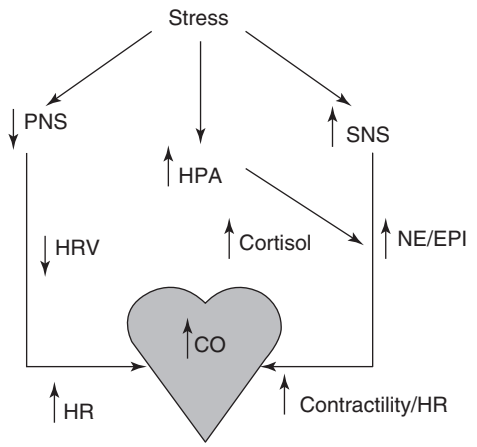

Figure 3.1 ■ Regulation of cardiac output (CO) under conditions of stress. Stress results in activation of the two branches of the autonomic nervous system, and of the hypothalamic–pituitary–adrenal (HPA) axis. Activation of the parasympathetic branch (PNS) results in parasympathetic withdrawal, demonstrated by a reduction in high-frequency heart rate variability (HRV), and consequent increase in heart rate (HR). Activation of the sympathetic branch (SNS) results in secretion of norepinephrine (NE) and epinephrine (EPI), and consequent increase in both cardiac contractility and HR. Lastly, activation of the HPA axis is demonstrated by secretion of cortisol by the adrenal cortex, which both potentiates the effects of NE and EPI, and independently contributes to the same effects as these catecholamines.

waves of excitation that then proliferate throughout the cardiac chambers, and (2) the atrioventricular (AV) node, which originates in the atrial septum, projects down to the ventricular septum, and has two branches that spread over the endocardial surfaces of the ventricles; AV node fibers rapidly conduct excitation across these chambers, ensuring coordinated contraction.

The autonomic nervous system, working directly and through the circulation, also plays a key role in the regulation of cardiac function. For example, while the SA node determines the rate at which the heart contracts, the regulation of AV node "firing" is influenced by nerve endings associated with the sympathetic and parasympathetic nervous system. Specifically, cholinergic nerve endings of the parasympathetic vagus nerve slow the firing rate of the SA node and, hence, the heart rate, whereas noradrenergic sympathetic nerve endings have the opposite effect. The reciprocal effect of these arms of the autonomic nervous system can be observed within an individual cardiac cycle. In addition, catecholamines released into the circulation by the adrenal glands—along with cortisol—further influence both the rate and force of cardiac contraction. Beyond these direct effects, the regulation of vascular tone by these two branches of the autonomic nervous system also contributes to cardiac performance. For example, greater ventricular filling consequent to more rapid venous return will produce a stronger and more rapid ventricular contraction, because

of the direct effects on the myocardial tissue, while an increase in peripheral vasoconstriction will also influence cardiac contraction as it works to move blood through the arterial system against the increased total peripheral resistance (TPR).

The CO depends both on the stroke volume—the volume of blood ejected by the ventricle during systole—and the heart rate—measured in beats per minute. The stroke volume is determined both by the amount of blood filling the heart during diastole (preload), and by the resistance to the heart's pumping (afterload). Essentially then, stoke volume depends on ventricular volumes at the end of the filling period—the end diastolic volume—and at the end of contraction—the end systolic volume. These volumes are determined by wide ranging factors including (1) venous return or preload, which contributes to the degree of stretch in the wall of the ventricle; because of the nature of myocardial tissue, an increase in venous return results in an increase in end diastolic volume and associated muscle stretch and, hence, an increase in stroke volume, and (2) afterload, reflected in TPR; an increase in afterload will tend to increase end systolic volume and implicitly reduce stroke volume. All of these factors will typically vary in an ongoing manner as determined by moment to moment changes in tissue metabolic requirements and autonomic tone.

Cardiac contractility is another index developed to describe the summation of factors that determine the speed of myocardial contraction and that thereby contribute to myocardial performance. Usually this term describes factors outside of preload and afterload, though because of the inherent contribution of preload to ventricular filling and afterload to the force of ventricular contraction necessary to eject blood into the circulation, these elements are inherently involved in contractility. Beyond these, autonomic factors can also play an essential role. Sympathetic stimulation, for example, can profoundly increase the heart rate (contractions per minute), the speed of individual ventricular contractions, and the force of these contractions, for example, shorter systolic and diastolic intervals, more forceful ejection, and faster acceleration of ventricular outflow velocities. Conversely, parasympathetic stimulation can have immediate and profound effects, by slowing the heart rate substantially.

Dynamic exercise provides one example to illustrate the heart at work. The exercise capacity of normal subjects is determined by the ability of the CV system to transport oxygen. Dynamic exercise increases the metabolic requirements of the muscles involved, for example, the large muscles of the leg during an exercise treadmill test. During such exercise, the CO increases substantially, which is achieved by both an increased heart rate and stroke volume. The heart rate increases in an approximately linear relationship to the increased oxygen demand of the muscles involved—which includes the heart itself, because of the extra contractile work being done (mostly) by the ventricles as they respond to the needs of the large muscles. The increase of heart rate is much larger (e.g., from 60 to 160 beats/minute, or about 150%) whereas the stroke increase in volume may be only by about 20% of the resting value. In addition to these changes to cardiac function, there are changes in the vasculature that affect the heart. For example, at the onset of exercise, metabolic products from the exercising muscles provoke an immediate dilation of the resistance vessels. The systolic pressure also increases, largely because of an increase in CO that is a product of both higher heart rate and stroke volume. Despite the increase in systolic pressure, diastolic pressure changes little under these circumstances, largely because of the dilation in the large muscles provoked by local metabolic reflexes. Resistance exercise, however, can produce very different circulatory changes. In the case of aerobic exercise, the main need is increased supply of oxygen, whereas in resistance exercise the need is to keep a contracting muscle perfused, which can only be done by increasing the local BP. Thus the sustained contraction of quite small muscle groups can produce a very marked increase of both systolic and diastolic pressure.

THE VASCULAR SYSTEM

As briefly described earlier, the vascular system comprises arteries, capillaries, and veins that are spread throughout the body in a highly branched distribution system. This system can be thought of as originating at the outflow arm of the left ventricle—the aorta, which is the largest artery in the vascular system—and terminating at the inflow arms—the superior and inferior vena cavae, the largest veins of the right atrium. In between, the system undergoes continual branching, so as to reach the various bodily organs and the distant musculature and surface areas of the body. There is an immediate branching in the *ascending* aorta so as to provide blood to the head and upper limbs. The *descending* aorta then distributes blood to the internal organs and the musculature and surface areas of the trunk and lower limbs. The size of each branch is largely determined by the distribution responsibilities inherent. So, for example, the descending aorta with the large areas for which it is responsible is very large in diameter, whereas the initial branches of the ascending aorta (e.g., subclavian and carotid arteries) are smaller. Again, as vessels continually branch, the branches decrease in size, achieving a capillary microvascular bed within each bodily organ, and on the venous return side, increasing in size as blood is returned eventually, through the vena cavae to the heart.

While the vascular system serves as a branching system that directs blood to each bodily organ according to its needs, it also serves as a "pressure reservoir" that absorbs and smoothes out the pulsations in blood flow produced by the alternating contraction and relaxation

of the heart's ventricles. This is accomplished most specifically by the arterial arm of this system, which has unique elastic properties that compensate for this pulsatile flow, thereby adjusting to the high pressure associated with ventricular contraction—the systole of a BP reading—while maintaining a minimal pressure during ventricular relaxation—the diastole of a BP reading. This elastic property of the arteries, with the arteries closest to the heart being the most elastic, is essential for proper CV function, and a reduction in elasticity is one of the first dysregulations that can be observed along the path toward essential hypertension (Kelly, Haywood, Avolio, & O'Rourke, 1989). Diastolic and systolic pressure can vary substantially as a function of metabolic needs and both physical and emotional stress, though diastolic pressure is prevented by bodily reflexes from dropping below between 40 and 60 mmHg so as to ensure a level of perfusion to the brain necessary to maintain consciousness.

Cross-sectionally, arteries are described by a lumen, the open interior through which blood passes (see Figure 3.2). A single layer of endothelial cells surrounds the lumen, and this cellular layer is in turn surrounded by a thicker layer of smooth muscle cells. These two layers provide avenues by which the autonomic nervous system and other local processes dynamically regulate vascular tone, as described in the following text. While the major arteries closest to the heart are highly elastic, smaller arteries and arterioles that are further along the arterial tree are notable for their greater muscularity. This property allows them to serve as sphincters that vasoconstrict or vasodilate, and thereby control the flow of blood to the capillary beds they serve. Through this involuntarily regulated function, blood flow to each bodily organ is precisely controlled according to factors that include relative local and systemic metabolic needs associated with levels and types of activity. For example, increased perfusion needs in the large muscles associated with physical work will result in a local vasodilation of these sphincters and a broader, systemic vasoconstriction in the viscera which, on balance, does not require higher levels of perfusion. Alternatively, after eating, there is an increase in perfusion directed to the viscera for digestion, and this is associated with a decrease in perfusion to the larger muscles, often accompanied by an intrapersonal experience of sleepiness or fatigue. One notable exception to this balancing process is the brain, which has a relatively steady metabolism and a vascular bed that supplies constant and consistent perfusion. Although perfusion to bodily organs can vary according to relative needs (e.g., increased blood flow to large muscles and heart can be associated with relative decrease in blood flow to digestive organs as observed during the "fight–flight" response), perfusion to the brain must be kept constant.

Having passed through the capillary bed, the flow of blood in the venous return system is at a low pressure and moves proportionately slower. In contrast to arteries, therefore, veins have a larger lumen and thinner walls so that resistance to flow is reduced. Internal 1-way valves ensure that blood flows back to the heart, whereas contractions of muscles around the veins, such as those in the legs and abdomen, support the flow of blood against the force of gravity as it returns from the lower body and extremities back to the heart, particularly in the context of work being done by these large muscles. Indeed, as described in the section on the heart, the increased rhythmic contraction of these large muscles during dynamic exercise ensures more rapid volumetric return of blood to the heart, thereby resulting in greater ventricular stretch as these chambers are filled with returned blood, and stronger ventricular contraction to get oxygenated blood back to the muscles at a rate to support the work being done.

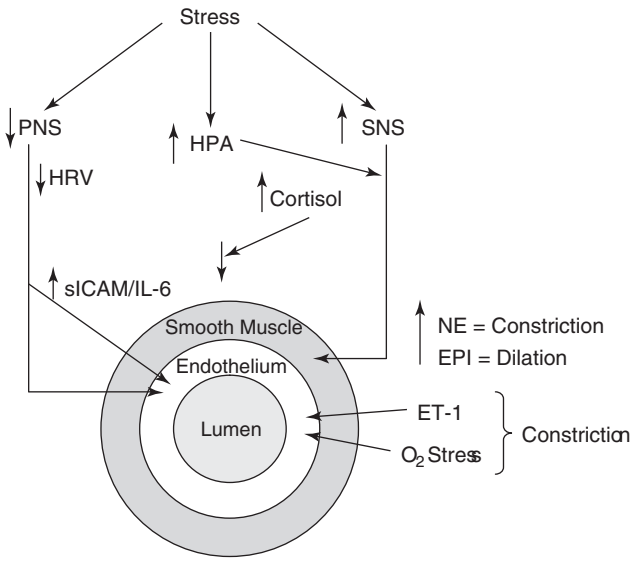

Figure 3.2 ■ Regulation of smooth muscle tone under conditions of stress. Activation of the parasympathetic nervous system (PNS) results in parasympathetic withdrawal (reduction in high-frequency heart rate variability [HRV]). The consequent effects on the healthy endothelium are vasodilation, but in the presence of atherosclerotic disease, vasoconstriction. Furthermore, parasympathetic withdrawal leads to an increased release of proinflammatory cytokines (e.g., interleukin-6 [IL-6]) and vasoactive proteins (e.g., intercellular adhesion molecule [sICAM]) from macrophages), due to the resulting disinhibition. Activation of the sympathetic nervous system (SNS) results in secretion of norepinephrine (NE) and epinephrine (EPI), with consequent effects on vascular smooth muscle. Release of NE causes vasoconstriction through its action on α-receptors. EPI, released into the circulation from the adrenal medulla, provokes an opposite, vasodilating effect through its action on β_1-receptors. Activation of the hypothalamic–pituitary–adrenal (HPA) axis and subsequent secretion of cortisol both potentiates the effects of NE and EPI, and independently contributes to the down-regulation of the inflammatory response through its action on IL-6, though in the presence of atherosclerotic disease, this negative feedback loop is impaired. Lastly, stress contributes to oxidative (O_2) stress, which contributes to endothelial dysfunction and consequent vasoconstriction, with endothelin-1 (ET-1) playing an essential role.

As with the heart, regulation of the vascular system is complex and multifactorial, involving local self-regulatory mechanisms, autonomic elements, and both direct and indirect ancillary processes. As described earlier, at any given time the needs vary between different organs and tissues (e.g., with muscular exercise blood flow needs to be increased in the muscles, and can be decreased in the gut, whereas after a meal the opposite may be the case). Regulation of the circulation is achieved by a combination of brain activity with local regulatory mechanisms. Such tight regulation can be achieved only by a series of feedback loops that detect changes in circulatory function by monitoring changes such as oxygenation, which is accomplished by chemoreceptors, and arterial pressure, which is accomplished by baroreceptors. For example, increased metabolic activity in muscles depletes oxygen while increasing levels of carbon dioxide and associated chemical reactants. Chemoreceptors detect these changes and, in addition to signaling the brain that there is a need for increased respiration, provoke relative dilation in local microvascular smooth muscle to increase blood flow and thereby provide the oxygen needed to support the continued work of the muscle. Reactive hyperemia (Corretti et al., 2002), an autoregulatory process by which the vascular endothelium responds with significant nitric oxide provoked dilation after release of temporary occlusion of blood flow, provides an example of the underlying mechanism.

Baroreceptors, which are essentially stretch-sensitive mechanoreceptors, also contribute to circulatory regulation, with the most sensitive baroreceptors being found in the carotid sinuses and aortic arch. Baroreceptors comprise part of a system of central nervous system feedback loops and circuits that, in part, control autonomic activity in the service of BP regulation. Generally, sympathetic activation leads to an elevation of TPR and CO via increased cardiac contractility, heart rate, and arterial vasoconstriction, which together tends to increase BP; conversely, parasympathetic activation leads to a decreased CO via decreased heart rate, resulting in a tendency to lower BP. Sympathetic and/or parasympathetic inhibition produces opposite results.

When BP rises, the carotid and aortic sinuses are distended, resulting in stretch and therefore activation and firing of the baroreceptors; greater stretch produces more rapid firing. Alternatively, when BP drops, firing of baroreceptors decreases. Baroreceptor activation provokes inhibition of sympathetic activity and excitation of parasympathetic activity. By coupling relative sympathetic inhibition and parasympathetic activation, the baroreflex maximizes BP regulation. For example, sympathetic inhibition leads to a drop in peripheral resistance, whereas parasympathetic activation leads to depressed heart rate and myocardial contractility. The combined effects will dramatically decrease BP. Conversely, a decrease in BP is detected by baroreceptors and through these circuits increases sympathetic activation, inhibits parasympathetic activity and, through an increase in CO and (potentially) peripheral resistance, elevates BP.

THE RENIN–ANGIOTENSIN–ALDOSTERONE SYSTEM

In addition to these direct effects on the vascular system by the two branches of the autonomic nervous system, another major vascular control mechanism is the hormonally defined renin–angiotensin–aldosterone system (RAAS). The RAAS system, which contributes to regulation of fluid volume and systemic vascular resistance (Brunner et al., 1972), is most prominently activated when there is a loss of blood and resulting drop in BP as observed during hemorrhage, though stress is also thought to play a role in the chronic activity of this system, perhaps working through proinflammatory processes (Schmeider, Hilgers, Schlaich, & Schmidt, 2007) or oxidative stress (Nistala, Wei, Sowers, & Whaley-Connell, 2009).

Renin is an enzyme that is released into circulation primarily by the kidneys. Release of this enzyme is provoked by sympathetic nerve activation, renal artery hypotension (e.g., caused by reduced blood volume and hence, systemic hypotension), or decreased sodium delivery to the distal tubules of the kidney. Juxtaglomerular cells in the kidney are the primary site of renin storage and release. Specifically, a reduction in arteriole pressure resulting from a reduction in perfusion causes the release of renin from these cells; conversely increased pressure/perfusion inhibits renin release. Similarly, β_1-adrenoceptors located on these cells respond to sympathetic nerve stimulation by releasing renin, whereas other specialized sodium (Na) and chloride (Cl) ion-sensing cells (macula densa) stimulate renin release when levels of NaCl in the blood are reduced. In contrast, when sympathetic activity is reduced and/or NaCl levels are elevated, renin release is inhibited.

When renin is released into the blood, it acts upon the circulating peptide angiotensinogen, converting it to angiotensin-I. Reaching the lungs by way of the circulation, angiotensin-I is converted to angiotensin-II, through an enzymatic process by the vascular endothelium that involves angiotensin converting enzyme. Angiotensin-II is the predominant bioactive product of the RAAS system, exerting a powerful constrictor effect on vascular smooth muscle in resistance vessels, thereby increasing systemic vascular resistance. Furthermore, this peptide locally facilitates norepinephrine release from sympathetic nerve terminals and inhibits norepinephrine reuptake, thereby increasing overall sympathetically mediated effects on the vasculature. Through the circulation, angiotensin-II stimulates release of aldosterone by the adrenal cortex and vasopressin by the pituitary, each of which in turn act on the kidneys to increase sodium and fluid retention; central nervous system effects on thirst centers provoke

fluid intake, thereby further increasing overall vascular volume load.

COGNITIVE/EMOTIONAL STRESS AND CV REGULATION

The response to cognitive and emotional stress is characterized by increased BP, with increased CO and TPR both contributing, and increased sympathetic nervous system activity playing a significant role (Julius, 1993). Concurrent to the increase in sympathetic nervous system activity is withdrawal of parasympathetic influence (Brosschot & Thayer, 1998), which contributes most directly to increased heart rate (and hence increased CO). Poor BP recovery after exposure to acute stress may be a marker of *chronic* autonomic imbalance—sympathetic activation and/or low parasympathetic tone (Julius, 1993; Verdecchia et al., 1996). This imbalance may persist long after the stress has ended, and may both potentiate and be sustained by continued stress, whether external or due to cognitive/ruminative processes (Anderson, Lane, Taguchi, Williams, Jr., & Houseworth, 1989; Borghi, Costa, Boschi, Mussi, & Ambrosioni, 1986). The sympathetic response to stress is a major putative mechanism for explaining the link between emotional stress and CVD (Light, Obrist, Sherwood, James, & Strogatz, 1987). In addition to these putative effects on the development and progression of disease, which are believed to be a function of several factors, including shear stress and consequent activation of proinflammatory processes (c.f., Ross, 1999), continued sympathetic activation maintains BP elevations, which is directly linked to end-organ damage, including left ventricular hypertrophy (Devereux et al., 1983; Verdecchia et al., 1996) and vascular stiffness (Yeragani, Tancer, Seema, Josyula, & Desai, 2006). These considerations provide support for causal explanations concerning the relative importance of poststress CV reactivity and poststress recovery for understanding the pathophysiology underlying the link between emotional stress and CVD (Christenfeld, Glynn, & Gerin, 2000; Gerin & Pickering, 1995; Jamieson & Lavoie, 1987; Linden, Earle, Gerin, & Christenfeld, 1997).

ENDOTHELIAL FUNCTION AND DYSFUNCTION

As briefly described earlier, the endothelium comprises a single layer of cells that lines the lumen of arterial vessels, serving as a bidirectional, biocompatible barrier that facilitates the passage of blood gases and various molecules to and from tissues. The endothelium maintains vascular homeostasis, responding to circulating and hemodynamic factors by releasing bioactive substances to affect vascular tone, with nitric oxide as the primary active agent in healthy vessels (Furchgott & Zawadzki, 1980). Endothelial dysfunction may be viewed as the failure of the endothelium to respond appropriately to these circulating and hemodynamic factors. This dysfunction provides the setting for paradoxical vasoconstriction, as observed in studies of mental stress during cardiac catheterization (Yeung et al., 1991). Endothelial dysfunction is seen in the earliest stages of coronary artery disease (CAD) and has been linked in non-CAD populations to traditional risk factors such as dyslipidemia, hypertension, diabetes, cigarette smoking, and family history of premature CAD (Verma, Buchanan, & Anderson, 2003). The prognostic importance of endothelial dysfunction has been demonstrated in several studies of patients with stable CAD (Gokce et al., 2003; Modena, Bonetti, Coppi, Bursi, & Rossi, 2002; Neunteufl et al., 2000; Verma et al., 2003). Research has also demonstrated endothelial dysfunction during and after periods of emotional stress (Gottdiener et al., 2003; Harris et al., 2000; Sarabi & Lind, 2001; Soufer, Arrighi, & Burg, 2002), with the effects of even a brief period of this stress lasting up to several hours (Ghiadoni et al., 2000; Spieker et al., 2002), and particularly among individuals susceptible to anger-related stress (Burg et al., 2009; Shimbo et al., 2007)

PATTERNS OF CO AND TPR STRESS RESPONSE IN BP REGULATION

It is well established that a BP response of a similar magnitude across conditions can reflect different patterns of response in CO, TPR, and endothelial function (cf., Eliot, Buell, & Dembroski, 1982). For example, BP might be increased by a greater increase in CO than TPR under one condition, and a greater increase in TPR than CO in another. Similarly, TPR can increase, decrease, or remain constant as a function of the interplay between vascular smooth muscle and endothelial cell activity. In an effort to understand the developmental pathophysiology of hypertension, researchers have tried to characterize people as a function of "hemodynamic profile"—whether they are "cardiac responders," because increased CO is their predominant response to stress or "vascular responders," because increased TPR is their predominant response. These researchers have then examined individual differences in hemodynamic profile—the relative contribution of CO versus TPR—during challenge, and whether this hemodynamic profile changes, for example, from predominantly CO to predominantly TPR, as individuals move along the hypertension trajectory (cf., Sherwood, Dolan, & Light, 1990). Hypertension is typically characterized by increased TPR; however, borderline hypertension is often characterized by an initial increase of CO, which in time evolves to increased TPR (Lund-Johansen, 1991). This is an overly simple notion, however. For example, increased CO that is not compensated for by a reduction in TPR and increased TPR that is not compensated for by a reduction in CO can lead by different paths to vascular damage. In the former case, the resulting tissue hyperperfusion can cause endothelial damage and alteration in vascular

function and structure; in the latter case, repeated or prolonged episodes of high TPR can permanently impair the capacity for vascular contractility. Clearly, both patterns can eventually lead to the elevated resting BP that defines essential hypertension.

The characterization of people as vascular or cardiac responders fails to account for the more subtle and complex interplay of the key factors involved or for the fact that most individuals display a mix of these two features. A recently articulated model (Gregg, Matyas, & James, 2002) captures more precisely the manner in which CO and TPR interact to produce arterial pressure (e.g., not additively but rather reciprocally), and characterizes individuals along a continuum as a function of (1) these two factors and (2) the resulting "compensation deficit" or failure of one factor to compensate for change in the other and thereby maintain a more constant BP. Using this model, the response to cognitive challenge (reactivity) has been found to predict 24-hour ambulatory BP better than the "standard" classification model which describes people merely as either cardiac or vascular responders (Ottaviani, Shapiro, Goldstein, James, & Weiss, 2006). More importantly, the pattern of compensatory change during recovery after cognitive challenge was found to improve the prediction of ambulatory BP above and beyond traditional resting, reactivity, and recovery BP. This latter study found that recovery was more vascular in nature, and that the predominantly "vascular profile" was highly associated with circulating levels of proinflammatory cytokines (Ottaviani, Shapiro, Goldstein, & Mills, 2007).

THE HYPOTHALAMIC–PITUITARY–ADRENAL AXIS AND CORTISOL

Cortisol is secreted by the adrenal cortex and acts synergistically with other agents in the physiological response to stress. Cortisol secretion potentiates the effect on vascular tone, both in terms of degree and persistence, of catecholamines (Kuhn, 1989). Furthermore, because of its influence on inflammatory processes (Chrousos, 1995), cortisol modulates the effect on the vasculature, both acutely and chronically, of proinflammatory cytokines. Cortisol secretion appears to be contingent, in part, on affective elements of stress experience, rather than merely on the level of demand alone (Kuhn, 1989). Secretion of cortisol is slow, occurring on the order of 20–30 minutes after initiation of a stressor, compared to the catecholamines, which can be measured in the blood within a few minutes. Sequential measurement in blood in the period after exposure to a stressor provides the most sensitive correlate of CV function.

ENDOTHELIN-1

Endothelin-1 (ET-1) is an endothelium-derived vasoactive peptide that is released into the circulation under a wide range of conditions and that has been implicated in the development of hypertension (Feldstein & Romero, 2007). It provokes significant and sustained systemic vasoconstriction (Kohan, 1997), and the renal circulation is a particular focus of its effects (Matsuura et al., 1997). The hypertensive effect of ET-1 is due not only to the direct action of the peptide on vascular tone, but also to the bidirectional potentiating effects that ET-1 has with norepinephrine (a positive feedback process [Feldstein & Romero, 2007]). Activity of ET-1 has been examined as an important element by which mental stress provokes clinically meaningful consequences (Spieker et al., 2002). In one study, a brief psychological stressor was paired with either infusion of saline or a potent ET-1 receptor blocker. Those receiving saline demonstrated stress-provoked endothelial dysfunction that was sustained for over 45 minutes, whereas in those receiving the ET-1 receptor blocker, the acute and prolonged effects of stress on endothelial function were largely mitigated (Spieker et al., 2002). These data point to ET-1 activity as a potential pathway by which mentally demanding events and emotional factors such as anger, and the rumination that often follows, can cause sustained BP elevation (placing a person on a hypertension trajectory) and contribute to the rupturing of vulnerable coronary artery plaques that are prerequisite for acute coronary syndrome.

INFLAMMATION

Inflammation is directly linked to the processes underlying vascular integrity, including endothelial function and arterial stiffness. The proinflammatory cytokine tumor necrosis factor-alpha impairs release of nitric oxide by the vascular endothelium, thereby contributing to sustained vasoconstriction (cf., Nakamura et al., 2000), and the production of this and other cytokines by macrophages is in part regulated by parasympathetic nervous system activity working through muscarinic receptors (Tracey, 2002). Furthermore, secretion of interleukin-6 (IL-6), which is regulated in part by the sympathetic nervous system (Black, 2003) and hypothalamic–pituitary–adrenal cortical axis (Kuhn, 1989), is increased 45–120 minutes after exposure to an acute stressor in the lab (Steptoe, Willemsen, Owen, Flower, & Mohamed-Ali, 2001); of note, these increases in IL-6 provoked by laboratory stress predict ambulatory BP 3 years later (Brydon & Steptoe, 2005). Cross-sectional data from the Physicians Health Study reveal a dose–response relationship of both systolic and diastolic BP with levels of IL-6 and soluble intercellular adhesion molecule (s-ICAM [Chae, Lee, Rifai, & Ridker, 2001]). Elicitation of the inflammatory response by vaccination has been found to increase arterial stiffness (Vlachopoulos et al., 2005), while individuals with the greatest inflammatory response to an acute stress in the lab have the highest level of arterial stiffness (Ellins et al., 2008). These data are consistent with a potential

role, most specifically for IL-6 and s-ICAM, in the developmental pathophysiology of hypertension.

OXIDATIVE STRESS

Oxidative stress describes the process by which the body produces ROS, small molecules that include oxygen ions, free radicals, and peroxides, as part of the metabolic process. During periods of stress, levels of these ROS can rise beyond the body's ability to further process or detoxify them, or to repair the cellular damage that is consequent to their formation. Oxidative stress negatively influences autonomic and endothelial function. Specifically, ROS inhibit nitric oxide production and directly damage the vascular endothelium, providing two pathways by which transient and lasting endothelial dysfunction and overall vascular damage can be realized (Harris & Matthews, 2004). Oxidative stress also accentuates sympathetically mediated vasoconstriction (Zhao et al., 2006), and increases the formation of ET-1 (Kahler et al., 2000), further contributing to endothelial dysfunction during stress (Spieker et al., 2002). Oxidative stress has been linked to the wide range of CVDs (Nistala et al., 2009; Zanzinger, 1999), along with disorders of other major bodily systems (Beckman & Koppenol, 1996). Urine levels of 8-epi-PGF_2 provide a convenient measure of whole body oxidative stress (Nourooz-Zadeh, Cooper, Ziegler, & Betteridge, 2005) that independently and sensitively predicts risk of CVD (Schwedhelm et al., 2004).

SUMMING UP

As noted at the beginning of this chapter, the CV system plays an essential role in maintaining the functioning and integrity of each of the major systems throughout the body, supporting the provision of oxygen and essential nutrients to bodily tissues and the transport of waste products to the appropriate sites for disposal and turnover. It is not surprising, given that the response to environmental demands, whether they be physical, mental, or emotional, must be instantaneous and precise, that the regulation of the CV system with its vast vascular network and associated pumping apparatus is complex and multifaceted. This chapter has sought to provide a concise description of this system and an overview of the key elements involved in its regulation that bear on the system's responsiveness to stressful stimuli. Further understanding of these processes will likely contribute in important ways to our understanding of the physical and mental health effects of stress.

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4 Effects of Stress on Immune Function: Implications for Immunoprotection and Immunopathology

Firdaus S. Dhabhar

INTRODUCTION

Stress is known to suppress immune function and increase susceptibility to infections and cancer. Paradoxically, stress is also known to exacerbate asthma and allergic, autoimmune, and inflammatory diseases although such diseases should be ameliorated by immunosuppression. Numerous studies have demonstrated adverse effects of stress on health and suggest that stress may suppress immune function under some conditions while enhancing it under others (Ader, 2006; Cohen, Janicki-Deverts, & Miller, 2007; Glaser & Kiecolt-Glaser, 2005; Heesen, Gold, Huitinga, & Reul, 2007; McEwen, 1998; Mohr, 2007; Stojanovich & Marisavljevich, 2008). Chronic stress has been shown to dysregulate immune responses (Chrousos & Kino, 2007; Glaser & Kiecolt-Glaser, 2005) by altering the cytokine balance from type-1 to type-2 cytokine-driven responses (Glaser et al., 2001) and accelerating immunosenescence (Epel et al., 2004), and to suppress immunity by decreasing numbers, trafficking (Dhabhar & McEwen, 1997), and function of protective immune cells while increasing regulatory/suppressor T cells (Saul et al., 2005).

While recognizing that long-term or chronic stress may play a role in the etiology of numerous diseases, it is also important to appreciate that the short-term fight-or-flight stress response is one of nature's fundamental defense mechanisms that enables the cardiovascular and musculoskeletal systems to promote survival. It is unlikely that this response would suppress or dysregulate immune function at a time when it is most required for survival (e.g., in response to wounding and infection by a predator or aggressor). During short-term stress responses such as those observed in nature, physiological systems act in synchrony to enable survival. Therefore, it was hypothesized that just as the stress response prepares the cardiovascular, musculoskeletal, and neuroendocrine systems for fight or flight, under certain conditions, stress may also prepare the immune system for challenges (e.g., wounding or infection) that may be imposed by a stressor (e.g., predator or surgical procedure) (Dhabhar, Miller, McEwen, & Spencer, 1995b; Dhabhar, 1996). In support of this hypothesis, studies have shown that short-duration stressors induce a redistribution of immune cells within the body and that immune function is significantly enhanced in organs such as the skin to which leukocytes traffic during acute stress. Studies have also identified mechanisms involving dendritic cell, neutrophil, macrophage, and lymphocyte trafficking, maturation, and function through which acute stressors may enhance innate as well as adaptive immunity. Therefore, we suggest that the acute stress response may serve as an endogenous psychophysiological adjuvant that enhances immune responses and may have evolved by virtue of the fact that many stressful situations (aggression, accident) result in immune activation (wounding, infection) and vice versa. Interestingly, in modern times, many medical situations involving immune activation (vaccination, surgery, injury) also induce a stress response. Such acute stress-induced immunoenhancement may serve to increase immunoprotection during exposure to infectious agents or wounding. However, it may also exacerbate immunopathology if the enhanced immune response is directed against innocuous or self-antigens, or is dysregulated following prolonged activation as seen during chronic stress.

The effects of stress are likely to be beneficial or harmful depending on the type (immunoprotective, immunoregulatory/inhibitory, or immunopathological) of immune response that is affected. Studies have shown that several critical factors influence the direction (enhancing versus suppressive) of the effects of stress or stress hormones on immune function: (1) Duration (acute versus chronic) of stress: Acute or short-term stress experienced at the time of immune activation can enhance innate and adaptive immune responses. Chronic or long-term stress can suppress immunity by decreasing immune cell numbers and function and/or increasing active immunosuppressive mechanisms (e.g., regulatory T cells). Chronic stress can also dysregulate immune function by promoting proinflammatory and type-2 cytokine-driven responses. (2) Effects of stress on leukocyte distribution: Compartments that are enriched with immune cells during acute stress show immunoenhancement, whereas those that are depleted of leukocytes show immunosuppression. (3) The differential effects of physiological versus pharmacological concentrations of glucocorticoids and the differential

effects of endogenous versus synthetic glucocorticoids: Endogenous hormones in physiological concentrations can have immunoenhancing effects. Endogenous hormones at pharmacological concentrations, and synthetic hormones, are immunosuppressive. (4) The timing of stressor or stress hormone exposure relative to the time of activation and time course of the immune response: Immunoenhancement is observed when acute stress is experienced at early stages of immune activation whereas immunosuppression may be observed at late stages of the immune response.

This chapter discusses the effects of stress on immune function and implications of these effects for immunoprotection versus immunopathology. We propose that it is important to study and, if possible, to clinically harness the immunoenhancing effects of the acute stress response that evolution has finely sculpted as a survival mechanism, just as we study its maladaptive ramifications (chronic stress) that evolution yet has to catch up with. In view of the ubiquitous nature of stress and its significant effects on immunoprotection as well as immunopathology, it is important to further elucidate the mechanisms mediating stress–immune interactions and to meaningfully translate findings from bench to bedside.

STRESS

Numerous definitions have been proposed for the concept of stress. Each definition focuses on aspects of an internal or external challenge, disturbance, or stimulus; on perception of a stimulus by an organism; or on a physiological response of the organism to the stimulus (Goldstein & McEwen, 2002; McEwen, 2002; Sapolsky, 2004). Physical stressors have been defined as external challenges to homeostasis and psychological stressors as the "anticipation justified or not, that a challenge to homeostasis looms" (Sapolsky, 2005). An integrated definition states that stress is a constellation of events, consisting of a stimulus (stressor) that precipitates a reaction in the brain (stress perception and processing) and activates physiological fight or flight systems in the body (stress response) (Dhabhar & McEwen, 1997). It is important to understand that the only way that a stressor can affect the brain or body is by inducing biological changes within the organism. Therefore, the physiological stress response is critical for mediating the effects of stress on health. This response results in the release of neurotransmitters, hormones, peptides, and other factors into the circulation and/or locally within tissues. Even cytokines, factors that were traditionally thought to be the domain of the immune system, have relatively recently been shown to be released in the systemic circulation during psychological stress (Altemus, Rao, Dhabhar, Ding, & Granstein, 2001; Pace, 2006).

The major distinguishing characteristics of stress are duration and intensity. *Acute stress* has been defined as stress that lasts for a period of minutes to hours, and *chronic stress* as stress that persists for several hours per day for weeks or months (Dhabhar & McEwen, 1997). Dysregulation of the circadian cortisol rhythm is one maker that appears to coincide with the deleterious effects of chronic stress (Dhabhar & McEwen, 1997; Saul et al., 2005; Sephton, Sapolsky, Kraemer, & Speigel, 2000; Sephton & Speigel, 2003). The intensity of stress may be gauged by the peak levels of stress hormones, neurotransmitters, and other physiological changes such as increases in heart rate and blood pressure, and by the amount of time for which these changes persist during stress and following the cessation of stress. It is important to note that significant individual differences in stress perception, processing, and coping have been observed (Dhabhar & McEwen, 2006; Gunnar & Quevedo, 2007; Marsland, Bachen, Cohen, Rabin, & Manuck, 2002; Taylor & Stanton, 2007). Individual differences become particularly relevant while studying human subjects because stress perception, processing, and coping mechanisms can have significant effects on the kinetics and peak levels of circulating stress hormones and on the duration for which these hormone levels are elevated. Animal studies showing significant strain differences in stress reactivity and peak hormone levels (Dhabhar, McEwen, & Spencer, 1993; Sternberg, Hill, et al., 1989), adaptation to stress (Dhabhar, McEwen, & Spencer, 1997), and in distribution and activation of adrenal steroid receptors and corticosteroid-binding globulin levels (Dhabhar, McEwen, & Spencer, 1993; Dhabhar, Miller, McEwen, & Spencer, 1995a) suggest that genetic as well as environmental factors play a role in establishing individual differences (Dhabhar, McEwen, & Spencer, 1993; Dhabhar et al., 1997; Dhabhar et al., 1995a; Gomez-Serrano, Tonelli, Listwak, Sternberg, & Riley, 2001). The ability of humans to generate and experience internal psychological stressors in the absence of external stressors can result in long-term activation of the physiological stress response that often has deleterious effects. The magnitude and duration of stress-induced elevations in catecholamine and glucocorticoid hormones can have significant effects on immune cell distribution and function (Benschop, Rodriguez-Feuerhahn, & Schedlowski, 1996; Dhabhar & McEwen, 2001; Pruett, 2001; Schwab et al., 2005).

IMMUNE RESPONSES DEFINED IN TERMS OF THEIR END EFFECTS

While discussing immune responses, it is useful to categorize them in terms of their principal cellular and molecular components. For example, innate, adaptive, type-1 and type-2 cytokine-driven immune responses are all defined in terms of their cellular and cytokine components. In addition to these categorizations, it is also useful to define immune responses in terms of their end effects. Therefore, we suggest that immune responses be categorized as being immunoprotective, immunopathological,

and immunoregulatory/inhibitory. It is important to bear in mind that while all these categories provide useful constructs with which to organize ideas, concepts, and models, an overall in vivo immune response is likely to consist of several types of responses with varying amounts of dominance from each category. Each of the proposed end-effect-based categories is defined below:

Immunoprotective responses are defined as responses that promote efficient wound healing, eliminate viral infections and cancer, and mediate vaccine-induced immunological memory. Key characteristics of immunoprotection involve active immune surveillance, a rapid and robust response upon immune activation, and efficient clearance of the activating agent or pathogen, followed by rapid resolution of inflammation. Immunoprotective responses are critical for completion of the proliferative and remodeling phases of wound healing. Wound healing is important not only for frank wounds where the initiating event is tissue damage itself, but also for tissue-intrinsic "wounds" where the initiating event is an immune response precipitated by intracellular infection during which there can be collateral tissue damage. Innate and/or adaptive type-1 or type-2 immune responses can all confer immunoprotection depending on the type of the pathogen (viral, bacterial, protozoan, fungal, helminthic), on whether the pathogen is intra- or extracellular, and on the accompanying wounding conditions (e.g., sterile, infected, external, or internal).

Immunopathological responses are defined as those that are directed against self-antigens (autoimmune disease such as multiple sclerosis, arthritis, lupus) or innocuous antigens (asthma, allergies) and responses that involve chronic, nonresolving inflammation. Immunopathology is also involved during low-level, long-term elevations in local and/or systemic inflammatory mediators that are thought to contribute to disorders such as cardiovascular disease, obesity (Aronne & Isoldi, 2007; Van Gaal, Mertens, & De Block, 2006), and depression (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008; Maes, 1993).

Immunoregulatory/inhibitory responses are defined as those that involve immune cells and factors that inhibit the function of other immune cells. Although the previous concept of suppressor T cells became mired in controversy, recent studies suggest that there is an arm of the immune system that functions to inhibit immune responses. Regulatory CD4+CD25+FoxP3+ T cells (Germain, 2008), IL-10, and TGF-β (Taylor, Verhagen, Blaser, Akdis, & Akdis, 2006) have been shown to have immunoregulatory/inhibitory functions. The physiological function of these factors is to keep proinflammatory, allergic, and autoimmune responses in check (Akdis, Blaser, & Akdis, 2006; Bluestone & Tang, 2005; Raghavan & Holmgren, 2005). However, it has also been suggested that immunoregulatory/inhibitory factors may suppress antitumor immunity and be indicative of negative prognosis for cancer (Finn, 2008).

FACTORS THAT DETERMINE WHETHER STRESS WILL ENHANCE OR SUPPRESS IMMUNE FUNCTION; POTENTIAL HEALTH CONSEQUENCES

Several critical factors are likely to influence the direction (enhancing versus suppressive) of the effects of stress or stress hormones, and the nature of the immune response (immunoprotective, immunoregulatory/inhibitory, or immunopathological) that is affected (Dhabhar & McEwen, 2001). These include: (1) The effects of stress on leukocyte distribution in the body. (2) The duration (short-term/acute versus long-term/chronic) of stress. (3) The differential effects of physiological versus pharmacological concentrations of glucocorticoids and the differential effects of endogenous (e.g., cortisol, corticosterone) versus synthetic (e.g., dexamethasone) glucocorticoids. (4) The timing of stressor or stress hormone exposure relative to the time of activation and ensuing timecourse of the immune response. Factors such as gender, genetics, age, the route of administration and nature of the immunizing antigen, and time of day may additionally affect the relationship between stress and immune function.

It is important to bear in mind that whether a stressor enhances or suppresses immune function, it is the end result of the affected immune response that affects the health of the organism or individual (Figure 4.1). Given the definitions in the preceding section, stress-induced enhancement of immunoprotection is likely to have beneficial effects whereas stress-induced suppression of immunoprotection is likely to be harmful. Similarly, stress-induced enhancement of immunopathology or long-term proinflammation is also likely to be harmful. Finally, stress-induced enhancement of active immunoregulation/inhibition is likely to be beneficial in case of autoimmune and proinflammatory disorders and harmful in case of infections and cancer.

STRESS-INDUCED CHANGES IN IMMUNE CELL DISTRIBUTION

Effective immunoprotection requires rapid recruitment of leukocytes into sites of surgery, wounding, infection, or vaccination. Immune cells circulate continuously on surveillance pathways that take them from the blood, through various organs, and back into the blood. This circulation is essential for the maintenance of an effective immune defense network (Sprent & Tough, 1994). The numbers and proportions of leukocytes in the blood provide an important representation of the state of distribution of leukocytes in the body and of the state of activation of the immune system. The ability of acute stress to induce changes in leukocyte distribution within different body compartments is perhaps one of the most

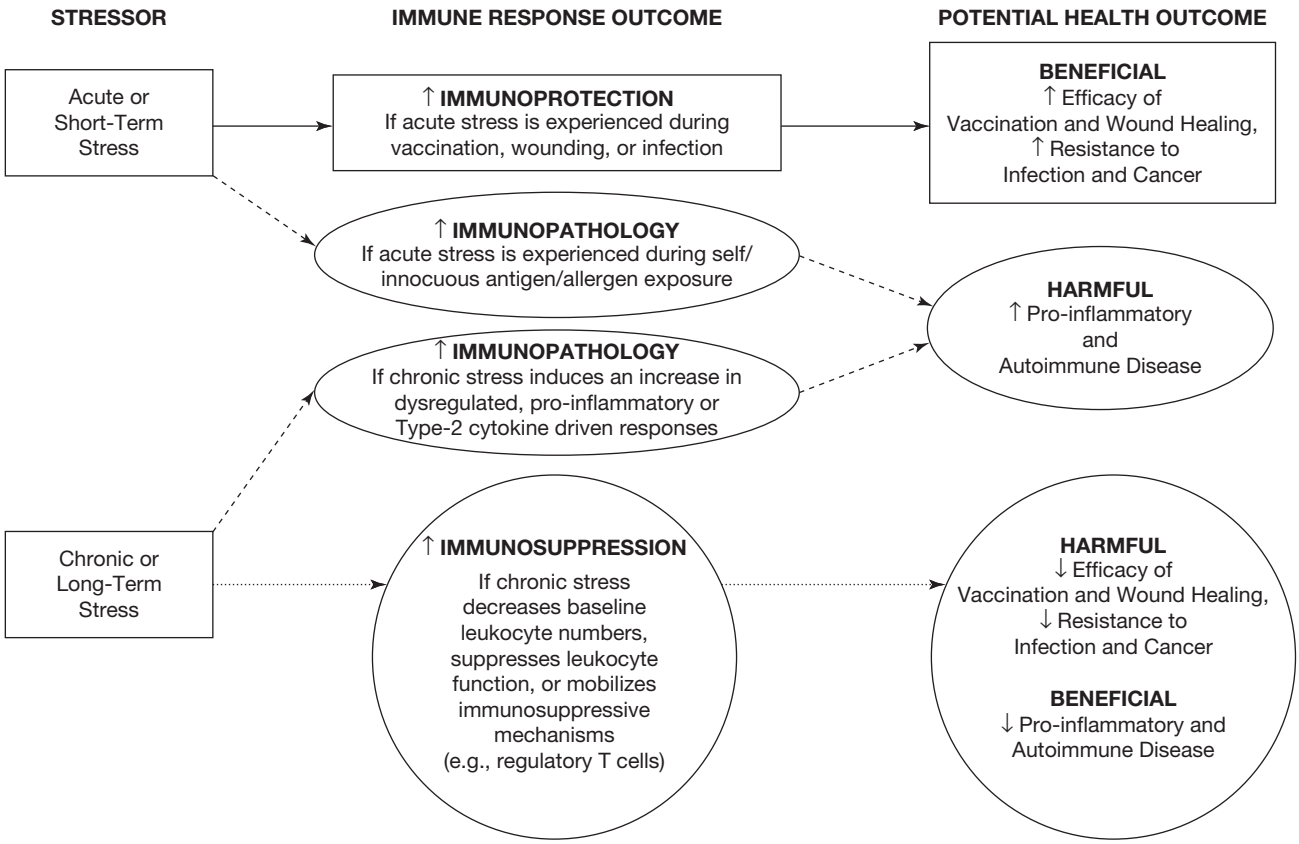

Figure 4.1 ■ The relationship among stress, immune function, and health outcomes. Acute stress experienced during vaccination, wounding, or infection may enhance immunoprotective responses. Acute stress experienced during immune activation in response to self/innocuous antigens or allergens may excerbate proinflammatory and autoimmune disorders. Chronic stress-induced increases in proinflammatory or type-2 cytokine mediated immune responses may also exacerbate inflammatory and autoimmune disease. Chronic stress-induced suppression of immune responses may decrease the efficacy of vaccination and wound healing and decrease resistance to infection and cancer. (*See color insert.*)

underappreciated effects of stress and stress hormones on the immune system (Dhabhar et al., 1995b).

Numerous studies have shown that stress and stress hormones induce significant changes in absolute numbers and relative proportions of leukocytes in the blood. In fact, changes in blood leukocyte numbers were used as a measure of stress before methods were available to directly assay the hormone (Hoagland, Elmadjian, & Pincus, 1946). Studies have also shown that glucocorticoid (Dhabhar, Miller, McEwen, & Spencer, 1996; Fauci & Dale, 1974; Fauci & Dale, 1975), and catecholamine hormones (Benschop, Oostveen, Heijnen, & Ballieux, 1993; Benschop, Rodriguez-Feuerhahn, & Schedlowski, 1996; Carlson, Fox, & Abell, 1997; Mills, Meck, Waters, D'Aunno, & Ziegler, 2001; Mills, Ziegler, Rehman, & Maisel, 1998; Redwine, Snow, Mills, & Irwin, 2003) induce rapid and significant changes in leukocyte distribution and that these hormones are the major mediators of the effects of stress. Stress-induced changes in blood leukocyte numbers have been reported in fish (Pickford, Srivastava, Slicher, & Pang, 1971), hamsters (Bilbo et al., 2002), mice (Jensen, 1969), rats (Dhabhar et al., 1995b; Dhabhar et al., 1996; Dhabhar, Miller, Stein, McEwen, & Spencer, 1994; Rinder et al., 1997), rabbits (Toft, Svendsen, Tonnesen, Rasmussen, & Christensen, 1993), horses (Snow, Ricketts, & Mason, 1983), nonhuman primates (Morrow-Tesch, McGlone, & Norman, 1993), and humans (Mills, et al., 1998; Herbert & Cohen, 1993; Schedlowski et al., 1993; Redwine et al., 2004; Bosch, Berntson, Cacioppo, Dhabhar, & Marucha, 2003). This suggests that the phenomenon of stress-induced leukocyte redistribution has a long evolutionary lineage, and that perhaps it has important functional significance.

Studies have shown that stress-induced changes in blood leukocyte numbers are characterized by a significant decrease in numbers and percentages of lymphocytes and monocytes, and by an increase in numbers and percentages of neutrophils (Dhabhar et al., 1994, 1995b). Flow cytometric analyses revealed that absolute numbers of peripheral blood T cells, B cells, NK cells, and monocytes all show a rapid and significant decrease (40–70% lower than baseline) during stress (Dhabhar et al., 1995b).

Moreover, it has been shown that stress-induced changes in leukocyte numbers are rapidly reversed upon the cessation of stress (Dhabhar et al., 1995b). In apparent contrast to animal studies, human studies have shown that stress increases rather than decreases blood leukocyte numbers (Bosch et al., 2003; Brosschot et al., 1994; Mills et al., 1995; Naliboff et al., 1991; Schedlowski et al., 1993). This apparent contradiction may be resolved by taking the following factors into consideration: First, stress-induced increases in blood leukocyte numbers in humans have been studied using stress conditions that result in the activation of primarily the sympathetic nervous system. These stressors are often of a short duration (few minutes) or relatively mild (e.g., public speaking) (Brosschot et al., 1994; Mills et al., 1995; Naliboff et al., 1991; Schedlowski et al., 1993). Second, the increase in total leukocyte numbers may be accounted for mainly by stress- or catecholamine-induced increases in granulocytes and NK cells (Benschop, Rodriguez-Feuerhahn, Schedlowski, 1996; Brosschot et al., 1994; Mills et al., 1995; Naliboff et al., 1991; Schedlowski et al., 1993). Third, stress or pharmacologically induced increases in glucocorticoid hormones induce a significant decrease in blood lymphocyte and monocyte numbers (Dhabhar et al., 1996; Hoagland et al., 1946; Schedlowski et al., 1993; Stein, Ronzoni, & Gildea, 1951). Thus, stress conditions that result in a significant and sustained activation of the hypothalamic-pituitary-adrenal (HPA) axis result in a decrease in blood leukocyte numbers.

It has been proposed that acute stress induces an initial increase followed by a decrease in blood leukocyte numbers (Dhabhar & McEwen, 2001). Stress conditions that result in activation of the sympathetic nervous system, especially conditions that induce high levels of norepinephrine, may induce an increase in circulating leukocyte numbers. These conditions may occur during the beginning of a stress response, very short-duration stress (order of minutes), mild psychological stress, or during exercise. In contrast, stress conditions that result in the activation of the HPA axis induce a decrease in circulating leukocyte numbers. These conditions often occur during the later stages of a stress response, long-duration acute stressors (order of hours), or during severe psychological, physical, or physiological stress. An elegant and interesting example of a study that supports this hypothesis comes from Schedlowski et al. who measured changes in blood T-cell and NK-cell numbers as well as plasma catecholamine and cortisol levels in parachutists (Schedlowski et al., 1993). Measurements were made 2 hours before, immediately after, and 1 hour after the jump. Results showed a significant increase in T-cell and NK-cell numbers immediately (minutes) after the jump, which was followed by a significant decrease 1 hour after the jump. An early increase in plasma catecholamines preceded early increases in lymphocyte numbers whereas the more delayed rise in plasma cortisol preceded the late decrease in lymphocyte numbers (Schedlowski et al., 1993). Importantly, changes in NK cell activity and antibody-dependent cell-mediated cytotoxicity closely paralleled changes in blood NK cell numbers, thus suggesting that changes in leukocyte numbers may be an important mediator of apparent changes in leukocyte "activity." Similarly, Rinner et al. have shown that a short stressor (1-minute handling) induced an increase in mitogen-induced proliferation of T and B cells obtained from peripheral blood, whereas a longer stressor (2-hour immobilization) induced a decrease in the same proliferative responses (Rinner, Schauenstein, Mangge, Porta, & Kvetnansky, 1992). In another example, Manuck et al. showed that acute psychological stress induced a significant increase in blood cytotoxic T lymphocyte (CTL) numbers only in those subjects who showed heightened catecholamine and cardiovascular reactions to stress (Manuck, Cohen, Rabin, Muldoon, & Bachen, 1991).

Thus, an acute stress response may induce biphasic changes in blood leukocyte numbers. Soon after the beginning of stress (order of minutes) or during mild acute stress, or exercise, catecholamine hormones and neurotransmitters induce the body's "soldiers" (leukocytes) to exit their "barracks" (spleen, lung, marginated pool, and other organs) and enter the "boulevards" (blood vessels and lymphatics). This results in an increase in blood leukocyte numbers, the effect being most prominent for NK cells and granulocytes. As the stress response continues, activation of the HPA axis results in the release of glucocorticoid hormones that induce leukocytes to exit the blood and take position at potential "battle stations" (such as the skin, lung, gastrointestinal and urinogenital tracts, mucosal surfaces, and lymph nodes) in preparation for immune challenges that may be imposed by the actions of the stressor (Dhabhar et al., 1995b; Dhabhar & McEwen, 1996, 2001). Such a redistribution of leukocytes results in a decrease in blood leukocyte numbers. Thus, acute stress may result in a redistribution of leukocytes from the barracks, through the boulevards, and to potential battle stations within the body.

Since the blood is the most accessible and commonly used compartment for human studies, it is important to carefully evaluate how changes in blood immune parameters might reflect in vivo immune function in the context of the specific experiments or study at hand. Moreover, since most blood collection procedures involve a certain amount of stress, since all patients or subjects will have experienced acute and chronic stress, and since many studies of psychophysiological effects on immune function focus on stress, the effects of stress on blood leukocyte distribution become a factor of considerable importance.

Dhabhar et al. were the first to propose that stress-induced changes in blood leukocyte distribution may represent an adaptive response (Dhabhar et al., 1994; Dhabhar & McEwen, 1999). They suggested that acute stress-induced changes in blood leukocyte numbers represent a redistribution of leukocytes from the blood to organs such as the skin, draining sentinel lymph nodes, and other compartments (Dhabhar & McEwen, 1996; Dhabhar & McEwen, 2001). They hypothesized that such a leukocyte redistribution may enhance immune

function in compartments to which immune cells traffic during stress. In agreement with this hypothesis, it was demonstrated that a stress-induced redistribution of leukocytes from the blood to the skin is accompanied by a significant enhancement of skin immunity (Dhabhar & McEwen, 1996; Dhabhar & McEwen, 1999; Dhabhar, Satoskar, Bluethmann, David, & McEwen, 2000).

FUNCTIONAL CONSEQUENCES OF STRESS-INDUCED CHANGES IN IMMUNE CELL DISTRIBUTION

When interpreting data showing stress-induced changes in functional assays such as lymphocyte proliferation or NK activity, it may be important to bear in mind the effects of stress on the leukocyte composition of the compartment in which an immune parameter is being measured. For example, it has been shown that acute stress induces a redistribution of leukocytes from the blood to the skin and that this redistribution is accompanied by a significant enhancement of skin cell-mediated immunity (CMI) (Dhabhar & McEwen, 1996; Dhabhar & Viswanathan, 2005). In what might at first glance appear to be contradicting results, acute stress has been shown to suppress splenic and peripheral blood responses to T-cell mitogens (Cunnick, Lysle, Kucinski, & Rabin, 1990) and splenic IgM production (Zalcman & Anisman, 1993). However, it is important to note that in contrast to the skin that is enriched in leukocytes during acute stress, peripheral blood and spleen are relatively depleted of leukocytes during acute stress (Dhabhar, 1998). This stress-induced decrease in blood and spleen leukocyte numbers may contribute to the acute stress-induced suppression of immune function in these compartments.

Moreover, in contrast to acute stress, chronic stress has been shown to suppress skin CMI and a chronic stress-induced suppression of blood leukocyte redistribution is thought to be one of the factors mediating the immunosuppressive effect of chronic stress (Dhabhar & McEwen, 1997). Again, in what might appear to be contradicting results, chronic stress has been shown to enhance mitogen-induced proliferation of splenocytes (Monjan & Collector, 1977) and splenic IgM production (Zalcman & Anisman, 1993). However, the spleen is relatively enriched in T cells during chronic glucocorticoid administration, suggesting that it may also be relatively enriched in T cells during chronic stress (Miller et al., 1994), and this increase in spleen leukocyte numbers may contribute to the chronic stress-induced enhancement of immune parameters measured in the spleen.

It is also important to bear in mind that the heterogeneity of the stress-induced changes in leukocyte distribution (Dhabhar et al., 1995b) suggests that using equal numbers of leukocytes in a functional assay may not account for stress-induced changes in relative percentages of different leukocyte subpopulations in the cell suspension being assayed. For example, samples that have been equalized for absolute numbers of total blood leukocytes from control versus stressed animals may still contain different numbers of specific leukocyte subpopulations (e.g., T cells, B cells, or NK cells). Such changes in leukocyte composition may contribute to the effects of stress even in functional assays using equalized numbers of leukocytes from different treatment groups. Therefore, stress may affect immune function at a cellular level (e.g., phagocytosis, antigen presentation, killing, antibody production) and/or through leukocyte redistribution that could increase or decrease the number of cells with a specific functional capacity in the compartment being studied.

EFFECTS OF ACUTE STRESS ON LEUKOCYTE TRAFFICKING TO A SITE OF SURGERY OR IMMUNE ACTIVATION

Viswanathan et al. used a subcutaneously implanted surgical sponge model to elucidate the effects of stress on the kinetics, magnitude, subpopulation, and chemoattractant specificity of leukocyte trafficking to a site of immune activation or surgery (Viswanathan & Dhabhar, 2005). Mice that were acutely stressed before subcutaneous implantation of the surgical sponge showed a two to three fold higher neutrophil, macrophage, NK cell, and T-cell infiltration than nonstressed animals. Leukocyte infiltration was evident as early as 6 hours and peaked between 24 and 48 hours. Importantly, at 72 hours, sponges from nonstressed and acutely stressed mice had comparable and significantly lower leukocyte numbers indicating effective resolution of inflammation in both groups. These authors also examined the effects of stress on early (6 hours) leukocyte infiltration in response to a predominantly proinflammatory cytokine, tumor necrosis factor (TNF)-α, and lymphocyte-specific chemokine, lymphotactin (LTN). Acute stress significantly increased infiltration of macrophages, in response to saline, LTN, or TNF-α; neutrophils, only in response to TNF-α; and NK and T cells only in response to LTN. These results showed that acute stress significantly enhances the kinetics and magnitude of leukocyte infiltration into a site of immune activation or surgery in a subpopulation and chemoattractant-specific manner, with tissue damage, antigen-, or pathogen-driven chemoattractants synergizing with acute stress to further determine the specific subpopulations that are recruited (Viswanathan & Dhabhar, 2005). Thus, depending on the primary chemoattractants driving an immune response, acute stress may selectively mobilize specific leukocyte subpopulations into sites of surgery, wounding, or inflammation. Such a stress-induced increase in leukocyte trafficking may be an important mechanism by which acute stressors alter the course of different (innate versus adaptive, early versus late, acute versus chronic) protective or pathological immune responses.

STRESS-INDUCED ENHANCEMENT OF INNATE/PRIMARY IMMUNE RESPONSES

As the skin is one of the target organs to which leukocytes traffic during stress, studies were conducted to examine whether skin immunity is enhanced when immune activation/antigen exposure occurs following a stressful experience. Studies showed that acute stress experienced at the time of novel or primary antigen exposure results in a significant enhancement of the ensuing skin immune response (Dhabhar & Viswanathan, 2005). Compared to controls, mice restrained for 2.5 hours before primary immunization with keyhole limpet hemocyanin (KLH) showed a significantly enhanced immune response when re-exposed to KLH after 9 months. This immunoenhancement was mediated by an increase in numbers of memory and effector helper T cells in sentinel lymph nodes at the time of primary immunization. Further analyses showed that the early stress-induced increase in T-cell memory may have stimulated the robust increase in infiltrating lymphocyte and macrophage numbers observed months later at a novel site of antigen re-exposure. Enhanced leukocyte infiltration was driven by increased levels of the type-1 cytokines, IL-2 and IFN-γ, and TNF-α observed at the site of antigen re-exposure in animals that had been stressed at the time of primary immunization. Given the importance of inducing long-lasting increases in immunological memory during vaccination, it has been suggested that the neuroendocrine stress response is nature's adjuvant that could be psychologically and/or pharmacologically manipulated to safely increase vaccine efficacy.

In a series of elegant experiments, Saint-Mezard et al. similarly showed that acute stress experienced at the time of sensitization resulted in a significant increase in the contact hypersensitivity (CHS) response (Saint-Mezard et al., 2003). These investigators showed that acute stress experienced during sensitization enhanced dendritic cell migration from skin to sentinel lymph nodes and also enhanced priming of lymph node CD8+ T cells. These CD8+ T cells responded in greater numbers at the site of antigen re-exposure during the recall phase of the CHS response. These studies also suggested that the effects of acute stress in this case were mediated primarily by norepinephrine (Saint-Mezard et al., 2003). Other investigators have similarly reported stress-induced enhancement of type-1 cytokine-driven CMI (Blecha, Barry, & Kelley, 1982; Coe, Lubach, & E. W. B, 1989; Wood, Karol, Kusnecov, & Rabin, 1993) and Type-2 cytokine-driven humoral immunity (Carr, Woolley, & Blalock, 1992; Cocke, Moynihan, Cohen, Grota, & Ader, 1993; Persoons, Berkenbosch, Schornagel, Thepen, & Kraal, 1995; Wood et al., 1993).

Viswanathan et al. further elucidated the molecular and cellular mediators of the immunoenhancing effects of acute stress (Viswanathan, Daugherty, & Dhabhar, 2005). They showed that compared with nonstressed mice, acutely stressed animals showed significantly greater pinna swelling, leukocyte infiltration, and upregulated macrophage chemoattractant protein-1 (MCP-1), macrophage inflammatory protein-3α (MIP-3α), IL-1α, IL-1β, IL-6, TNF-α, and IFN-γ gene expression at the site of primary antigen exposure. Stressed animals also showed enhanced maturation and trafficking of dendritic cells from skin to lymph nodes, higher numbers of activated macrophages in skin and lymph nodes, increased T-cell activation in lymph nodes, and enhanced recruitment of surveillance T cells to skin. These findings showed that important interactive components of innate (dendritic cells and macrophages) and adaptive (surveillance T cells) immunity are mediators of the stress-induced enhancement of a primary immune response. Such immunoenhancement during primary immunization may induce a long-term increase immunological memory resulting in subsequent augmentation of the immune response during secondary antigen exposure.

In addition to elucidating mechanisms that could be targeted to reduce stress-induced exacerbation of allergic, autoimmune, and proinflammatory reactions, the earlier mentioned studies provide further support for the idea that a psychophysiological stress response is nature's fundamental survival mechanism that could be therapeutically harnessed to augment immune function during vaccination, wound healing, or infection.

ACUTE STRESS-INDUCED ENHANCEMENT OF ADAPTIVE/SECONDARY IMMUNE RESPONSES

Studies have shown that in addition to enhancing primary cutaneous immune responses, acute stress experienced at the time of antigen re-exposure can also enhance secondary or recall responses in skin (Dhabhar & McEwen, 1996). Compared with nonstressed controls, mice that were acutely stressed at the time of antigen re-exposure showed a significantly larger number of infiltrating leukocytes at the site of the immune reaction. These results demonstrated that a relatively mild behavioral manipulation can enhance an important class of immune responses that mediate harmful (allergic dermatitis) as well as beneficial (resistance to certain viruses, bacteria, and tumors) aspects of immune function.

Blecha et al. reported a similar stress-induced enhancement of CHS reactions in mice (Blecha Barry, & Kelley, 1982), and Flint et al. showed that acute stress enhanced CHS responses in both male and female mice and that immunoenhancement was partially dependent on glucocorticoid hormones (Flint, Miller, & Tinkle, 2000). A stress-induced enhancement of the elicitation phase of skin CMI has also been reported in hamsters (Bilbo et al., 2002). Taken together, studies show that acute stress can significantly enhance the immunization/sensitization/induction as well as the re-exposure/elicitation/recall phases of skin CMI.

HORMONE AND CYTOKINE MEDIATORS OF STRESS-INDUCED IMMUNO-ENHANCEMENT

Although much work remains to be done to identify molecular, cellular, and physiological mechanisms mediating the adjuvant-like, immunoenhancing effects of acute stress, several studies have begun to identify endocrine and immune mediators of these effects. Studies have shown that corticosterone and epinephrine are important mediators of an acute stress-induced immunoenhancement (Dhabhar & McEwen, 1999). Adrenalectomy, which eliminates the glucocorticoid and epinephrine stress response, eliminated the stress-induced enhancement of skin CMI. Low-dose corticosterone or epinephrine administration significantly enhanced skin CMI (Dhabhar & McEwen, 1999). In contrast, high-dose corticosterone, chronic corticosterone, or low-dose dexamethasone administration significantly suppressed skin CMI. These results suggested a novel role for adrenal stress hormones as endogenous immunoenhancing agents. They also showed that stress hormones released during a circumscribed or acute stress response may help prepare the immune system for potential challenges (e.g., wounding or infection) for which stress perception by the brain may serve as an early warning signal. Studies by Flint et al. have also suggested that corticosterone is a mediator of the stress-induced enhancement of skin CHS (Flint et al., 2000), and Saint-Mezard et al. have suggested that the adjuvant-like effects of stress on dendritic cell and CD8+ T-cell migration and function are mediated by norepinephrine (Saint-Mezard et al., 2003).

Studies have also examined the immunological mediators of an acute stress-induced enhancement of skin immunity. Since gamma interferon (IFNγ) is a critical cytokine mediator of CMI and delayed as well as CHS, studies were conducted to examine its role as a local mediator of the stress-induced enhancement of skin CMI (Dhabhar et al., 2000). The effect of acute stress on skin CMI was examined in wildtype and IFNγ receptor gene knockout mice (IFNγR-/-) that had been sensitized with 2,4-dinitro-1-fluorobenzene (DNFB). Acutely stressed wildtype mice showed a significantly larger CMI response than nonstressed mice. In contrast, IFNγR-/- mice failed to show a stress-induced enhancement of skin CMI. Immunoneutralization of IFNγ in wildtype mice significantly reduced the stress-induced enhancement of skin CMI. In addition, an inflammatory response to direct IFNγ administration was significantly enhanced by acute stress. These results showed that IFNγ is an important local mediator of a stress-induced enhancement of skin CMI (Dhabhar et al., 2000). In addition to IFNγ, TNF-α, MCP-1, MIP-3α, IL-1, and IL-6 have also been associated with a stress-induced enhancement of the immunization/sensitization phase of skin CMI (Dhabhar & Viswanathan, 2005; Viswanathan et al., 2005). It is clear that further investigation is necessary to identify the most important molecular, cellular, and physiological mediators of a stress-induced enhancement of skin immunity.

ACUTE STRESS PSYCHOPHYSIOLOGY AS AN ENDOGENOUS ADJUVANT

We initially suggested that just as the acute stress response prepares the cardiovascular, musculoskeletal, and neuroendocrine systems for flight or flight, it may also prepare the immune system for challenges such as wounding and infection that are likely to result due to the actions of the stressor (predator, or process of undergoing surgery) (Dhabhar & McEwen, 1996; Dhabhar, 1998). Upon seeing the evidence in support of the earlier hypothesis we put forth the novel hypothesis that a psychophysiological stress response is nature's fundamental survival mechanism that could be therapeutically harnessed to augment immune function during vaccination, wound healing, or infection (Dhabhar &Viswanathan, 2005). In keeping with this hypothesis, studies conducted by our group have shown that patients undergoing knee surgery, who show a robust and adaptive immune cell redistribution profile during the acute stress of surgery, also show significantly enhanced recovery. Similarly, studies conducted by Edwards et al. have shown that acute stressors can enhance vaccine-induced humoral and cell-mediated immunity in human subjects (Edwards et al., 2006, 2007, 2008). Further research is required to test the hypothesis that behavioral and/or pharmacological induction of the acute psychophysiological stress response can be used therapeutically to enhance protective immunity during wound healing, infection, and cancer, and to enhance vaccine efficacy. Such intervention is likely to allow for safe and effective enhancement of protective immunity because it would tap into the body's natural, endogenous adjuvant mechanisms to enhance immune function.

CHRONIC STRESS CAN SUPPRESS IMMUNOPROTECTION AND ENHANCE IMMUNOPATHOLOGY

In contrast to acute stressors, chronic stress has been shown to suppress type-1 cytokine-driven protective immune responses while enhancing proinflammatory and type-2 cytokine-driven immune responses (Glaser & Kiecolt-Glaser, 2005; Gouin, Hantsoo, & Kiecolt-Glaser, 2008; Marshall & Agarwal, 2000). Chronic stress also appears to mobilize immunoregulatory/inhibitory mechanisms (Saul et al., 2005). Therefore, chronic stress is likely to exacerbate proinflammatory diseases and increase susceptibility to infections and cancer. Dhabhar et al. conducted studies designed to examine the effects

of increasing the intensity and duration of acute stress as well as the transition from acute to chronic stress on skin immune function (Dhabhar & McEwen, 1997). These studies showed that acute stress administered for 2 hours before antigenic challenge significantly enhanced skin CMI (Dhabhar & McEwen, 1997). Increasing the duration of stress from 2 hours to 5 hours produced the same magnitude immunoenhancement. Interestingly, increasing the intensity of acute stress produced a significantly larger enhancement of the CMI response that was accompanied by increasing magnitudes of leukocyte redeployment. In contrast, these studies found suppression of the skin immune response when chronic stress exposure was begun 3 weeks before sensitization and either discontinued upon sensitization, or continued an additional week until challenge, or extended for 1 week after challenge (Dhabhar & McEwen, 1997). Interestingly, acute stress-induced redistribution of peripheral blood lymphocytes was attenuated with increasing duration of stressor exposure and correlated with attenuated glucocorticoid responsivity. These results suggested that stress-induced alterations in lymphocyte redeployment may play an important role in mediating the bidirectional effects of stress on cutaneous CMI (Dhabhar & McEwen, 1997). An association between chronic stress and reduced skin CMI has also been reported in human subjects (Smith et al., 2004).

Given the importance of cutaneous CMI in elimination of immunoresponsive tumors such as squamous cell carcinoma (SCC) (Granstein & Matsui, 2004; Kripke, 1994), Saul et al. examined the effects of chronic stress on susceptibility to ultraviolet radiation (UV)-induced SCC (Saul et al., 2005). Mice were exposed to a minimal erythemal dose of UVB three times a week for 10 weeks. Half of the UVB-exposed mice were left nonstressed (i.e., they remained in their home cages) and the other half were chronically stressed (i.e., restrained during weeks 4–6). UV-induced tumors were measured weekly from week 11 through week 34, blood was collected at week 34, and tissues were collected at week 35. mRNA expression of IL-12p40, IFN-γ IL-4, IL-10, CD3ε, and CCL27/CTACK, the skin T cell-homing chemokine, in dorsal skin was quantified using real-time polymerase chain reaction. CD4+, CD8+, and CD25+ leukocytes were counted using immunohistochemistry and flow cytometry. Stressed mice had a shorter median time to first tumor (15 versus 16.5 weeks) and reached 50% incidence earlier than controls (15 weeks versus 21 weeks). Stressed mice also had lower IFN-γ, CCL27/CTACK, and CD3ε gene expression and lower CD4+ and CD8+ T cells infiltrating within and around tumors than nonstressed mice. In addition, stressed mice had higher numbers of tumor-infiltrating and circulating CD4+CD25+ suppressor cells than nonstressed mice. These studies showed that chronic stress increased susceptibility to UV-induced SSC by suppressing skin immunity, type-1 cytokines, and protective T cells, and increasing active immunosuppression through regulatory/suppressor T cells (Saul et al., 2005).

Chronic stress has also been shown to suppress immunoprotective parameters such as CMI (Basso, Depiante-Depaoli, Cancela, & Molina, 1993; Kelley, Greenfield, Evermann, Parish, & Perryman, 1982), antibody production (Edwards & Dean, 1977; Fleshner, Laudenslager, Simons, & Maier, 1989), NK activity (Bartrop, Lazarus, Luckhurst, Kiloh, & Penny, 1977; Cheng, Morrow-Tesch, Beller, Levy, & Black, 1990; Irwin et al., 1990; Kiecolt-Glaser et al., 1984), leukocyte proliferation (Bartrop et al., 1977; Cheng et al., 1990; Regnier & Kelley, 1981), skin homograft rejection (Wistar & Hildemann, 1960), virus-specific T-cell and NK-cell activity (Bonneau, Sheridan, Feng, & Glaser, 1991), vaccine-induced immune responses (Glaser, Kiecolt-Glaser, Malarkey, & Sheridan, 1998; Glaser, Sheridan, Malarkey, MacCallum, & Kiecolt-Glaser, 2000), and antimycobacterial activity of macrophages from susceptible mouse strains (Brown & Zwilling, 1994), and to enhance proinflammatory and type-2 cytokine-driven conditions and disorders (Elenkov, 2004; Glaser et al., 2001; Marshall & Agarwal, 2000).

IMMUNOMODULATORY EFFECTS OF THE TIMING OF STRESS OR STRESS HORMONE ADMINISTRATION RELATIVE TO THE TIME COURSE OF THE ENSUING IMMUNE RESPONSE

Under certain conditions, physiological levels of endogenous glucocorticoids have immunoenhancing effects whereas under other conditions similar hormone levels suppress autoimmune and inflammatory reactions. We hypothesize that these differential effects are achieved by differences in overall glucocorticoid sensitivity or receptivity of the immune response being affected. At the very beginning of an immune response, certain components such as leukocyte trafficking, antigen presentation, helper T-cell function, leukocyte proliferation, cytokine and chemokine function, and effector cell function may all be receptive to glucocorticoid-mediated immunoenhancement. In contrast, at a later, more advanced stage of an immune response these components may be more receptive to glucocorticoid-mediated immunosuppression. While this hypothesis needs to be tested through further experiments, examples from studies showing temporal differences in the sensitivity of immune reactions to the effects of physiological concentrations of glucocorticoid hormones are presented in the following text.

Studies examining the effects of corticosterone on T lymphocyte proliferation in vitro support the hypothesis that there may be temporal differences in the receptivity of an immune response to the enhancing versus suppressive effects of endogenous glucocorticoid hormones (Wiegers et al., 1995). These studies have shown that during the early stages of T-cell activation, low levels of corticosterone potently enhance anti-TCR-induced

lymphocyte proliferation. However, during later stages of culture, the same levels of corticosterone suppress T lymphocyte proliferation (Wiegers et al., 1995). Furthermore, Wiegers et al. showed that corticosterone had to be present during the process of TCR activation to enhance the proliferative response. If corticosterone was added to the culture system more than 2 hours after the initiation of TCR activation, the enhancement of lymphoproliferation was not observed.

Interestingly, Weigers et al. have shown that these bidirectional effects of corticosterone on different stages of T lymphocyte proliferation are mediated by opposing effects of corticosterone on IL-2 receptor (IL-2R) versus the cytokine itself (for review see: Wiegers & Reul, 1998). Thus, during the early stages of lymphocyte proliferation, corticosterone induces an increase in IL-2Rα expression. This increases the IL-2 receptivity of lymphocytes and is reflected by an increase in lymphocyte proliferation (Wiegers et al., 1995). Although corticosterone reduces the production of IL-2 under these conditions, this decrease is not rate limiting at this stage since exogenously added IL-2 fails to increase proliferation. However, if corticosterone is administered at later stages, the enhancement in IL-2R expression is absent, while the suppression of IL-2 production is still present. Under these conditions, the availability of IL-2 does become rate limiting, and hence corticosterone suppress the lymphoproliferative response. Thus, these studies indicate an important mechanism mediating an endogenous glucocorticoid-induced immunoenhancement during the early stages, and an endogenous glucocorticoid-induced immunosuppression during the later stages of an immune response.

In a series of seminal studies, Sternberg et al. (1989) showed that decreased HPA axis reactivity to inflammatory stimuli results in increased susceptibility to experimental arthritis (Sternberg et al., 1989, Sternberg, Young, et al. 1989; Sternberg et al., 1992). A similar role for HPA axis-mediated endogenous immunoregulation has been shown for development of autoimmune thyroiditis, lupus erythematosus, and avian scleroderma in Obese strain (OS) chickens (Wick, Sgonc, & Lechner, 1998) and experimental autoimmune encephalomyelitis in rats (Whitacre, Dowdell, & Griffin, 1998). Sternberg et al. investigated the influence of the HPA axis on the development of streptococcal cell wall (SCW)-induced arthritis in female rats belonging to the genetically related Lewis/N (LEW/N) and Fischer 344/N (F344/N) strains (Sternberg, Hill, et al., 1989, Sternberg, Young, et al., 1989; Sternberg & Wilder, 1989; Webster, Tonelli, & Sternberg, 2002). The F344/N strain is resistant to the development of SCW-induced arthritis whereas the LEW/N strain is susceptible. Interestingly, the F344/N strain mounts a significantly greater corticosterone and adrenocorticotropin (ACTH) response than the LEW/N strain when challenged with various stressors or with inflammatory mediators such as SCW peptidoglycan polysaccharide, or interleukin-1α (IL-1α) (Dhabhar et al., 1993, 1995a; Sternberg, Hill, et al., 1989, Sternberg, Young, et al., 1989), and compared to the F344 strain, the Lewis strain shows a significantly greater habituation or adaptation to an acute or chronic stressor (Dhabhar et al., 1997). F344/N rats treated with the glucocorticoid receptor antagonist, RU486, are rendered susceptible to SCW-induced arthritis indicating that they do carry the immune response genes with potential for triggering autoimmunity. Conversely, LEW rats treated with pharmacological doses of dexamethasone become completely resistant to the development of SCW-induced arthritis (Sternberg, Hill, et al., 1989, Sternberg, Young, et al., 1989). Furthermore, compared with Fischer 344 (F344 rats), adrenal steroid receptors in neural and immune tissues of Lewis (LEW) rats show a significantly lower magnitude of activation in response to stress-induced increases in plasma corticosterone (Dhabhar et al., 1993, 1995). Thus, strain differences in plasma corticosterone levels are also manifest as significant differences in the extent of activation of corticosterone receptors in target tissues.

Experimental allergic encephalomyelitis (EAE) is another animal model of an autoimmune disease in which a similar immunosuppressive role for the HPA axis has been proposed (for review see: Mason, MacPhee, & Antoni, 1990; Mason, 1991; Whitacre et al., 1998). The Lewis strain shows a greater susceptibility to EAE (Mason, 1991). MacKenzie Leonard, and Cuzner (1989) have suggested that during the preclinical phase of EAE, elevations in plasma corticosterone may regulate the lymphoproliferative stage of the disease, and that during the clinical phase of the disease, elevations in plasma corticosterone as well as splenic norepinephrine may regulate other recovery-oriented immune mechanisms. Similar correlations between HPA axis hyporeactivity and susceptibility to autoimmune disease have been observed for autoimmune conditions in chickens (Wick et al., 1998) and mice (Lechner et al., 1996). In an elegant series of studies using an EAE model, del Rey et al. demonstrated that a proinflammatory/autoimmune response itself stimulates the HPA axis primarily through cytokines such as IL-1, and that HPA axis activation is independent of the stress and discomfort associated with EAE-induced paralysis (del Rey, Klusman, & Besedovsky, 1998).

Complementing these preclinical studies, a series of elegantly conducted clinical studies (Buske-Kirschbaum & Hellhammer, 2003; Torpy & Chrousos, 1996) have shown that patients with atopic dermatitis (Buske-Kirschbaum et al., 1997; Buske-Kirschbaum, Geiben, & Hellhammer, 2001; Buske-Kirschbaum, Jobst, & Hellhammer, 1998), and asthma (Buske-Kirschbaum et al., 2003), show decreased reactivity of their HPA axis (Priftis, Papadimitriou, Nicolaidou, & Chrousos, 2008). Studies of pediatric rheumatic diseases suggest a similar HPA axis deficiency coupled with other proinflammatory hormonal biases (Chikanza, Kuis, & Heijnen, 2000). Differences in NK cell stress reactivity and β-2-adrenoreceptor upregulation on *peripheral blood mononuclear cell* have been observed

in patients with systemic lupus erythematosus (Pawlak et al., 1999). A more complex role for sympathetic nervous system involvement in autoimmune disease has also been proposed (Kavelaars, de Jong-de Vos van Steenwijk, Kuis, & Heijnen, 1998; Kuis et al., 1996).

Glucocorticoid hormones may exert their protective immunosuppressive effects by inhibiting the production or actions of proinflammatory molecules as discussed previously. In addition, it has been hypothesized that glucocorticoids may suppress certain autoimmune reactions by inducing a shift toward a Th2 or humoral immune response (Chrousos, 2000; Elenkov, 2004; Elenkov & Chrousos, 2006; Mason et al., 1990; Mason, 1991). For example, stimulation of the HPA axis by inflammatory mediators released during the initiation of an autoimmune response results in increased plasma corticosterone. Increased corticosterone levels may shift the balance of the ongoing immune reaction from a TH1-directed (cell-mediated) response toward a TH2-directed (antibody-mediated) response, by promoting the production of IL-4 and suppressing the production of IL-2 (Danes & Araneo, 1989).

THE STRESS SPECTRUM

It is often overlooked that a stress response has salubrious adaptive effects in the short run (Dhabhar et al., 1995b; Dhabhar & McEwen, 1996, 1999, 2006; Dhabhar & Viswanathan, 2005; Dhabhar, 2008; Viswanathan & Dhabhar, 2005) although stress can be harmful when it is long lasting (Dhabhar & McEwen, 1997; Glaser & Kiecolt-Glaser, 2005; McEwen, 1998; Sapolsky, Romero, & Munck, 2000). To reconcile these seemingly contradictory effects of stress, we proposed that a stress response and its effects on immune function be viewed in the context of a *stress spectrum* (Dhabhar & McEwen, 1997, 2001) (Figure 4.2). One region of this spectrum is characterized by *acute stress* or *eustress*, that is, conditions of short-duration stress that may result in immunopreparatory, or immunoenhancing physiological conditions. An important characteristic of acute stress is a rapid physiological stress response mounted in the presence of the stressor, followed by a rapid shut-down of the response upon cessation of the stressor. The other region of the stress spectrum is characterized by *chronic stress* or *distress*, that is, repeated or prolonged stress that may result in dysregulation or suppression of immune function. An important characteristic of chronic stress is that the physiological response either persists long after the stressor has ceased, or is activated repeatedly to result in an overall integrated increase in exposure of the organism to stress hormones. The concept of "allostatic load" has been proposed to define the "psychophysiological wear and tear" that takes place while different biological systems work to stay within a range of equilibrium (allostasis) in response to demands placed by internal or external chronic stressors (for review see: McEwen, 1998, 2002). We suggest that conditions of high allostatic load would result in dysregulation or suppression of immune function. Importantly, a disruption of the circadian corticosterone/cortisol rhythm may be an indicator and/or mediator of distress or high allostatic load (Dhabhar & McEwen, 1997; Sephton et al., 2000). The Stress Spectrum also proposes that acute or chronic stress is generally superimposed on a psychophysiological health maintenance equilibrium (Figure 4.2). The extent and efficiency with which an organism returns to its health maintenance equilibrium after stress depends on resilience, which we define as reserve capacity of psychophysiological systems to recover from challenging conditions (Figure 4.2). Factors such as coping mechanisms, sense of control, optimism, social support, early life experiences, learning, genetics, and sleep may be important mediators of psychological resilience (Figure 4.2). Factors such as neuroendocrine reactivity, genetics, environment, nutrition, and sleep may be important mediators of physiological resilience (Figure 4.2). The psychophysiological basis of resilience (Charney, 2004) and reserve capacity are underinvestigated and provide an important opportunity for future research.

The Stress Spectrum, taken together with the preceding discussion, shows that *the duration, intensity/concentration, and timing of exposure to stressor-induced physiological activation (neurotransmitters, hormones, and their molecular, cellular, organ-level, and systemic effects) are critical for determining whether stress will enhance or suppress/dysregulate immune function*. The model shows that the stressor itself can be acute or chronic (Figure 4.2). Stress perception and processing by the brain and mechanisms mediating psychological and physiological resilience are critical for determining the duration and magnitude of the physiological stress response (Figure 4.2). Psychological resilience mechanisms are especially important in humans because they can limit the duration and magnitude of chronic stress responses. Psychogenic stressors are also very important in human subjects because they can generate stress responses long after stressor exposure (e.g., post-traumatic stress disorder following a severe traumatic experience, or in a milder form, lingering anger/mood disturbance following a social altercation) or even in the absence of a physical stressor or salient threat (e.g. worrying about whether one's romantic feelings will be reciprocated). Therefore, following stressor exposure and its processing by the brain, there ensues a *physiological stress response*. This response may consist of acute or chronic physiological activation (neurotransmitters, hormones, and their molecular, cellular, organ-level and systemic effects) which results in *psychophysiological states* that have different effects on overall health and immune function as shown in Figure 4.2. Although there is significant evidence from animal studies to support this model, it needs to be further examined in studies involving human subjects.

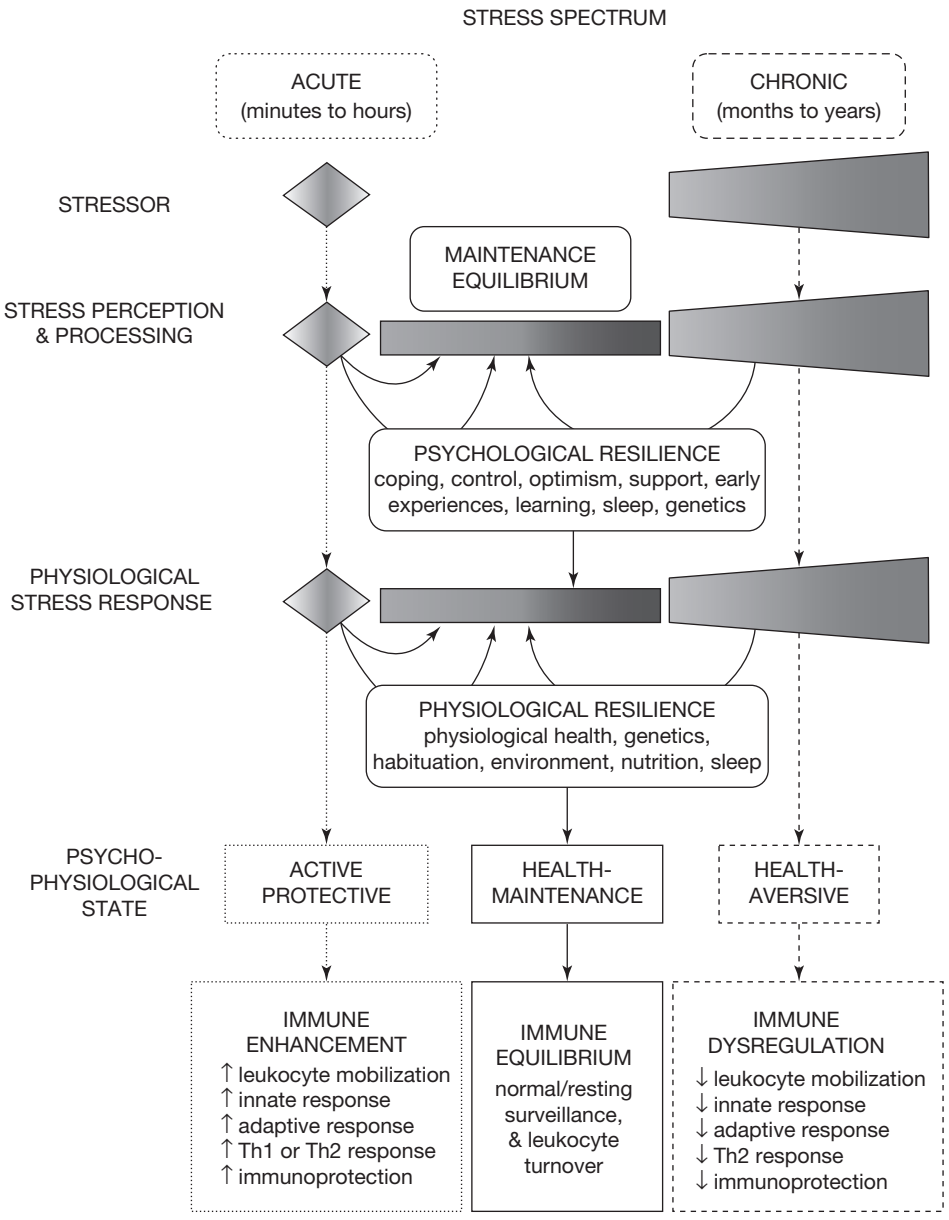

Figure 4.2 ■ The stress spectrum model. We have proposed a definition of stress as a constellation of events, consisting of a stimulus (stressor), that precipitates a reaction in the brain (stress perception & processing), that activates physiologic fight or flight systems in the body (physiological stress response) (Dhabhar & McEwen, 1997). The duration of a physiological stress response is the critical determinant of its effects on immune function and health. The stressor itself may be acute (e.g., narrowly missing being hit by a car) or chronic (e.g., caring for a chronically ill child, spouse, or parent). Stress perception and processing by the brain are critical for determining the duration and magnitude of the physiological stress response stimulated by any given stressor. Acute or chronic stress is generally superimposed on a psychophysiological health maintenance steady state. The extent and efficiency with which an organism returns to its health maintenance steady state after stress depends on resilience, which we define as the *capacity of psychological and interacting physiological systems to recover from challenging conditions*. Factors such as coping mechanisms, sense of control, optimism, social support, early life experiences, learning, genetics, and sleep are important mediators of psychological resilience. Factors such as neuroendocrine reactivity, genetics, environment, nutrition, and sleep are important mediators of physiological resilience. Psychological resilience mechanisms are especially important in humans because they can limit the duration and magnitude of chronic stress responses. By the same token, psychogenic stressors can be particularly detrimental in human subjects because they may generate stress responses long after stressor exposure or even in the absence of physical stressors or salient threats. The physiological stress response is the ultimate effector arm of the stress spectrum. It may consist of acute or chronic physiological activation (neurotransmitters, hormones, and their molecular, cellular, organ-level, and systemic effects) that results in psychophysiological states that have different effects on health. Acute stress generally results in activation of mechanisms that include enhancement of immune function while chronic stress results in health-aversive conditions that result in dysregulation or suppression of immune function. The molecular mechanisms mediating conversion from positive to negative effects of stress on immune function and health are slowly beginning to emerge, and merit further investigation. Reprinted from Dhabhar, F. S., & McEwen, B. S. (2006). Bidirectional effects of stress on immune function: Possible explanations for salubrious as well as harmful effects. In R. Ader (Ed.), *Psychoneuroimmunology IV*. San Diego: Elsevier. (*See color insert.*)

CONCLUSION

Stress has long been suspected to play a role in the etiology of many diseases, and numerous studies have shown that stress can be immunosuppressive and hence may be detrimental to health. Moreover, glucocorticoid stress hormones are widely regarded as being immunosuppressive, and are used clinically as anti-inflammatory agents. However, studies have shown that the acute stress response may play a critical adaptive and protective role, with stress hormones and neurotransmitters preparing the immune system for potential challenges (e.g., wounding or infection) that are perceived by the brain (e.g., the detection of predator or attacker) (Dhabhar & McEwen, 1997; Dhabhar et al., 1994; Dhabhar & McEwen, 1996; Dhabhar & Viswanathan, 2005; Viswanathan & Dhabhar, 2005). It may be useful to further study, and clinically harness, the acute stress response that evolution has finely sculpted to be one of nature's crucial survival mechanisms, at least as much as we study its maladaptive ramifications (chronic stress) that evolution yet has to catch up with.

This chapter illustrates that stress can either enhance or suppress immune function depending on the following factors: (1) The duration (acute versus chronic) of stress. (2) Changes in leukocyte distribution within the body, and the compartments in which the immune response occurs. (3) The concentration (physiological versus pharmacological), duration (acute versus chronic), and nature (endogenous versus synthetic) of glucocorticoid hormone exposure. (4) The timing of stress or stress hormone exposure relative to the stage (early versus late) of an immune response. Further elucidation of the interactions among the earlier mentioned factors and other nervous, endocrine, and genetic factors in mediating the effects of stress on immune function is necessary. Importantly, whether a stressor enhances or suppresses immune function, it is the end effect of the affected immune response that affects the health of the organism or individual. For example, stress-induced enhancement of immunoprotective responses is likely to be beneficial whereas stress-induced enhancement of immunopathology is harmful. These findings need to be explored and investigated further and translated from bench to bedside.

It is important to recognize that humans as well as animals experience stress as an intrinsic part of life, and in conjunction with many standard diagnostic, clinical, and experimental manipulations. Unintended stressors may significantly affect these measures and overall health outcomes. Thus, when conducting clinical, diagnostic, or experimental procedures, it may be important to account for the effects of stress on the specific physiological parameter or health outcome being measured. For example, it is critical to elucidate and account for the effects of stress and/or stress hormones on changes in leukocyte distribution within different body compartments. Where possible, redistribution needs to be monitored in terms of changes in absolute numbers of specific subpopulations of leukocytes. Stress-induced changes in immune cell numbers and/or function could significantly affect results (in case of experiments), diagnosis (in case of medical tests), or outcome (in case of treatment procedures and surgery).

Due to a host of psycho-socio-political factors, stress has unfortunately become an increasing and inevitable part of people's lives. Stress is also a major factor during diagnosis, treatment, and follow-up for most diseases. Chronic stress has been shown to dysregulate immune function and is thought to play a role in the etiology of many diseases. In contrast, it has been shown that activation of acute stress physiology may enhance protective immune responses (Dhabhar et al., 1995b; Dhabhar & McEwen, 1996; Dhabhar & Viswanathan, 2005; Viswanathan et al., 2005). We propose that it is important to further study and clinically harness the immunological effects of the acute stress response that evolution has finely sculpted as a survival mechanism, just as we study its maladaptive ramifications (chronic stress) with which evolution has yet to catch up with. A determination of the physiological mechanisms through which stress and stress hormones enhance or suppress immune responses is critically important for evaluating risk, developing preventative and therapeutic interventions, and optimizing a patient's response to treatment. The elucidation of such mechanisms would facilitate development of biomedical treatments designed to harness an individual's physiology to selectively enhance (during vaccination, wounding, infections, or cancer) or suppress (during autoimmune or inflammatory disorders) the immune response depending on what would be most beneficial for the patient.

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5 Behavioral, Emotional, and Cognitive Sequelae of Immune System Activation

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INTRODUCTION

Stress is commonly conceptualized from the perspective of psychogenic origins (discussed extensively in other chapters in the current volume). However, stress can also arise from changes in physiological states (termed systemic stress), particularly during immune system (IS) activation. This conceptualization arose within the field of psychoneuroimmunology (PNI), which investigates mind–body interactions through the meditational role of the IS. Although the term psychoneuroimmunology was coined by Robert Ader and first used in the context of a discussion of stress and conditioning research in his presidential address to the American Psychosomatic Society (Ader, 1980), the concept of neural-immune interactions has far earlier origins (Ader, 1981). Research in PNI has focused on the IS as a target of central nervous system (CNS) function, as well as the converse effects of immune activity on the brain. The historical perspective in which the CNS was viewed as an immune-privileged organ that operated independently of influences from the IS has been dismissed and replaced by a contemporary view in which the brain is a major target of various soluble and cellular products that emerge subsequent to activation of the IS. This targeting is ostensibly adaptive and useful for the organism, although as with any adaptive process there is potential for pathological "fallout," as exemplified by increasing interest in neuroinflammation in the context of psychiatric and neurodegenerative diseases (Ashdown et al., 2006; Griffin & Mrak, 2002; McGeer, Rogers, & McGeer, 1994; Wilke et al., 1996).

Briefly, some major lines of evidence for the so-called "immune-to-brain" pathway include: (i) immune products influence neurotransmitter activity (Muller & Ackenheil, 1998), (ii) cytokine receptors are found in the brain (Parnet, Kelley, Bluthe, & Dantzer, 2002), and (iii) many psychiatric disorders parallel autoimmune development and pathology (Muller & Ackenheil, 1998) (for a comprehensive review, see Besedovsky & del Rey, 1996). As we discuss further in the following text, a full understanding of this complex relationship has yet to be achieved and, in particular, the behavioral and affective sequelae of immune activation—especially in human subjects—have yet to be delineated. In what follows, we will endeavor to examine how immune activation serves as a systemic stressor to influence behavior and emotional states, and to specify what the implications of this activation are for mental and physical health.

IMMUNE SYSTEM–CNS INTERACTIONS

The following summaries are intended to provide the basic framework from which to conceptualize the effect of immune activation on behavior. For an extensive and detailed review of literature that cannot be covered here, consult Besedovsky and Rey (2007), Anisman, Merali, and Hayley (2008), and Dantzer et al. (2008). In addition, because there is copious evidence for the effect of the CNS on immune activity (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002), the present discussion will focus on how the IS acts as a systemic stressor to influence CNS function and behavior.

CNS RESPONSE TO IMMUNE CHALLENGE: SICKNESS BEHAVIOR

When an organism is exposed to a pathogen, the result is a constellation of physiological and behavioral manifestations, broadly recognized as sickness behavior (Hart, 1988). Sickness behavior is often characterized by hypophagia, hyperalgesia, lethargy, psychomotor retardation, anhedonia, and cognitive impairments, and is considered to be an adaptive response allowing the organism to focus its resources on recovery (Hart, 1988). This view has been expanded to construe sickness behavior as a manifestation of adaptive motivational states (Dantzer, 2004). However, when the activation of these systems is sustained, the burden may result in an increased vulnerability for developing other pathologies, such as depression (Anisman & Merali, 2003). Many of the symptom manifestations of sickness behavior parallel depression (i.e., lethargy, anhedonia, hypophagia) and anxiety (i.e., decreases in locomotor activity and in social interactions) (Anisman & Merali, 2003). As such, sickness behavior is one of the most useful and direct indicators of the effect of systemic stress on the CNS and of the various behavioral

sequelae that emerge from this CNS stimulation. Much of the focus on how the IS alters CNS function is concerned with cytokines, soluble mediators of immune cell activation, which result in a range of immunoregulatory effects, including proliferation and differentiation. Indeed, sickness behaviors can be readily elicited by administration of purified or recombinant cytokines, most notably those falling into the class of proinflammatory cytokines, which include interleukin-1β (IL-1β), IL-6, and tumor necrosis factor-α (TNFα) (Anisman, Merali, Poulter, & Hayley, 2005; Capuron, Ravaud, & Dantzer, 2000).

ANIMAL MODELS OF SYSTEMIC STRESS VIA IMMUNE CHALLENGE

Lipopolysaccharide

To create an analog of the effects of illness in humans and better elucidate the underlying physiological mechanisms of systemic stress, many animal models of immune challenge have been developed. For the most part, research has focused on bacterial toxins, the most popular being the endotoxins derived from the cell walls of the gram negative bacteria, *Escherichia coli (E. coli)*. Because of their chemical structure, these endotoxins are known as lipopolysaccharides (LPS), and the terms typically are used interchangeably in the literature (although "endotoxins" as a category of toxic molecules are integral to the cell membrane or other components of bacteria, as opposed to genetically encoded proteins that are synthesized and secreted, and are referred to as "exotoxins").

Challenge with LPS results in a wide range of immune-derived effects, particularly the development of sepsis-related symptoms (referred to as endotoxemia when induced by LPS). This includes the production of the proinflammatory cytokines IL-1β, IL-6, and TNFα (Besedovsky & del Rey, 1996; Dantzer, 2004; Oberbeck, Kromm, Exton, Schade, & Schedlowski, 2003), and is associated with many of the characteristic behavioral effects of sickness behavior, such as hypophagia, decreased locomotor activity, and fatigue or weakness (Dantzer, 2004). These behavioral effects of peripherally administered LPS are mediated by neural afferents, such as the vagus nerve (Dantzer et al., 1998), although humoral mechanisms exerting CNS effects through active transport of molecules across the blood–brain barrier have also been reported (Banks & Kastin, 1997; Kastin & Akerstrom, 1999).

Another prominent effect of LPS administration is anhedonia, which is also one of the key symptoms of depression (Anisman & Merali, 2002). Indeed, there is some evidence that LPS-induced anhedonia can be attenuated by antidepressant treatment (Yirmiya, 1996). However, this was observed only in rats and not mice (Dunn, Swiergiel, & de Beaurepaire, 2005), suggesting species specificity, as well as genetic influences, on anhedonia. Nonetheless, the observation of anhedonia and other behavioral changes that are associated with clinical depression (e.g., anorexia, cognitive impairment, lethargy) has led to the argument that the systemic stress of LPS exposure may be a useful animal model for studying the neurobiology of depression (Dunn et al., 2005).

Challenge with LPS has been used in behavioral conditioning models based on the behaviorally conditioned immunomodulation (BCI) paradigm developed by Ader and Cohen (Ader & Cohen, 1982). Initially, this involved classical conditioning of the IS using immunosuppressive drugs, such as cyclophosphamide. For example, this drug was used as an unconditioned stimulus in the taste aversion paradigm, in which a novel saccharine solution was used as a conditioning stimulus (CS). Pairing of the CS with cyclophosphamide led to a conditioned taste aversion, but also resulted in a conditioned diminution of the antibody response to sheep erythrocytes (Ader & Cohen, 1975). This phenomenon was replicated and extended to other nonappetitive conditioning paradigms and unconditioned stimuli. The latter came to include antigens, to which antibody responses could be conditioned, thereby demonstrating that when an immune response is induced by an antigen, this event is associated by the brain with environmental stimuli that serve as conditioned stimuli capable of re-enlisting and/or influencing immune responses (Ader, 2003). Although these studies involved benign, nonpathogenic protein antigens (e.g., keyhole limpet hemocyanin; ovalbumin), other studies have used LPS as an unconditioned stimulus. Repeated exposure to LPS can produce a loss of immunologic reactivity referred to as LPS (or endotoxin) tolerance. Using the conditioned taste aversion paradigm, investigators have found that after trained associations between a saccharine drinking solution and small doses of LPS, the saccharine solution alone was able to induce endotoxin tolerance, as evidenced by cessation of LPS-induced TNFα production (Oberbeck et al., 2003).

To summarize, LPS, which acts as a potent IS activator, has been associated with depression and contextual conditioning in animal models. As such, this model of systemic stress in many ways parallels the behavioral and affective consequences of psychogenic stress. Another powerful model of systemic stress is that of superantigen (SAg) exposure, which will be discussed in the following section.

Superantigens

The traditional notion of an immunological stimulus is that of an "antigen," defined as any substance that induces an immune response. In a stricter sense, antigens are short peptide sequences that are recognized by the internal groove of T cell receptors that possess clonal specificity for the antigenic peptide (also known as antigenic determinant or epitope). SAgs, in contrast, are a special class of molecules that belong to the group of exotoxins produced by *Staphylococcus aureus* and other

gram positive bacteria, as well as by viruses (Petersson, Forsberg, & Walse, 2004). The exotoxins of *S. aureus* are referred to as staphylococcal enterotoxins, and are responsible for food poisoning and toxic shock syndrome associated with septicemia. What distinguishes SAgs from regular antigens is their profound ability to stimulate multiple clones of T cells (i.e., T cells with varying specificity for antigenic peptides derived from foreign proteins), and to accomplish this independently of initial processing by antigen-presenting cells (e.g., dendritic cells or macrophages). However, the activation of T cells by SAgs is still carried out in association with either class I or II molecules of the major histocompatibility complex (MHC). Therefore, as for shorter peptide antigens, SAg T cell activation is said to be MHC dependent (Petersson et al., 2004; Zamoyska, 2006).

In recent years, there has been increased attention devoted to the neural and behavioral effects of bacterial SAgs, in particular the staphylococcal enterotoxins A and B (i.e., SEA and SEB). Administration of SEA and SEB to mice and rats results in activation of the hypothalamic–pituitary–adrenocortical (HPAC) axis (Del Rey, Kabiersch, Petzoldt, Randolf, & Besedovsky, 2000; Kusnecov & Goldfarb, 2005; Serrats & Sawchenko, 2006; Shurin et al., 1997), which is associated with increased activity of corticotropin-releasing hormone (CRH; aka CRF) (Kaneta & Kusnecov, 2005; Kusnecov, Liang, & Shurin, 1999; Rossi-George, Urbach, Colas, Goldfarb, & Kusnecov, 2005). The latter has been confirmed by studies in which CRH mRNA was measured in the paraventricular nucleus of the hypothalamus (Kusnecov et al., 1999), which is the primary source of neurosecretory cells accounting for stimulation of adrenocorticotropic hormone (ACTH) from the pituitary. Moreover, administration of CRH antagonists or antibodies attenuates the corticosterone and ACTH response to bacterial SAgs (Kusnecov et al., 1999; Rossi-George et al., 2005). Finally, determination of immediate early gene induction in the brain after administration of SEA or SEB has revealed extensive recruitment not only of hypothalamic, but also amygdaloid, septal, and hippocampal nuclei (Goehler et al., 2001; Rossi-George et al., 2005; Serrats & Sawchenko, 2006; Wang et al., 2004). Together with activation of the prefrontal cortex (Serrats & Sawchenko, 2006), it appears that challenge with these SAg systemic stressors results in widespread engagement of brain regions that form important circuits mediating motivational and emotional responses.

The neuronal and endocrine alterations consequent to the systemic stress of SAg exposure are associated with distinct behavioral changes. Of interest is the observation that doses of SEA or SEB known to activate the HPAC axis and increase the activity of neurons in limbic brain circuits are not associated with frank illness or malaise. For example, animals neither show major weight loss, nor display an avoidance of regular, familiar foods. However, when exposed to novel environments wherein they are also exposed to novel food, SAg-challenged animals display a significant reduction of food intake (Kusnecov & Goldfarb, 2005). In addition, if exposed to an open field wherein they are exposed to a novel, cylindrical object, there is increased avoidance of the novel object (Kawashima & Kusnecov, 2002). These behaviors have been interpreted as indicative of augmented anxiety-like reactions, although additional paradigms commonly used to assess anxiety in rodents (e.g., elevated plus maze) fail to reveal behavioral evidence of heightened fear. Although further behavioral analysis is still required, it was suggested that the neurobiological effects of SAg exposure may sensitize animals to heightened anxiety-like states if psychogenic stressors precede the systemic stress of immunological challenge (Rossi-George, LeBlanc, Kaneta, Urbach, & Kusnecov, 2004). At the very least, however, it does appear that behavioral changes observed in response to SEA or SEB challenge are unique to the particular behavioral tests used to reveal underlying CNS processing of the environment.

Because exposure to SEA or SEB produces elevated circulating levels of cytokines, it may be asked whether this cytokine response served as a mediating influence on the neural and behavioral changes that have been observed. This question was investigated by Rossi-George et al. (2005), who focused on the role of TNFα. Administration of this cytokine produces increased neuronal activation, corticosterone, and anorexic responses similar to those observed following SEA challenge (Hayley, Staines, Merali, & Anisman, 2001). Consistent with these effects, it was observed that TNF-deficient mice challenged with SEA failed to show activation of the HPAC axis, anorexia, and increased expression of the immediate early gene, c-fos, in the brain (Rossi-George et al., 2005). Moreover, in the same study, it was found that normal, wildtype mice administered antibodies to TNFα also showed attenuated anorexic and corticosterone responses. Therefore, it appears that, at least in response to an acute challenge with SEA, the observed neurobehavioral changes are dependent on TNFα. Whether this is the case with other bacterial SAgs remains to be determined.

Like LPS, the systemic stress of SAg exposure activates the HPAC axis and neural substrates associated with emotional, cognitive, and motivational states. However, this systemic stressor differs in that SAgs are not sufficient to produce outright sickness behavior, but instead require the additional element of novelty to elicit reduced food consumption and anxiety-like behaviors. These behaviors are cytokine-dependent, which leads to the next topic.

Cytokines

Activated immune cells synthesize and release cytokines. As discussed in the prior sections, induction of cytokines by immunopathogens can serve as a systemic stressor to induce sickness behaviors. Direct cytokine administration can exert the same effect. Furthermore, cytokines

have been shown to influence cognitive function (Dantzer, 2004). The presence of IL-1 receptors in the dentate gyrus of the hippocampus initiated investigations of the effects of proinflammatory cytokines on learning and memory (Dantzer, 2004). For the most part, IL-1 appears to impair performance on memory tasks such as the Morris water maze (Gibertini, Newton, Friedman, & Klein, 1995), contextual fear conditioning (Pugh, Fleshner, Watkins, Maier, & Rudy, 2001), and Pavlovian conditioning (Aubert, Vega, Dantzer, & Goodall, 1995). Repeated systemic administration of the cytokine IL-2 also impaired an aspect of Morris water maze performance involving working memory, suggesting that T cell-derived cytokines can also affect memory processes (Lacosta, Merali, & Anisman, 1999).

The ability of cytokines, such as IL-1 and IL-6, to produce depression-like symptoms may be linked to their ability to stimulate the release of CRH (Dunn et al., 2005; Juttler, Tarabin, & Schwaninger, 2002). However, cytokines also have direct effects on neurotransmitter levels (Anisman et al., 2005). IL-1β increases serotonin (5-HT) turnover in the hippocampus, prefrontal cortex, and hypothalamus, and increases norepinephrine (NE) turnover (Brebner, Hayley, Zacharko, Merali, & Anisman, 2000; Dunn, Wang, & Ando, 1999). Like IL-1β, TNFα administration in the paraventricular nucleus of the hypothalamus resulted in sensitization of NE activity (Hayley, Brebner, Lacosta, Merali, & Anisman, 1999), although this finding may be due to TNFα's stimulation of IL-1 production (Dunn et al., 2005). Although not as robust as the findings regarding IL-1 and TNFα, IL-2 administration also produces anhedonic effects (Anisman et al., 2005), which may be mediated by its inhibitory influence on dopamine (Anisman, Kokkinidis, & Merali, 1996). Moreover, the "depressogenic" effects of IL-1 and IL-6 administration can be attenuated by antidepressant treatment (Merali, Brennan, Brau, & Anisman, 2003).

In summary, there is ample evidence that the systemic stress of immune activation or treatment with cytokines produced by T lymphocytes and macrophages results in neuromodulation and emergent behavioral changes suggestive of a depressive-like profile. Most of this research has been carried out using animal models, but in the next section we address research that shows the applicability of the animal findings to humans.

HUMAN MODELS OF SYSTEMIC STRESS VIA IMMUNE CHALLENGE

Immunotherapy

The advent of immunotherapy to treat a host of diseases such as cancer, autoimmune disorders, and transplant rejection sheds further light on the psychological sequelae of the systemic stress of immune dysregulation. Cytokines (i.e., IFN, IL-2, TNFα, IL-6), or agents that directly have an effect on cytokines, are used in the treatment of immune-related disorders because of their potent immunomodulatory functions. Given that cytokines alter neuroendocrine and neurotransmitter levels (Anisman & Merali, 1999), it is likely that these effects serve as the basis for the neuropsychiatric complications often associated with cytokine-based immunotherapy (Anisman et al., 2005). Although the implication here is that elevated circulating levels of cytokines have a stressor-like effect on the CNS, reductions in cytokines may similarly be associated with stress-like effects. For example, decreasing IFNγ levels with the use of cyclosporin A has been associated with elevated levels of anxiety and depression in transplant patients (Kahan, Pellis, Leinikki, Yoshimura, & Schreiber, 1987). Conversely, treatment of chronic Hepatitis C virus with IFNα resulted in increased levels of IL-6, IL-8, and IL-10, and the elevated levels of IL-6 were further associated with heightened depression and anxiety 2–4 weeks after initiation of treatment (Bonaccorso et al., 2001). IFNα has direct influences on the serotonergic system, increasing 5-HT transporter mRNA (Morikawa, Sakai, Obara, & Saito, 1998), decreasing brain levels of 5-HT (Kamata, Higuchi, Yoshimoto, Yoshida, & Shimizu, 2000), and elevating 5-HT catabolism (Bonaccorso et al., 2001). Subsequent studies have revealed that the elevated depression scores associated with IFNα therapy were also negatively correlated with serum 5-HT levels (Bonaccorso et al., 2002; Capuron & Miller, 2004). Although it may seem that the somatic effects of treatment may be responsible for the affective manifestations, the two effects can be dissociated in that the somatic symptoms arise very early and wane whereas the mood-related changes generally appear later (Capuron, Hauser, Hinze-Selch, Miller, & Neveu, 2002) and are the only symptoms responsive to antidepressant treatment (Musselman et al., 2001). Yet, this depressogenic effect of IFNα treatment can be seen as early as 3 days after treatment, and appears to act synergistically with IL-2 to exaggerate these early effects (Capuron et al., 2000). Indeed, only in conjunction with IL-2 are the anxiogenic effects of IFN observed so early, although the majority of this effect can be attributed to heightened somatic symptoms observed as side effects of treatment itself (Capuron et al., 2000).

Psychological Sequelae of Immune-Related Disease States

As with psychogenic stressors, duration of systemic stress can have widely varying consequences for behavior and emotion. Given the constraints of chronic administration of immunomodulators in humans, examining immune-related disease states offers insight into the affective and behavioral sequelae of chronic systemic stress. That depression, anxiety, and other affective disorders are often comorbid with immune-related disease states (i.e., rheumatoid arthritis, multiple sclerosis, cancer) may indicate the extent to which immune dysregulation affects neurobiological and behavioral functions (Marques-Deak, Cizza, & Sternberg, 2005). For example, rheumatoid

arthritis has long been associated with major depressive disorder, and this association remains even when psychosocial and pain-related factors are taken into account (Marques-Deak et al., 2005). Multiple sclerosis is also associated with an increased prevalence of depression (Minden & Schiffer, 1990), and the disease state precedes affective abnormalities (Foley et al., 1992). However, it is not only overactivation of the IS that is associated with depressive symptomatology. Disease states characterized by loss of immune function, such as HIV infection, can also be linked to depression (Kopnisky, Stoff, & Rausch, 2004). This points to the likelihood that the emergence of systemic stress from *dysregulation* of the IS, rather than static elevation or inhibition, is the potential mediator of affective pathology.

Endotoxin Challenge

Though constrained by the ability to administer pathogenic doses in humans, limited work has been done investigating how *in vivo* endotoxin challenge affects human emotion and behavior. To maintain ethical standards, doses of LPS sufficient to induce cytokine production but not illness are used in humans. Cortisol-independent memory deficits and increased anxiety in healthy young men have been observed following endotoxin-induced cytokine activation (Reichenberg et al., 2001). IL-6 dose-dependent changes in declarative memory have also been found, with impaired declarative memory following a large increase in IL-6 and improved declarative memory subsequent to a small increase in this cytokine (Krabbe et al., 2005), indicating that alterations in memory performance are contingent upon robustness of the proinflammatory cytokine response. Memory alterations subsequent to endotoxin challenge are not confined to declarative memory. Consistent with Krabbe and colleagues (2005), Cohen and collaborators found that endotoxin-induced cytokine production caused a reduction in declarative memory; however, they found an unexpected *enhancement* in working memory (Cohen et al., 2003). From an evolutionary perspective, it may be that certain forms of memory (e.g., working memory) are more important for an organism's immediate survival during or after exposure to a systemic stressor. That is, facilitation of working memory during immune activation increases neural processing of relevant stimuli and the retention of this information for generating adaptive responses.

SUMMARY

Although more challenging from a mechanistic perspective than animal studies, examinations of the effect of systemic stress on human behavior, emotion, and cognition have revealed some intriguing insights. Psychiatric complications, especially anxious and depressive symptomatology, have been reported with immunotherapy. Elevated levels of anxiety and depression have been found with both lowered and enhanced levels of certain cytokines, highlighting the importance of cytokine specificity and general immune dysregulation in the effects of this systemic stressor. This latter point is further emphasized when considering the emotional consequences of immune-mediated disease states. Although immune-mediated disease states and immunotherapy have provided a convenient population from which to estimate the effect of the systemic stress of immune dysregulation on human behavior and emotion, they are limited by the fact that any associations can only be inferred. As such, to more directly assess the CNS consequences of immune activation, limited studies on the effect of endotoxin challenge in healthy humans have revealed elevated anxiety and memory alterations subsequent to LPS exposure. Interestingly, increases in the cytokine IL-6 produced enhancements in working memory and decrements in declarative memory, pointing to the potential adaptive nature of the cognitive response to this form of systemic stress.

PRESENCE OF CYTOKINE RECEPTORS IN THE CNS

Another line of evidence implicating IS activation in behavior and emotion, and thus potential effector pathways for systemic stress, is the presence of receptors for various cytokines in the brain. It has been reported that the hippocampus and hypothalamus show a high level of expression for cytokine receptors (Mehler & Kessler, 1997; Rothwell, Luheshi, & Toulmond, 1996). Specifically, IL-1 receptors have been found on neurons in the hippocampus (Besedovsky & del Rey, 1996) and hypothalamus, linking IL-1 to memory and neuroendocrine functions (Besedovsky & Rey, 2007). IL-2 receptors also have been localized to neurons, particularly in the hippocampus (Araujo, Lapchak, Collier, & Quirion, 1989). Although astrocytes and microglial cells are a major source of cytokines in the brain, and can express receptors for cytokines (see following text), IL-2 may directly affect neuronal function by binding to receptors on neurons (Shimojo et al., 1993).

Cell Specificity

Not only can the IS exert its effects on the CNS through active transport of peripheral cytokines into the CNS across the blood–brain barrier, but also, endogenous to the CNS itself, are immunocompetent cells—astrocytes and microglia (Sredni-Kenigsbuch, 2002; Xiao & Link, 1998). Activated microglia secrete IL-1, IL-2, IL-6, IL-10, and a small amount of TNFα, whereas activated astrocytes produce IL-1, IL-6, and TNFα (Muller & Ackenheil, 1998; Sredni-Kenigsbuch, 2002). Interestingly, the cell type that produces IL-6 is dictated according to stimulation, with TNFα and IL-1-stimulating astrocytes (Sawada, Suzumura, & Marunouchi, 1992) and granulocyte-colony

stimulating factor inducing microglia to secrete IL-6 (Muller & Ackenheil, 1998). Some reports even indicate that neurons themselves can produce IL-6 (Schobitz, Voorhuis, & De Kloet, 1992) and TNFα (Breder, Tsujimoto, Terano, Scott, & Saper, 1993; Gendron, Nestel, Lapp, & Baines, 1991).

Indeed various systemic and psychogenic stressors have been shown to produce activation of brain microglial cells (Long et al., 2007; Nair & Bonneau, 2006; Nair, Hunzeker, & Bonneau, 2007; Sugama, Fujita, Hashimoto, & Conti, 2007), and increased measures of IL-1 have been found in the brains of psychogenically stressed rats (Gibb, Hayley, Gandhi, Poulter, & Anisman, 2008; Maier, Nguyen, Deak, Milligan, & Watkins, 1999). Therefore, while microglial cells (and astrocytes) will produce cytokines in response to endotoxin (Zheng, Ryu, Kwon, Lee, & Suk, 2008), it appears that they are also reactive to changes in the internal neurochemical profile of the brain following stressor exposure. At present, it has not been determined whether these "neuroinflammatory" changes have behavioral effects that contribute to those already induced by stressors, or even whether the behavioral sequelae of psychogenic (and even systemic) stressor exposure are dependent on the presence of inflammatory mediators.

To review, evidence that cytokine receptors are found in neuroanatomical regions associated with memory and motivational responses (i.e., the hippocampus and hypothalamus, respectively) lends further evidence of the direct effect of systemic stressors on behavior, emotion, and cognition. Furthermore, the cells of the CNS themselves produce cytokines in response to both psychogenic and systemic stress. This reduction of systemic stress to the cellular level leads us to the next degree of physiological specificity: that of variation at the genetic level.

CYTOKINE GENE VARIATION AND MENTAL DISORDERS

The double-hit hypothesis (Warner & Schapira, 2003) asserts that genetic predisposition coupled with environmental insult may combine to make certain individuals much more highly susceptible to the development of disease. This is particularly relevant to the effects of variation in cytokine genes on vulnerability to immune dysregulation and potential neuropathological consequences upon exposure to a stressor. Kustova and colleagues (1998) examined the combined effects of genetic background (i.e., parental strain) and targeted IFNγ gene deletion on emotional behaviors in mice. In the "hardier" C57 strain, the targeted deletion of IFNγ had a much more noticeable effect, with dramatic changes in the expression of emotional behaviors, whereas the effect was much less obvious in the innately more emotional BALB strain, indicating the importance of examining single genetic changes in the context of overall genetic background (Kustova, Sei, Morse, & Basile, 1998).

A host of CNS disease states may be linked to immune activation, particularly to inflammation. Examining the underlying genetic variants that may influence the expression of cytokines has become one avenue by which to better elucidate the mechanisms by which cytokines exert stress-like effects in the CNS. Candidate gene studies use a solid theoretical foundation from which to postulate that certain polymorphisms may act as risk factors in the development and/or progression of certain disorders. Most such studies focus on functional polymorphisms, or those that influence protein production and/or function, to better ascertain their likely subtle effects. The following will give brief overviews of how cytokines are implicated in various CNS disorders and how gene variants may play a role in the cytokine-mediated pathology.

SCHIZOPHRENIA

Given the hypothesized link between maternal exposure to viruses and the development of schizophrenia in offspring, cytokines have been postulated to play a role in the etiology and pathogenesis of this disorder. Additionally, schizophrenia was once considered to be the result of either autoimmune mechanisms (Heath, Krupp, Byers, & Lijekvist, 1967) or dysregulated immune processes (Dameshek, 1930). Furthermore, that stress acts as a trigger for the manifestation of latent disease remains a popular etiological hypothesis (Yuii, Suzuki, & Kurachi, 2007). Proinflammatory cytokines, such as TNFα, IL-6, and IFNγ, have been the focus of investigation, as schizophrenic individuals frequently display elevated levels of these cytokines (Boin et al., 2001; Maes, Meltzer, & Bosmans, 1994; Naudin, Capo, Giusano, Mege, & Azorin, 1997). Interestingly, duration of illness has been related specifically to increased circulating levels of IL-6 (Monteleone, Fabrazzo, Tortorella, & Maj, 1997; Naudin et al., 1997). IL-2 has also received attention due to the consistent finding of elevated circulating levels of the IL-2 receptor in schizophrenic patients (Wilke et al., 1996; Yolken & Torrey, 1995), as well as the induction of psychotic symptoms by IL-2 administration (Denicoff et al., 1987). Neuroleptic medications used to treat schizophrenia have known effects on circulating levels of cytokines, acting to normalize elevated TNFα levels (Monteleone et al., 1997), lending further credence to the notion that schizophrenia possesses an immune component.

Considering the number of findings associating immune factors with schizophrenia, examining the relationship between functional polymorphisms and schizophrenia should provide a more direct link between cytokine levels and this form of psychopathology. Because the TNFα gene is located in a chromosomal region with potential linkage to schizophrenia (Schwab et al., 2000), TNFα polymorphisms have received a great deal of attention. Numerous functional single nucleotide polymorphisms (SNPs) in the promoter region of the TNFα gene have been identified, which may be linked to

schizophrenia. The TNF2 allele (-308A), associated with a sevenfold increase in TNFα production (Wilson, Symons, McDowell, McDevitt, & Duff, 1997), has been observed with increased frequency in schizophrenic samples relative to healthy controls (Boin et al., 2001; Meira-Lima et al., 2003; Saviouk, Chow, Bassett, & Brzustowicz, 2005). Furthermore, Boin and colleagues (Boin et al., 2001) found TNF2 homozygosity exclusively in the patient sample. However, this relationship is inconsistent, with some studies finding no association (Hashimoto et al., 2004; Tsai, Hong, Yu, Lin, & Liu, 2003) and others the reverse association (Schwab et al., 2003). In a Finnish sample (Hanninen et al., 2005) and a Chinese sample (Tan et al., 2003), the more common TNF1 allele was associated with chronic schizophrenia, whereas other TNFα SNPs showed no distribution differences between patients and controls (Tan et al., 2003). As each of these samples were taken from disparate regions, it is possible that population-specific genetic factors are in linkage disequilibrium with the TNFα polymorphisms, that epigenetic factors may be influencing the nature of the relationship, or that overall genetic background may influence the effect of these polymorphisms on schizophrenia. Indeed, upon examination of two IL-1-related polymorphisms (IL-1b -511C/T and IL-1RA VNTR) in relation to schizophrenia, the protective effect of each was only evident when both were considered together (Zanardini et al., 2003). This highlights the importance of considering the effects of multiple interacting polymorphisms on a complex phenotype such as schizophrenia. Another potential explanation for discrepant findings is the differences in clinical manifestation of schizophrenia (i.e., negative versus positive symptomatology, severity of symptoms, responsiveness to medications, classes of medications being utilized). By specifying narrower criteria, it may be more feasible to detect the subtle influences of candidate genes.

ALZHEIMER'S DISEASE

Like schizophrenia, Alzheimer's Disease (AD) is also thought to have a critical inflammatory component. While Amyloid Precursor Protein (APP), Presenilin 1 and 2 (PSEN1 and 2), and Apolipoprotein E (APOE) genes have received considerable attention for their association with AD, these genes only represent less than 30% of the overall genetic risk variance associated with this degenerative disease (Tanzi & Bertram, 2001). As such, investigators have begun to explore less conventional paths in understanding the pathophysiology of AD, and many have pursued the role cytokines and cytokine genes may play in its pathogenesis. This stems from the evidence that numerous proinflammatory cytokines (i.e., IL-1α and β, IL-6, and TNFα) show elevated expression profiles in AD (McGeer et al., 1994), and microglia express APP (Xiao & Link, 1998). The two isoforms of IL-1 (α and β), in particular, have been studied in relation to AD predisposition and pathology due to elevated expression in AD CNS tissue (Sheng et al., 2001), which is related to progression of pathology (Griffin et al., 1989). Also, IL-1 may induce the cell injury cascade of AD by stimulating AD-specific pathways (Griffin & Mrak, 2002).

When examining how variation at the gene level in IL-1 may influence AD risk, both the IL-1α -889T allele and IL-1β +3954T allele have consistently been implicated (Griffin & Mrak, 2002; Hedley et al., 2002; Nicoll et al., 2000), and the IL-1α -889T allele acts in a dose-dependent manner with two copies of the T allele doubling the risk of AD (Combarros, Sanchez-Guerra, Infante, Llorca, & Berciano, 2002). Indeed, individuals homozygous at both IL-1 alleles display a tenfold increased risk of AD development (Nicoll et al., 2000). Furthermore, IL-1α -889T/T is associated with earlier age of onset (Grimaldi et al., 2000).

Evidence also implicates IL-6 in the pathogenesis of AD, as it has been shown to stimulate APP production in microglia (Royston, Rothwell, & Roberts, 1992). In addition, IL-6 is consistently elevated in the cerebrospinal fluid of AD patients (Blum-Degen et al., 1995), and neuropathological AD symptoms follow the appearance of IL-6 within amyloid plaques (Sredni-Kenigsbuch, 2002). With findings consistently linking IL-6 levels to AD, researchers then sought to determine whether variation in the IL-6 gene correlated with disease. Results of such endeavors have been contradictory. A sample of Japanese AD cases revealed an association between the Il-6 -174G allele and elevated IL-6 levels and risk for AD (Shibata et al., 2002), whereas another study demonstrated the opposite relationship of -174C allele overexpression in AD patients, particularly that women homozygous for the C substitution were at greatest risk of AD (Licastro et al., 2003). Further, when considering an additional polymorphism, the IL-6 VNTR, presence of the D allele, which was in linkage disequilibrium with -174C, elevated the risk for AD, whereas the VNTR C allele conferred protection (Licastro et al., 2003). Yet another study found no relationship between the -174 polymorphism and AD, neither as a risk factor nor in association with certain symptoms (Zhang et al., 2004). The same factors are likely at play for IL-6 and AD as for TNFα and schizophrenia when attempting to reconcile these disparate findings. Although further research is required to determine precisely which IL-6 allelic variations are linked with AD, there is a good deal of encouraging evidence to suggest that this may be a promising avenue of research.

Given TNFα's role in inflammation and the finding of TNFα overexpression in AD, researchers have pursued the relationship between polymorphisms in this gene and AD. Two functional polymorphisms in the promoter region (-308G/A and -238G/A) have been the focus of this attention, as the -308A allele increases transcriptional activity (Wilson et al., 1997), whereas the -238A allele decreases transcriptional activity (Kaluza et al., 2000). Although neither of these alleles were found more predominantly in patients, when compared with controls,

there has been an association of the –308A allele with earlier onset of AD (Alvarez et al., 2002). In another study, although none of the TNFα polymorphisms acted as risk factors for AD independently, when considering the combined effects of the polymorphisms, the absence of the -308A, -238G, and TNFα2 haplotype was associated with AD (Culpan et al., 2003). This appears to imply that this haplotype (or combination of genetic variants) acts in a protective fashion against the development of AD (Culpan et al., 2003). These IL-1, IL-6, and TNFα findings all exemplify the importance of examining not just one polymorphism in isolation, but the overall effects of multiple polymorphisms.

DEPRESSION

Given that proinflammatory cytokines produce depressive-like behavioral changes (see above), it has been suggested that depression may have an immunologically driven component. Numerous studies have found elevated levels of cytokines and/or their soluble receptors (i.e., IL-2, sIL-2R, IL-1β, IL-6, sIL-6R, IFNγ) in depressed patients (Maes et al., 1995a; Maes et al., 1995b; Maes, 1999). IL-6 has been identified as a key cytokine candidate in the etiopathology of depression due to the elevated levels of both the cytokine (Zorrilla et al., 2001) and its soluble receptor (sIL-6R) in the serum of patients with major depression (Maes et al., 1993a; Maes et al., 1993b). Furthermore, the inverse correlation between plasma IL-6 and tryptophan in depressed individuals also implicates IL-6 in the manifestation of depressive symptomatology (Maes et al., 1993b). In addition, it has been found that baseline levels of plasma IL-6 predicted greater depressive symptomatology in patients recovering from myocardial infarction (Hekler et al., 2007).

IL-1β has also received attention for possible associations with depression, and although results have been inconsistent (Brambilla & Maggioni, 1998; Owen, Eccleston, Ferrier, & Young, 2001), one study showed a positive correlation between increases in IL-1β and severity of depression (Levine et al., 1999). Examination of a panel of IL-1-related polymorphisms in relation to dysthymia, a less severe form of depression, found a certain haplotype (IL-RA2, IL-1α -889T, IL-1β -511C) with greater frequency in dysthymic patients (Fertuzinhos et al., 2004). IL-1β has been associated with symptoms more consistent with atypical depression, whereas the IL-2 response appears to be more aligned with motivational aspects (Anisman et al., 2005). Hence, it seems that different cytokines may mediate different subtypes of depressive states (Anisman et al., 2005).

Given the popular 5-HT dysregulation hypothesis of depression, it is important to consider that if cytokines play a role in the etiology and/or pathology of depression, their interaction with serotonergic systems should be investigated. Instead of the anticipated negative effect of cytokines on 5-HT availability, most research has pointed toward IL-1, TNFα, and IL-6 actually *increasing* 5-HT availability (Dunn et al., 2005). However, the -308A TNFα polymorphism has been linked to Major Depressive Disorder (Jun et al., 2003). Also, IFNα and IFNγ have excitatory influence on the serotonin transporter, which could effectively reduce synaptic availability of 5-HT (Morikawa et al., 1998). The reasons for these discrepancies could be multifold: (i) cytokines do not play a role in depression (unlikely, due to all the evidence implicating cytokines, at least partly, in depression), (ii) acute versus chronic administration of cytokines could have differential effects on 5-HT activity (a possibility, but one that has not been extensively investigated [Dunn *et al*., 2005]), (iii) serotonin's role in depression may be misunderstood, (iv) cytokine and cytokine polymorphism profiles (and not single cytokines/polymorphisms) could influence the varying clinical presentations of depression. For the most part, the last explanation appears to be the most parsimonious.

SUMMARY

With respect to understanding the likely subtle influence of individual cytokine polymorphisms on systemic stress and ultimately affective states, traits, and disorders, it would be more useful to consider an interactive cytokine pattern or "cytokine footprint." Cytokines do not exert their effects in isolation from other cytokines, neurotransmitters, and peptides. Instead, they form a complex pattern of synergism, inhibition, potentiation, and/or stimulation and must be considered thusly. A strong theoretical and empirical foundation must be established from which to select the "cytokine footprint" and thus the subsequent polymorphisms. Only by linking genetic polymorphisms to protein expression/function, then to cellular activity and interactions, and finally to behavior and cognition can we truly begin to test and understand the complex interactions between the underlying factors contributing to systemic stress susceptibility and neuropathology.

CONCLUSIONS

Just as stressors of a psychological nature can induce sleep and memory alterations, hypophagia, anxiety, and anhedonia, so too can systemic stressors arising from immunological activation. Both the animal and human literature supports the notion that immunological activation, as a systemic stressor, can influence memory, depression, and CNS disease states. Also similar to psychogenic stress, whether systemic stress disrupts homeostasis and psychological well-being is contingent upon individual variation. The genetic literature points to ethnic background, constellations of interplaying genetic polymorphisms, background biological status, and likely epigenetics (an emerging field examining the effect of

factors such as diet, toxin exposure, and exercise on gene expression) all contributing to the predisposition for systemic stress to result in pathology. Another important aspect to consider is that psychogenic and systemic forms of stress are likely to co-occur, making the understanding of the individual and combined dynamics crucial to the well-being of an organism.

The most transparent application of these findings is in the psychiatric and medical clinics. It is universally acknowledged that chronic illness is often accompanied by psychological distress arising from a number of factors including but not limited to fear, symptoms, disruptions in daily life, and disease management difficulties. However, the added burden of systemic stress is rarely, if ever, considered. It is possible that the superimposition of systemic stress onto psychogenic stress could push the homeostatic threshold toward behavioral, cognitive, and/or emotional pathology. Thus, when designing treatment and management strategies for chronic illnesses, particularly those that are immune-mediated, it would be prudent to consider the dual roles of psychogenic and systemic stress. Likewise, it is possible that systemic stress may be an underlying but overlooked factor contributing to the emergence of mental illness. By thoroughly investigating this potential pathway, novel immune-targeted interventions could be designed that may, alone or in combination with standard regimens, more effectively treat such disorders. Although much intriguing work remains to be conducted, a wealth of findings support the notion that immunological activation is equally influential as psychogenic stress on behavioral, cognitive, and emotional well-being.

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6 Genetic Epidemiology of Stress and Gene by Stress Interaction

Jeanne M. McCaffery

INTRODUCTION

Psychological stress has become a critical environmental exposure in the search for genes that modify the impact of the environment or gene × environment interaction. Although the idea that psychological stress may amplify genetic risk is not new, heightened interest in this topic followed two studies by Caspi and colleagues in 2002 and 2003. The first reported that the risk of conduct disorder and antisocial traits varied by a polymorphism in the promoter region of the monoamine oxidase A (*MAOA*) gene and degree of childhood maltreatment (Caspi et al., 2002). In the second, the impact of childhood maltreatment and stressful life events (SLE) on depression in young adulthood differed by genotype at an insertion/deletion polymorphism upstream from the serotonin transporter gene (Caspi et al., 2003). The extent to which such gene × environment interaction findings will withstand the test of replication remains a subject of controversy (Kim-Cohen et al., 2006; Munafo, Durrant, Lewis, & Flint, 2009; Risch et al., 2009; Uher & McGuffin, 2008), but they nonetheless point to the experience of psychological stress as a potential factor in the path from genetic vulnerability to disease outcome.

THEORETICAL MODEL OF THE ROLE OF GENETICS IN STRESS

In a formative model developed by Lazarus and Folkman, psychological stress was defined as "a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being" (p. 19; Lazarus & Folkman, 1984). In this context, stress was conceptualized as multilevel process, involving antecedents, intervening psychological processes, and outcomes. The antecedents included characteristics of the environment, such as situation demands of a stressor, as well as person variables, such as personality and resources available to the person. Psychological processes were conceptualized as primary appraisal of the threat posed by the environment and secondary appraisal of the ability to cope with the threat and assessment of social support. The outcomes consisted of immediate outcomes, such as acute positive or negative feelings and physiological changes, and more distal outcomes, such as physical and mental illness.

Lazarus and Folkman (1984) hypothesized that genetic factors could influence the process of stress. Specifically, they argued that the impact of stress on physiological responses to environmental demands and vulnerability to chronic physical illness could vary based on genetic background, a form of gene × stressor interaction. The work of Lazarus and colleagues was also critical in defining the role of person processes in stress reactions. Indeed, Lazarus espoused defining stress in terms of transactions between the person and the environment (Lazarus, 1966). Many of the person characteristics hypothesized to contribute to the stress process in these models have now been demonstrated to show genetic influence, or heritability, in twin studies. To take a few examples, personality traits (Ebstein, Benjamin, & Belmaker, 2003), coping style (Kato & Pedersen, 2005), and perceived social support (Kendler, 1997; Raynor, Pogue-Geile, Kamarck, McCaffery, & Manuck, 2002) are each heritable when examined among twins. To the extent that the effects of environment vary in impact based on heritable person characteristics, it suggests that gene × environment interaction may play a role. As we limit the environments of interest to stressors and recognize that the occurrence of stressors may be influenced by both genetic and environmental factors, we will use the term *gene × stressor interaction* to describe effects of stress that vary by genetic vulnerability.

Heritable person processes may also impact stress by influencing the likelihood of encountering a stressor. It is well known that individuals play an active role in shaping their environment (Plomin, DeFries, & Loehlin, 1977). To the extent that exposure to stressors is heritable or correlated with genetic markers, it implies that heritable person characteristics are involved in selecting environments that increase likelihood of stress exposure (Kendler & Baker, 2007). For example, a person who scores high on novelty seeking may be more likely to choose race car driving as a hobby than those who score lower on measures of novelty seeking. As driving at high speeds increases the likelihood of motor vehicle

accidents and physical injury, this scenario would serve as an example of how heritable person characteristics can increase risk for stressful or even traumatic events. The association between genetic factors and the environment has been labeled gene × environment correlation (Plomin et al., 1977). As this chapter limits environmental exposures to those that have been defined as "stressors," we will use the term *gene × stressor correlation* to describe genetic effects on exposure to stressors.

Figure 6.1 presents the components of the stress process, as adapted from Lazarus and Folkman (1984). The shaded boxes represent aspects of the stress response that may be influenced by genetic factors, either based on the original conceptualization described in Lazarus and Folkman (1984), or added based on more recent twin or molecular genetic data supporting genetic influences on the component constructs. Within this model, we hypothesize that person variables are a primary contributor to the heritability of environmental demands (gene-stressor correlation). Thus, the antecedent person variables are labeled with potential genetic influence, whereas environmental demands are not. Once an environmental demand is encountered, the impact of the environmental demand may be altered by the heritable mediating processes, or genetic vulnerability to short- or long-term outcomes, suggesting gene × stressor interaction. Thus, we argue that both gene × stressor correlation and gene × stress interaction must be taken into consideration to fully encompass the potential role of genetics in the stress process. Further, we expand earlier conceptualizations of the role of genetics in the stress process to explicitly include the impact of heritable psychological characteristics, such as personality, coping style, and ability to engender social support, in addition to the heritable physical characteristics, such as genetic vulnerability to a disease state.

Two general approaches have been taken to understand the role of genetics in stress. The first involves estimating a heritability coefficient, or the percentage of trait variance in a population attributable to genetic factors. These research designs infer the degree of genetic influence by comparing the degree of similarity among family members, often twins, and do not necessarily include measures of genetic material, or DNA. The second approach, the candidate gene study, tests whether a particular genetic marker and an outcome of interest co-occur above chance level, given the frequency of the allele and the distribution of the outcome in the population (Cordell & Clayton, 2005). The selection of genes is most often based on the biological function of the gene. Variants within the genes are prioritized by apparent significance for gene function or location within in a region most likely to affect gene function (coding, promoter, or splice regions). These typically include single nucleotide polymorphisms (SNPs), variable number tandem repeats, or insertion/deletion polymorphisms. For a more detailed review of twin and candidate gene study methodology, please see McCaffery, Snieder, Dong, and de Geus (2007). We will highlight examples of twin and family studies and candidate gene studies supporting the role of genetic factors in the experience of stress and gene × stress interaction.

EMPIRICAL STUDIES

Gene × Stressor Correlation

The preponderance of evidence for gene × stressor correlation is derived from studies using self-report of SLE and/or exposure to trauma. We will review these as examples of how genetic factors may influence the likelihood of encountering a stressor.

Stressful Life Events

Twin and family studies indicate that the total number of SLEs experienced is moderately heritable. Using a weighted mean across existing studies, Kendler and Baker (2007) reported a small to moderate heritability for the total number of life events reported. Not surprisingly, the heritability is greater for SLEs that are highly dependent on the individual, such as getting married or getting divorced, than life events that are more independent of the individual, such as a serious illness or death of a family member. Although most of the prior studies have focused on major life events, it is interesting to note that

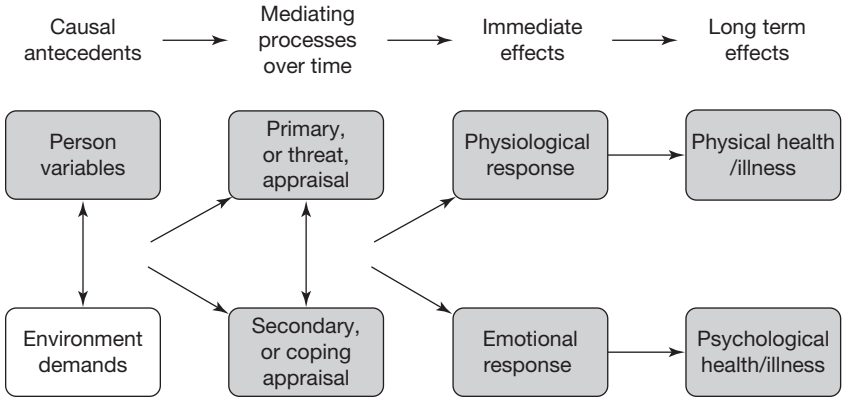

Figure 6.1 ■ Theoretical mode of the role of genetics in the stress response based on the models of the stress process. Shaded boxes reflect putative components of the stress process in which genetic factors may play a role. Stress model adapted from Lazarus and Folkman (1984).

at least one twin study found genetic effects on the number and severity of daily stressors (Charles & Almeida, 2007), suggesting that both major life events and the number and severity of stressor encountered in a day show genetic influence.

For genetic factors to influence exposure to an SLE, they likely contribute to variability in a psychological or behavioral trait that influences the probability of exposure to a stressful life circumstance. As personality characteristics are strongly heritable and can influence the selection of environments, they have been evaluated as contributing to the likelihood of SLEs. Neuroticism has been shown to predict the likelihood of an SLE (Kendler, Gardner, & Prescott, 2003) and more negative life events (Magnus, Diener, Fujita, & Pavot, 1993), while extraversion appears to predict positive life events (Magnus et al., 1993). Overall, it is clear that individuals can influence their likelihood of exposure to SLEs, in particular those life events in which the individuals can play a direct role.

Exposure to Trauma

One of the critical contributions of twin research to the study of post traumatic stress disorder (PTSD) is the documentation of genetic influences on exposure to trauma. The first twin study to examine twin concordance for exposure to trauma was conducted in the Vietnam-era Twin Registry. Lyons and colleagues (1993) reported that male identical twins were more likely to be concordant for volunteering for service and for service in South East Asia during the Vietnam War than male fraternal twins. Further, in twin pairs in which both twins served in South East Asia, self-reported combat experiences were also heritable. A follow-up paper identified pre-existing conduct disorder and substance abuse as psychological predictors of exposure to trauma in the Vietnam-era Twin Registry (Koenen et al., 2002), pointing to pre-existing psychopathology as an individual characteristic that may increase risk for trauma exposure.

A second twin study examined the heritability of noncombat trauma in a predominantly female sample (Stein, Jang, Taylor, Vernon, & Livesley, 2002). Exposure to an assaultive trauma was influenced by both genetic and familial environmental factors, while nonassaultive traumas (e.g., motor vehicle accidents and natural disasters) showed almost no genetic influence. Jang, Stein, Taylor, Asmundson, and Livesley (2003) demonstrated that personality factors, predominantly reflecting antisocial traits, accounted for a significant proportion of the genetic variance in assaultive trauma in this sample. Similar to the literature on SLEs, twin studies of trauma exposure strongly indicate that certain types of trauma are indeed influenced by genetic factors and that the genetic influences on trauma exposure may reflect personality characteristics and/or psychopathology that impact the likelihood of being in an environment in which a traumatic event may occur.

GENE × STRESSOR INTERACTION

Once the stressor is encountered, genetic influence on the response to the stressor reflects gene × stressor interaction. We will review genetic predictors of acute emotional and physiological response to stress as well as long-term physical and mental health outcomes as examples of gene × stressor interaction.

EMOTIONAL REACTIVITY TO STRESSORS

Only a few studies have assessed potential interaction of genetic vulnerability with stress in predicting acute emotional response. Furmark and colleagues (2004) examined the association of the insertion/deletion polymorphism upstream of the serotonin transporter gene, or the serotonin transporter linked polymorphic region (5-HTTLPR) with subjective measures of anxiety and amygdala activation in response to public speaking among patients with social phobia. Those who carried at least one copy of the s allele reported greater anxiety and showed greater activation in the right amygdala than l/l homozygotes. Gunthert and colleagues (2007) examined the extent to which variation at 5-HTTLPR moderated the association between severity of daily stress and mood at two time points. They used the tri-allelic version of this marker, in which an SNP within the "l," or long allele results in a version of the l allele that is functionally similar to the s allele (Wendland, Martin, Kruse, Lesch, & Murphy, 2006). Results indicated that genotype moderated the impact of daily stress on evening anxiety, and to a lesser extent hostility and depression. In each case, those carrying at least one copy of the s allele or the functionally similar l_G allele showed greater emotional reactivity on high stress days, whereas little difference by genotype was seen on low stress days. In a third study, perceived stress was reported to be greater among cardiac patients among s allele carriers, relative to those with l/l genotypes (Otte, McCaffery, Ali, & Whooley, 2007). Finally, although not formally a stressor per se, it is notable that carriers of the s allele appear to show greater amygdala reactivity to the presentation of pictures of fearful and angry faces, suggesting a potential bias among s allele carriers to show a greater response to negative emotional stimuli (Hariri et al., 2002; Munafo, Brown, & Hariri, 2008). This handful of studies suggest that genetic factors, in particular 5-HTTLPR, may influence acute emotional response to psychological stress.

CARDIOVASCULAR REACTIVITY TO STRESSORS

The majority of previous twin studies of cardiovascular reactivity to stressors have been consistent in finding significant genetic variation (Hewitt & Turner, 1995; Turner & Hewitt, 1992). For example, moderate to strong estimates of heritability were reported for heart rate (HR; heritability range: 0.30–0.90) (Carmelli et al.,

1991; Carroll, Hewitt, Last, Turner, & Sims, 1985; Ditto, 1993; McCaffery, Pogue-Geile, Ferrell, Petro, & Manuck, 2002; Shapiro, Nicotero, Sapira, & Scheib, 1968; Theorell, de Faire, Schalling, Adamson, & Askevold, 1979; Turner, Carroll, Sims, Hewitt, & Kelly, 1986) and blood pressure responses (heritability range: 0.20–0.80) (Carmelli, Chesney, Ward, & Rosenman, 1985; Carmelli et al., 1991; McCaffery et al., 2002; Shapiro et al., 1968; Smith et al., 1987) to laboratory-based psychological stressors. Nonetheless, caution in interpretation of these results is clearly warranted as studies vary widely in sample composition, sample size, and the nature of the challenges (Snieder, van Doornen, & Boomsma, 1995).

In an elegant application of twin models, De Geus, Kupper, Boomsma, and Snieder (2007) determined whether psychological stress elicited differential heritability of cardiovascular parameters relative to baseline in adolescent and middle-aged twins. Results indicated that the same genes influence both resting and stress levels of systolic blood pressure (SBP), diastolic blood pressure (DBP) and HR in adolescents, and SBP in middle age, but that stress augments the effect of these genes (gene × stressor interaction). In addition to the augmentation effect, novel genes appeared to impact stress HR and stress SBP in adolescents that do not impact the respective cardiovascular parameters at rest.

Variation in genes that code for adrenergic receptors has been investigated as a predictor of cardiovascular responsivity. Two SNPs that appear to impact gene function, the G allele of a C → G SNP at base pair (bp) 1165 in *ADRB1* and the G allele of an A → G substitution at bp 46 in *ADRB2*, were consistently related to increased resting SBP and DBP, respectively (McCaffery et al., 2002). The variant at bp 1165 in *ADRB1* also predicted elevated DBP responses to psychological stress. However, the A allele at bp 46 in *ADRB2* was associated with baseline SBP and DBP and heightened DBP responses to mental and physical stress in a second study (Li et al., 2001).

The serotonin transporter gene-linked polymorphic region (5-HTTLPR) has also been studied in relation to cardiovascular reactivity. In a first study, individuals carrying two copies of the short (s) allele showed blunted HR and blood pressure elevations in response to an anger challenge (Williams et al., 2001). A similar result was recently reported in a larger sample (Williams et al., 2008). However, in a third study (McCaffery, Bleil, Pogue-Geile, Ferrell, & Manuck, 2003), the main effect of genotype was in the opposite direction and qualified by a sex interaction. Females with an s/s genotype exhibited substantially larger HR responses combined across a Stroop and mental arithmetic task than males of the same genotype and females carrying at least one long (l) allele. Thus, initial studies of specific genetic markers from plausible biological candidate genes have yielded inconsistent results in relation to cardiovascular response to acute psychological stress despite a consistent body of twin studies documenting heritability.

CORTISOL RESPONSIVITY TO STRESSORS

A lesser number of investigations have used twin methods to examine genetic variation in HPA phenotypes. Nonetheless, basal levels of cortisol appear heritable when aggregated across multiple measurements in the morning (Bartels, de Geus, Kirschbaum, Sluyter, & Boomsma, 2003; Meikle, Stringham, Woodward, & Bishop, 1988) and late afternoon (Bartels et al., 2003; Kirschbaum, Wust, Faig, & Hellhammer, 1992). In addition, it has been shown that the free cortisol response to morning awakening (Kupper et al., 2005; Wust, Federenko, Hellhammer, & Kirschbaum, 2000), cortisol response to corticotropin-releasing hormone (Kirschbaum et al., 1992), and cortisol responses to psychological stress, particularly in familiar low anxiety contexts (Federenko, Nagamine, Hellhammer, Wadhwa, & Wust, 2004) are each significantly heritable. In the HERITAGE family study, significant familial effects were found on the correlations between cortisol and measures of abdominal fat and overall body adiposity (Feitosa et al., 2002). Lastly, one recent study suggested gene × familial adversity interaction in predicting cortisol response to novel situations among 19-month-old twins (Ouellet-Morin et al., 2008). In families marked by high degrees of adversity, environmental factors accounted for twin similarities in cortisol response levels, whereas in families with lesser degrees of adversity, twin similarities were accounted for entirely by genetic effects.

Molecular genetic studies of HPA function have focused primarily on the gene that codes for the glucocorticoid receptor (*GRL*). Early studies focused on an SNP (alleles labeled 4.5 and 2.3 kilobases, corresponding to G and C, respectively) within *GRL* revealed by the restriction enzyme BclI (Murray, Smith, Ardinger, & Weinberger, 1987). It has been reported that the G allele at this site predicts body mass index, waist-to-hip ratio, and salivary cortisol (Rosmond et al., 2000) and diminished cortisol response to stress (Wust et al., 2004). Several other polymorphisms have been reported in *GRL* (Bray & Cotton, 2003). In one study, no association was found between five of these variants and responsivity to a dexamethasone suppression test (Koper et al., 1997). Nonetheless, one site, an A → G substitution causing an amino acid change from asparagine to serine at codon 363 (Asp363Ser), has been associated with cortisol response to psychological stress (Wust et al., 2004) and cortisol suppression to a dexamethasone test (Huizenga et al., 1998). No association between variation at Asp363Ser and sensitivity to glucocorticoids was observed in another investigation (Rosmond, Bouchard, & Bjorntorp, 2001).

Variation within the serotonin transporter gene has also been shown to predict cortisol (Gotlib, Joormann, Minor, & Hallmayer, 2008; Jabbi et al., 2007) and adrenocorticotropic hormone (ACTH) response (Jabbi et al., 2007) to psychological stress as well as to show interaction with family history of depression to predict basal plasma cortisol and ACTH (Jabbi et al., 2007). Further, an interaction

between two putatively functional variants in *MAOA* the *COMT* (catechol-O-methyltransferase) gene in predicting ACTH response to stress has also been reported (Jabbi et al., 2007). Overall, it appears different measures of HPA activity, different timing, and differences in whether an eliciting challenge is used may contribute to variability in results for both twin and molecular genetic studies in this area.

LONG-TERM OUTCOMES

Despite being one of the earliest hypotheses about the potential role of genetics in the stress response, little is known about genetic factors that modify risk for physical illness after exposure to a stressor. Three studies now report that variation within adrenergic receptors may interact with work stress to impact blood pressure or risk for hypertension (Ohlin, Berglund, Nilsson, & Melander, 2007, 2008; Yu, Zhou, Jiang, Gu, & Wang, 2008); however, the specific gene targeted differs in each of the studies. Given the small number of studies in this area, more are clearly warranted.

In contrast, gene × stressor interactions have been reported for a number of psychiatric outcomes, including depression (Uher & McGuffin, 2008), PTSD (Binder et al., 2008; Koenen, Nugent, & Amstadter, 2008), and externalizing disorders, such as attention-deficit hyperactivity disorder and conduct disorder (Thapar, Harold, Rice, Langley, & O'Donovan, 2007). These include two prominent reports on gene × stressor interactions, one predicting conduct disorder and a second predicting depression. In the first study (Caspi et al., 2002), a promoter polymorphism in the *MAOA* gene associated with low MAOA activity interacted with childhood maltreatment to predict risk of conduct disorder. In the second study, the s allele at 5-HTTLPR interacted with childhood maltreatment and the number of SLE to predict major depression in young adulthood (Caspi et al., 2003). Recent attempts to replicate these associations, in particular, the interaction of 5-HTTLPR with SLE in predicting depression, have raised the possibility that these results may not be confirmed. Munafo, Durrant, Lewis, and Flint (2009) found that only a few studies reported qualitatively similar replications and, upon meta-analysis of five of these studies, found a main effect for the presence or absence of SLE but no evidence of 5-HTTLPR × environment interaction or 5-HTTLPR main effects for a categorical diagnosis of depression. Risch and colleagues (2009) conducted a meta-analysis of interactions involving the number of short alleles at 5-HTTLPR and the number of life events in predicting depression diagnoses across 14 studies. They again found a main effect for SLE but no gene main effect or gene × SLE interaction.

The meta-analyses confirmed statistically concerns about the nature of the replications that had previously been voiced in the literature. For example, Monroe and Reid (2008) highlighted the variability in measures used to index SLE in replications attempts. Caspi and colleagues (2003) identified the number of SLE over the past 5 years using an interview-based life-history calendar. In subsequent replication attempts, the timeframe for identifying relevant events ranged from 1 month to lifetime and the resultant data were operationalized in different ways, ranging from presence versus absence of SLE to total number of SLE or the highest rating from different categories of SLE. In addition, most measures in the replication attempts were self-report checklists, many not used in the previous literature, and often with unknown psychometric properties. As such, Monroe and Reid argued that these inconsistencies contribute to "replication drift" or mutation of the original findings due to varied and often inadequate measures and that lack of replication in this context may not be informative as to the validity of the original study. Thus, they argued that the measurement of "candidate stressors" should be held to the highest level of methodological rigor and should also be informed by prior research on the type of event that is most likely to trigger depression, namely an event that is of a distinct onset, recent, major, and primarily focused on the individual at risk.

The meta-analyses of Munafo and colleagues (2009) and Risch and colleagues (2009) focused primarily on SLE experienced as an adult and largely did not consider interactions with stress experienced as a child. As Caspi and colleagues had reported interaction of 5-HTTLPR with both SLE in the past 5 years and childhood maltreatment in predicting depression, it remains plausible that the stage of development at which the stress occurs may be critical to understanding how the experience of stress may interact with genetic vulnerability to influence risk for depression. Brown and Harris (2008) have argued that SLE, particularly those occurring up to 5 years prior to the onset of depression, may serve as a marker for childhood maltreatment and not make a direct contribution to gene × environment interaction. Further, they postulated that 5-HTTLPR may be associated with early changes in neurodevelopment in the context of childhood maltreatment. These early changes in neurodevelopment may manifest as changes in behavior that initiate a chain of adverse experiences over the lifecourse, thereby increasing risk for depression, or as persistent changes in brain function that increase risk for depression. Brown and Harris (2008) also noted that childhood maltreatment is more strongly associated with a chronic course of depression than the presence or absence of depression per se, underscoring how a life course perspective and improved measurement of both stress and the nature of depression may enhance our understanding of the mechanisms of gene × stressor interaction.

An additional concern is whether an interaction between genotype and environment is likely to occur in the absence of a main effect of genotype. Although a recent meta-analysis did find increased risk of depression

associated with the s allele (odds ratio = 1.11; Lopez-Leon et al., 2009), the effect was small and several large studies have not reached the same conclusion (Willis-Owen et al., 2005; Wray et al., 2009). It is plausible that a statistical interaction in the absence of genetic main effects may occur if the direction of association is reversed in distinct environmental conditions. For example, the s allele may confer greater risk for depression in the presence of SLE but lower rates of depression in the absence of SLE or in positive environments (Risch et al., 2009; Uher & McGuffin, 2008). Indeed, the possibility has been raised that 5-HTTLPR may better be described as a plasticity gene, simultaneously conferring risk to adverse environments and benefit from supportive environments (Belsky et al., 2009). Nonetheless, it should be noted that the pattern of results from the original paper were not consistent with a substantial reduction in depression among s allele carriers reporting few SLE, a pattern of results that would produce a small marginal main effect in sufficiently large data sets (Musani et al., 2007). In addition, the action of 5-HTTLPR as a plasticity gene remains largely hypothetical as its impact has not been tested in positive environments.

With regard to the interaction of variation in the promoter region of *MAOA* and childhood maltreatment in predicting conduct disorder and antisocial behavior (Caspi et al., 2002), one meta-analysis purportedly confirming this association was reported (Kim-Cohen et al., 2006); however, the outcome of the meta-analysis was childhood mental health and not conduct disorder or antisocial traits per se. Additional nonreplications (Huizinga et al., 2006) and two partial replications of an interaction predicting antisocial behavior have also been reported. In the first partial replication, the interaction effect was limited to Caucasians (Widom & Brzustowicz, 2006); in the second, interaction effects were observed at moderate levels of trauma but overshadowed at extreme levels of trauma (Weder et al., 2009). Thus, it appears that some of the concerns about the extent and quality of replication may also hold for the interaction of variation within *MAOA* and childhood maltreatment in predicting antisocial traits.

One consistent result to emerge from studies of gene × stressor interaction is the replicated association of psychological stress with depression. In the meta-analyses by Munafo et al. (2009) and Risch et al. (2009), no main effects for 5-HTTLPR were observed nor were 5-HTTLPR × stressor interactions. However, a main effect of psychological stress on depression across studies was observed despite the methodological limitations previously discussed. Associations of SLE and childhood maltreatment with depression are not new (Brown & Harris, 2008). It has further been shown that, among discordant cotwins, childhood sexual abuse increases risk for smoking and illicit substance use (Nelson et al., 2006) and early alcohol use (Sartor et al., 2007). In addition, in discordant cotwins, SLE increase risk for depression. These twin studies suggest that stress can increase risk for psychiatric disorder independent of genetic vulnerability. The consistent effect of stressors on depression and other psychiatric disorders, particularly in the context of cotwin control designs, highlights the importance of stress in the etiology of these disorders. It would be expected that when the genes contributing to depression are identified, they will add to or interact with the effects of stress.

LIMITATIONS

While provocative, it is important to note that the evidence to support genetic associations with stress and gene × stressor interaction is limited in a number of ways. In addition to difficulty with replication as noted earlier, the vast majority of these studies focused on one or a few variable markers within a given gene. In most cases, this provides very limited coverage of variability throughout the gene and neglects to address whether other regions of the gene may also contribute to the outcome of interest. The candidate gene approach is also limited by the candidates selected. For example, based on the studies reviewed, it appears that the serotonin transporter gene may have unique pleiotropic effects on a number of stress-related outcomes. While this may hold true, it should be noted that in many cases, other genes coding for critical elements of the serotonin pathway or other stress-related pathways have not yet been investigated. Candidate gene studies are also necessarily limited by the current knowledge of the biology of stress and should be complemented with genome-wide association to further the identification of novel genes and pathways that contribute to the responses to stress.

Very little is also known about the characteristics of stressors that permit these genetic effects of emerge. To date, the stressors studied have generally involved a composite of SLEs or a specific traumatic exposure. It is quite plausible that a number of stressor characteristics, such as the specific nature of the stressor (e.g., physical vs. emotional threat), its severity, and its chronicity, will impact the potential role of modifying genetic factors and the specific genes involved. For example, it is quite plausible that certain stressors are so severe that they overwhelm any potential impact of genetic background on the outcome, whereas genetic modification may emerge for less severe stressors.

Taken together, this review suggests that the study of the genetics of stress and gene × stressor interaction is in many ways still in its infancy. It is likely that twin/family, candidate gene, and other genetic research methodologies will continue to inform our understanding of the manner in which environmental stress and genetic factors combine and interact in promoting mental and physical disease outcomes. This work may also yield important insights into the psychology and biology of stress processes themselves.

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7 The Molecular Biology of Stress: Cellular Defense, Immune Response, and Aging

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Stress can be defined in a number of ways, but one thing that most, if not all, theorists agree on is that it involves or affects nearly every system of the body. Beginning with perceptual, interpretative, and other psychological processes mediated by brain activity, stress involves activation of nervous system and endocrine system responses that modulate bodily activity, altering functioning of the cardiorespiratory, skeletal muscle, digestive, reproductive, and immune systems, among others. Various changes in these systems can also effect a cascade of responses in other systems, as in the case of stress-related cytokine activity and consequent alterations in mood, cognitive function, and key physiological processes. The nature and "purposes" of these changes are the topics of other chapters of this *Handbook* and will not be reviewed here. It is sufficient to note that stress affects organisms in many ways, generating many different levels of analysis for investigators to study. This chapter focuses on one, basic level of analysis, namely, molecular changes associated with stress. Many of these changes are central to initiating or maintaining stress responses operating at other levels of analysis.

There are several ways to think about these different levels of analysis. Clearly, evaluation of stress in specific effector systems is important in determining possible consequences of stress: If one is interested in the ways in which stress increases the distribution of oxygen and glucose to organ systems that need them, study of the cardiovascular and respiratory systems is indicated. Similarly, if one is interested in the consequences of prolonged stress, allostatic load, and/or acute stress on health and well-being, investigation of a broader array of systems is indicated. Interest in inflammation or healing might warrant attention to immune system function, and efforts to reduce stress may best be focused on the brain and psychological levels of analysis. Finally, there may be reason to include evaluation of endocrine or immune systems if one is interested in the effects of metabolic hormones or the development of metabolic syndromes, or in some forms of mental health disturbance and pain. The general rule is that one focuses on particular levels of analysis depending on the properties and hypotheses of interest.

Another reason to choose different levels of analysis is that it allows evaluation of the extent to which stress effects converge across different levels. This is particularly important in studying stress changes in one or more systems that underlie, enable, or cause effects or changes in other systems. The extent to which these effects converge can be used as an index of whether these various changes are related to one another or to central integration of components of stress. It also identifies the degree to which the changes constitute an action pattern or integrated response. When the various levels of analysis can be "lined up" in a sequence, it may allow mediational analyses and investigation of causal and constituent relationships among systems or levels. Traditionally, for example, studies have been directed at psychological, endocrine, or cardiovascular levels. They measure sympathetic nervous system (SNS) or hypothalamic–pituitary–adrenocortical (HPA) axis responses or changes in resting or reactive blood pressure, heart rate, or platelet characteristics. Connections among these and other changes in levels of analysis were mostly drawn post hoc.

More recent research has advanced beyond this, using receptor blockade and other strategies to isolate and manipulate potential mechanisms underlying stress effects. The development of technologies to study increasingly difficult-to-access systems at levels that reflect this basic activity have also expanded opportunities to evaluate mediation and causality. The development of magnetic resonance imaging (MRI) and its use to study basic brain structure and function is one salient example. Simultaneous study of neurocognitive changes can provide important information about underlying bases of thought and memory and the ways in which stress-induced physiological changes are accomplished.

Another "new" technology that is particularly useful in the study of stress is loosely subsumed under the rubric "molecular biology." Over the past 30 years, our interest in and knowledge of processes that occur at a cellular or subcellular level have grown considerably. In part, this is due to technological and scientific breakthroughs that allow examination of smaller and smaller constituent units of cellular and systematic activity. Regardless of the reasons, the world of opportunities to learn about stress at these molecular levels has and will continue to lead to important knowledge about the cellular basis for most other aspects of stress-related change and their effects

on health, disease, and aging. In this chapter, we briefly characterize molecular biology and then discuss some of its applications and accomplishments in the study of key stress processes.

MOLECULAR BIOLOGY

The field of molecular biology has been at the forefront of scientific breakthroughs over the last 30 years and continues to play a key role in many areas of science and technology. But what is molecular biology and what are the implications of applying analysis at this level of stress and stress-related effects? Molecular biology generally refers to the specialization of biological theory and methods to investigate the process by which the structure and function of molecules affect basic life processes. It is also concerned with cell replication and the transmission of genetic information. There are a number of different processes and pathways that mediate cellular and subcellular activity. For our purposes, we will subdivide the field into studies on transcription, translation, DNA replication, and cell signaling. In this section, we will provide an overview of these four areas of molecular biology and build some background for understanding how stress can influence disease and disease outcomes at a molecular level. This overview is not meant to be exhaustive and does not cover the entire field of molecular biology. Textbooks have been written to cover this broad and expansive area; we will only consider some important illustrations.

Typically, integration of new areas or disciplines into the study of particular processes in other disciplines has run into language boundaries, and so we will define some key terms before we begin reviewing major processes in which their referents are involved. One main area is transcription—the production of RNA using a DNA template, generally referring to the creation of messenger RNA (mRNA). Transcription involves the "writing" of genetic information to RNA. These processes enable translation—the production of proteins from individual mRNA molecules. Thus, the flow of genetic information in a eukaryotic cell is DNA to mRNA to protein. The mechanisms and internal and external signals used to control this flow are at the heart of molecular biology. The end product of a DNA gene is protein. Every gene encodes at least one protein and to make this protein requires the production of mRNA by the process of transcription.

Eukaryotic cells contain thousands of individual genes encoding thousands of separate proteins, not all of which are necessary. Each cell does not need access to all of these proteins but rather requires specific proteins at different times in its life cycle. As a result, the production of different proteins is tightly regulated in each cell. This regulation is most often found at the level of transcription. Transcription of individual genes is controlled by a DNA sequence located immediately upstream of the gene, called a promoter. The promoter sequence contains binding sites for the RNA polymerase complex as well as other transcriptional factors. The RNA polymerase complex is responsible for the production of the mRNA. The transcriptional factors are proteins that can bind either directly to the DNA or with other DNA-binding proteins. The binding of these factors to DNA can result in either upregulation or downregulation of transcription. Thus, the decision of whether a gene is transcribed is often based upon the binding of transcriptional regulatory proteins to individual promoters, which either allows or prevents binding of the RNA polymerase complex and subsequent transcription. Among the goals of molecular biology is identification of promoter sequences and transcriptional binding sites as well as of the proteins that serve as transcriptional factors.

Translation of mRNA to proteins is typically less tightly regulated than transcription. Nonetheless, protein levels can be controlled post-transcription. Proteins can be targeted for degradation through a process termed ubiquination, and this process is controlled by cellular proteins that are produced as a result of both intercellular and extracellular signaling. Many proteins require post-translational modification such as glycosylation and phosphorylation; without these processes they will not be functional. The addition or removal of phosphate groups is a key regulatory mechanism that can turn a nonfunctional protein (nonphosphorylated) to an activated, functional protein (phosphorylated). Thus, eukaryotic cells can take advantage of protein modifications as a mechanism for controlling protein function. Another focus of molecular biology is identifying individual proteins, characterizing their functions, and determining any post-translational modifications.

Replication of eukaryotic DNA is a very complex process and its success is vital for the continuation of a species. The DNA polymerase that copies DNA into daughter strands must make an exact copy of the DNA genome every time the cell replicates. This means that the polymerase must copy every base pair (guanosine, cytosine, adenosine, or thymidine) precisely in order to make an identical copy. A single mistake such as inserting a cysteine instead of a glycine can lead to an amino acid change resulting in a modification of the protein that affects its function. It has been estimated that DNA polymerases make mistakes at a rate of approximately one base per every 10,000 bases copied. Human DNA contains over 1×10^9 base pairs, which means that every time a cell divides, approximately 100,000 errors could reasonably be expected. However, this cannot be possible given that this number of errors is so large that the cell would certainly be unable to survive even a single round of division. The actual error rate is believed to be about one in every 1×10^9 bases.

One explanation for the difference between the expected and observed rate of errors during DNA replication is the fact that the DNA polymerase has the ability to

recognize and correct errors produced during DNA replication. DNA synthesis occurs during the S (synthetic) phase of the cell cycle. The S phase is the longest of the four cell cycle periods [M (mitotic), G1 (gap 1), S, and G2 (gap 2)]. A eukaryotic cell typically divides in approximately 24 hours, with 10 hours spent in the S phase. If the cell detects DNA mutations, it is programmed by intracellular signaling to restrict any further cell cycle progression and to repair the DNA lesions. Failure to do this results in accumulation of DNA errors that are subsequently treated as normal in future replicative cycles. As a result, if the DNA mutations are not corrected when made, they become part of the normal DNA sequence and are passed on to future generations. If the DNA lesions are extensive, additional signals can occur, resulting in the cell triggering apotosis (cell death). All these processes are part of a general "cell defense" or integrated defense against passing on damaged DNA or otherwise increasing genomic instability. Molecular biology seeks to identify the cellular proteins involved in detection and repair of DNA mutations as well as the intracellular signals that are processed once a DNA lesion is identified, resulting in cell cycle arrest.

Another area of molecular biology discussed later in this chapter is cell signaling. Every cellular process and every reaction that a cell has toward external stimuli is governed by cell signaling. From cell cycle control in all dividing cells to the production of individual proteins, one or more cell signaling pathways are involved in ensuring the event is properly controlled. Unraveling signaling pathways is not unlike unraveling a Gordian Knot: There are thousands of cellular proteins present inside individual cells, and attempts to determine which ones are involved in an individual pathway are very difficult. Most signaling pathways involve multiple proteins, often starting with a ligand–receptor interaction at the cellular membrane. This protein–protein interaction triggers a cytoplasmic event (often the phosphorylation of one or more proteins) resulting in activation of a signaling cascade that can involve from just a few to dozens of individual proteins. Frequently, the final outcome of the signaling cascade is the transcription of one or more genes. Thus, cell signaling can unite transcription and translation as well as DNA replication.

These considerations may be interesting, but what do they have to do with stress? Stress typically has been viewed as a psychological event and a CNS-integrated systems syndrome, and many of the underlying genetic and often molecular processes supporting these events have only recently been recognized. We will discuss some of these using the effect of stress on immune system activity as an exemplar.

STRESS AND IMMUNITY

Although the notion of stress and speculation about its origins, functions, and consequences have been around for many years, most observers of the field credit Hans Selye with the popularization of stress research. Selye's descriptions of stress and research on its effect are classic studies that address a range of important issues (Selye, 1956, 1976). One aspect of his work that received less attention than was warranted by its importance was his view that stress operated at a molecular level as well as at more systemic levels. This allows for phenomena such as immune system modulation of brain activity and behavior and established cellular and subcellular events or entities as initiators of the General Adaptation System (Selye, 1976). This notion still finds expression in work that links superantigens to cytokine production and stimulation of neurons (Kusnecov & Goldfarb, 2005). Clearly, the foundation for examining molecular aspects of stress has been developed.

As we have suggested, research has progressed from broad attempts to identify effects of stress on immunity to more targeted studies of specific effects and presumed mechanisms. The earliest work was intent on assessing stress-related changes in various immune cells or activities in free-living populations experiencing naturalistic stressors. Studies identified immune-related effects of bereavement, disasters, and academic stress, typically comparing affected with less-affected groups and/or observing immune function over time and how it was altered by changing stressors (Bartrop, Lazarus, Luckhurst, Kiloh, & Penny, 1977; McKinnon, Weisse, Reynolds, Bowles, & Baum, 1989). A series of studies in academic settings by Kiecolt-Glaser, Glaser, and their colleagues (1984) identified a range of outcomes that were associated with increases in stress, widening the search for affected processes and mediators. Extension of this work to caregiving and interpersonal conflict continued to broaden the perspectives guiding this work and began to identify potential mechanisms and clinical outcomes such as wound healing (Kiecolt-Glaser et al., 2005; Kiecolt-Glaser, Page, Marucha, MacCallum, & Glaser, 1998). At the same time, studies of acute laboratory stress evolved to test specific hypotheses and examine mediators by controlling key variables. The first few of these studies showed that some of the effects of stress occur rapidly and can be observed in the context of laboratory settings (Manuck, Kasprowicz, & Muldoon, 1990; Zakowski, Hall, Cohen, Wollman, & Baum, 1994; Zakowski, McAllister, Deal, & Baum, 1992). Lymphocyte proliferation was suppressed by the end of 10- to 15-minute stressor periods with effects lasting for variable amounts of time (Zakowski et al., 1994), and natural killer (NK) cell numbers seemed to be affected quickly and for as long as the stressor was applied. Shortly after onset of stress, NK cell numbers increase in circulation and do not fall to or below baseline until after the stressor is terminated (Delahanty, Dougall, Browning, Hyman, & Baum, 1998; Schedlowski et al., 1992). Changes in lymphocyte numbers likely represent broader changes in trafficking and migration that also include numbers of CD8+T cells and

CD8/CD4 ratios (Dhabhar, 2000; Dhabhar & McEwen, 1996, 1997, 1999; Dhabhar, Miller, McEwen, & Spencer, 1996; Sheridan, Padgett, Avitsur, & Marucha, 2004).

Underlying mechanisms appear to be hormonal and may be cytokine-driven as well. Stress produces several responses that could modulate immune function. The most obvious of these are hormones that drive systemic stress responding. Cortisol, the primary glucocorticoid produced in humans, and corticosterone, the comparable steroid in rodents, are produced by the HPA axis and are a primary driver of stress and stress response (Chrousos, 1998; Harbus & Lightman, 1992; Sapolsky, Romero, & Munck, 2000; Selye, 1956). Increased production of the catecholamines epinephrine (E) and norepinephrine (NE) by the SNS axis, and consequent activation of skeletal, cardiovascular, respiratory, and other metabolic processes, are also key components of stress responding. Laboratory stressors produce reliable increases in sympathetic hormones (Gerra et al., 2001; Pike et al., 1997). Evidence of catecholamine responses to more chronic, naturalistic stressors has been harder to document, but data from 15- to 24-hour urine samples suggest persistent chronic effects on production of E and NE (Baum, Cohen, & Hall, 1993; Frankenhaeuser, Dunne, & Lundberg, 1976; Lundberg & Forsman, 1980). There is also evidence that both of these hormones are correlated with changes in some immune markers and that applying receptor blockades for adrenergic receptors on cell surfaces can reverse these effects and negate stress-related changes (Bachen et al., 1992; Redwine, Jenkins, & Baum, 1996; Sanders & Straub, 2002; Wang, Delahanty, Dougall, & Baum, 1998). A number of other systems also exhibit changes during stress but many are secondary to HPA or SNS axis stimulation. Acute stressors applied under controlled laboratory conditions cause immediate changes in the numbers of different immune cells and in their ability to function, and more chronic stressors unfolding in real-world settings also affect the system and its activity. Many of these changes are correlated with changes in HPA and SNS axis activity.

This growing literature has established that stress affects the immune system in several ways. The extent to which these effects influence disease processes or have any clinical significance is unknown, but studies of susceptibility to infectious illness, wound healing, and the effect of some stress management interventions have provided good reasons to believe that stress-related immune changes can be meaningful (Cohen et al., 1998; Cohen, Tyrrell, & Smith, 1991; Miller & Cohen, 2001). However, we know considerably less about the pathways within immune cells that mediate stress effects on immunity. Expansion of this knowledge and its extension to clinical problems are important priorities, and may be accomplished by advancing knowledge of subcellular pathways and cellular defense.

The importance of adding molecular levels of analysis to existing armamentaria can be demonstrated in many ways. We draw upon a few examples of molecular effects of stress on immune system activity. Although research has not established the practical or clinical effect of stress-related immune-mediated consequences, we do know that acute stress, such as that examined in many laboratory studies, can affect the numbers of particular subsets of lymphocytes (e.g., B cells, T cells, T-helper cells) and may affect individual cell function. In many of these studies, acute stress is associated with increased numbers of cytotoxic T cells and NK cells in circulation, suggesting a change in migration of cells to and from bodily "compartments." Some of these studies also find evidence of reduced cell function, typically measured as proliferation following mitogen stimulation. Considerably less is known about how or why these changes occur but, through evaluation of these kinds of effects at molecular levels, we may learn more about the causes and "purposes" of these immune system adjustments.

STRESS AND MOLECULAR MODULATION OF IMMUNE SYSTEM ACTIVITY

As we have suggested, cells are continually communicating information through external and internal networks that are controlled by the expression and activation of their receptors and receptor modulators (Houslay & Koltch, 2000). Communication must include both intercellular and intracellular transfer and transduction of extracellular information that begins with the binding of a ligand to a receptor. This initiates the release of an effector enzyme to produce a second messenger within the cell (Alberts et al., 1994). Second messengers that respond during psychological stress, such as cyclic adenosine monophosphate (cAMP), have broad effects, ranging from control of the cell cycle and gene transcription to the regulation of cell metabolism (Houslay & Miligan, 1997).

As new methods have become available, we have learned a great deal about this level of analysis. In this section, we will develop our knowledge of cellular activity within lymphocytes as an example of the advantages to be gained by broadening our approach. We do this by considering consistent findings indicating that stress is associated with redistribution of immune cells in circulation and can alter immune cell function as well—all in the context of research that addresses underlying molecular changes. Among the stress hormones that may be involved, the catecholamines E and NE appear to cause redistribution of lymphocytes into circulation (Benschop, Nijkamp, Ballieux, & Heijnen, 1994). Changes in immune cell function associated with this activation are mediated through β-adrenoreceptors and the second messenger cAMP (Redwine et al., 1996; Van Tits et al., 1990).

EXTRACELLULAR TRANSDUCTION AND ASSOCIATED RELEASE OF E AND NE

As has been discussed in many other chapters in this *Handbook*, stress is associated with predictable psychological and physiological changes that include SNS activation and release of adrenal hormones into circulation. Other pathways, affecting inflammation and availability of glucose, also increase systemic levels of cortisol (Goren, Kampfer, Podda, Pfeilschifter, & Frank, 2003). In the absence of stressors, these systems synchronize to carry out normal bodily functions and maintain equilibrium within the body (Chrousos, 1995). However, during stress, this balance is disturbed and elevations of stress hormones needed to accomplish important activities may also interfere with immune function. This occurs through processes whereby catecholamines bind to protein molecules (receptors) on the cell membrane, causing them to undergo conformational changes and to allow the transduction of extracellular information and the initiation of intracellular signaling (Neves, Ram, & Iyengar, 2002).

Physiological responses to extracellular information can be inhibited or stimulated depending on factors surrounding the expression and activation of receptors and the interactions between them and their modulators (Houslay & Koltch, 2000). Signal transduction is affected by the activation of intermediate proteins, such as G proteins that consist of three subunits (α, β, γ). All these subunits respond to conformational change that occurs when the receptor is stimulated by the binding of ligand (Neves et al., 2002). If all of the subunits become dissociated, a cascade of intracellular signaling events is set off, starting with the initiation of a specific effector enzyme to produce a second messenger (Alberts et al., 1994). For example, in response to stress, β-adrenoreceptors are expressed and activated, as these receptors have a high affinity for catecholamines. High levels of second messenger cAMP are then produced by the effector enzyme adenylyl cyclase (Stock, Schaller, Baum, Liesen, & Weiss, 1995). Accumulation of this second messenger accounts for changes in the immune cell function observed during or briefly following a stress response (Kohm & Sanders, 2001).

LEUKOCYTE TRAFFICKING IN CIRCULATION

The ability of catecholamines to alter distributions of lymphocytes in circulation is well documented. Changes in the catecholamines E and NE are positively related to numbers of helper T (CD4) cells and cytotoxic T (CD8) cells in circulation (Dimitrov et al., 2009). Several studies have shown that increases in the numbers of leukocytes in circulation occur immediately after catecholamine elevations and then return to baseline roughly 15 minutes following cessation of the stressor (Schedlowski et al., 1992). During a 20-minute infusion of NE, leukocyte numbers increased sharply, reached maximal levels within 5 minutes, declined, and then returned to close to baseline levels a few minutes after infusion ceased, confirming that redistribution is influenced by the availability of catecholamines (Schedlowski et al., 1996).

Without debating the function of changes in leukocyte trafficking into the periphery (see Dhabhar, 2000; Dhabhar et al., 1996; Dhabhar & McEwen, 1996, 1997, 1999; Sheridan et al., 2004), questions arise about how those changes are accomplished. As noted earlier, investigation of the expression of β-adrenoreceptors on lymphocyte membranes in response to acute stressors has suggested that catecholamines bind to these (extracellular) receptors, causing increases in the second messenger cAMP (Van Tits et al., 1990), which may mediate redistribution (Selliah, Bartik, Carlson, Brooks, & Roszman, 1995; Valitutti, Dessing, & Lanzavecchia, 1993). It follows that mental stress, physical exercise, and β-adrenoreceptor agonists increase numbers of leukocytes in the periphery (Benschop et al., 1994; Schedlowski et al., 1996; Van Tits et al., 1990), and that pretreatment with β-adrenoreceptor antagonists eliminates catecholamine effects on redistribution of immune cells in response to acute stressors (Benschop et al., 1994; Murray et al., 1992). It is possible that under certain conditions, most notably, after continual exposure to agonists (Redwine et al., 1996), β-adrenoreceptors may be pulled from the surface of the membrane and sequestered inside the cell (becoming inactive). This might explain the fluctuations of leukocytes in circulation with respect to the duration of the stressor, and the gradual decrease in cell numbers after peak increases in agonist levels.

Leukocyte adhesion to endothelial cells, another important process, is partially mediated by interactions between the endothelial cell and the immune cell that involve integrins, such as fibronectin, which initiate the phosphorylation of several proteins (e.g., paxillin; Rabinowich, Lin, Manciulea, Herberman, & Whiteside, 1995). However, the integrity of the cytoskeleton is compromised by increases in cAMP, suggesting that adhesion is to some degree maintained by the function of cytoskeleton and disrupted by expression and activation of β-adrenoreceptors and increases in cAMP (Selliah et al., 1995; Valitutti et al., 1993). These changes could also contribute to changes in cells in the circulation.

As one might suspect, the number of leukocytes in circulation has been implicated as a factor in the quality or efficacy of immune function. For example, because there are more effectors like NK cells in the periphery during SNS arousal, overall cytotoxicity may increase (Bachen et al., 1992). Not controlling for number of cells in peripheral blood, overall efficacy might increase as a simple function of greater numbers of effectors and their proximity to sites where they are needed, with more cells equaling a "better" response. However, if the cytotoxicity of each cell decreases (Delahanty et al., 1998), effects of having more cells will be reduced or cancelled and overall

cytotoxicity may not be increased. Similarly, there are more T cells observed in the periphery during response to acute stress, but they appear to be less responsive to mitogens (Delahanty et al., 1996).

CYCLIC AMP SIGNALING AND CELLULAR PROCESSES

Cellular processes such as cell maturation, cytolytic activity, antibody production, and proliferation can be inhibited or suppressed depending on what receptors are expressed and activated. For instance, when T-cell receptors are activated, a conformational change occurs in a G protein to initiate release of protein kinases, such as protein kinases A (PKA) or mitogen-activated protein kinases (MAPKs). These kinases lead to the phosphorylation of transcriptional factors (i.e., proteins that bind to specific DNA sequences and ultimately influence the expression or inhibition of certain genes), such as Creb and kinase Rsk (Crabtree, 1989). The phosphorylation of Creb and kinase Rsk can cause the synthesis of transcriptional factors, like *fos, jun,* and, *myc,* and lead to the stimulation of cyclin-dependent protein kinases that promote the cell cycle. However, adrenoreceptors on immune cells have the ability to slow cell maturation because they cause alterations in the concentration of cAMP in either direction: Where β-adrenoreceptors increase cAMP, α-adrenoreceptors cause decreases in intracellular cAMP concentrations (Milligan, Svoboda, & Brown, 1994). The selectivity of receptors for specific ligands is a contributing factor in the regulation of cellular processes to and responses to extracellular events.

Cell Maturation

A small amount of cAMP is necessary for development of immune cells and for their subsequent growth and function (e.g., cytolytic activity, antibody production, and/or proliferation; Sanders, 1995). However, the accumulation of intracellular levels of cAMP can inhibit cytolytic activity (Whalen & Green, 1998), antibody production (Panina-Bordignon et al., 1997), and proliferation (for review see Houslay & Koltch, 2000). Heterotrimeric G protein is stimulated by the binding of catecholamine molecules to a β-adrenoreceptor. Different types of immune cells are differentially affected by the stimulation of the G protein depending on how well their subunits are linked to adenylyl cyclase (Pochet & Delespesse, 1983). One study showed that where B cells express twice as many β-adrenoreceptors as do T cells in response to an agonist, T cells accumulate larger amounts of cAMP. Further, immature T cells accumulate four to five times as much cAMP as do their mature counterparts (Pochet & Delespesse, 1983). This is consistent with the fact that innate immunity is a frontline defense against infection and is critical for immune-surveillance and killing of nonself cells.

Natural Killer Cell Cytolytic Activity

NK cells are large lymphocyte-like granulocytes that do not require prior contact for antigen recognition. These cells appear to become less cytolytic as a result of stress (Delahanty et al., 1998). In assays that control for cell numbers, overall lysis of tumor cells by NK cells is lower during or immediately after stress. As we have discussed, increases in intracellular cAMP diminish cytolytic activity (Whalen & Green, 1998; Witham et al., 2003) and the ability to lyse tumors. One study pretreated NK cells with protein tyrosine kinase (PTK) antagonists, and found that adenylyl cyclase was not activated, cAMP elevation was not observed, and NK activity did not decrease when exposed to lysis-sensitive tumor cells (Whalen & Green, 1998). This is consistent with the idea that cytolytic activity is regulated by cAMP and that its production is facilitated through expression of PTKs. Further, catecholamines suppress the proinflammatory cytokine IL-12 and increase antiinflammatory cytokine IL-10 (Elenkov, Papanicolaou, Wilder, & Chrousos, 1996). Glucocorticoids also demonstrate a downregulatory effect on NK cell activity and antigen-primed CD4 cells by inhibiting IL-12 and IFN-y (DeKruyff, Fang, & Umetsu, 1998; Schedlowski et al., 1992). These changes also contribute to stress-related decreases in cytolytic responses.

Humoral Immunity: B-Cell Differentiation and Antibody Production

Research on stress and immunity also indicates a shift from T-helper 1 cells to T-helper 2 cells (see "Effects of Stress on Immune Function" chapter by Dhabhar in this *Handbook*). In addition, stress has been linked to the production of type 2 cytokines (antiinflammatory) over type 1 cytokines (proinflammatory; Elenkov & Chrousos, 1999). One study showed that acute stress inhibits the ability of T cells to express receptors (CD40) involved in stimulating the differentiation of B cells into antibody producing cells, again by increasing levels of cAMP (Suarez, Mozo, Gayo, Zamorano, & Gutierrez, 1997). However, the effects of cAMP on B-cell differentiation and proliferation are difficult to generalize (Kohm & Sanders, 2001), possibly because they are regulated by cytokine expression. Because it is difficult to measure concentrations and time courses of cytokine production as they respond to catecholamines and glucocorticoids, there are many inconsistent findings in this area (Kohm & Sanders, 2001). Despite these discrepancies, support for the notion that catecholamines and glucocorticoids inhibit the development of T-helper 1 cell and promote T-helper 2 cell differentiation has been reported. This change reflects a shift from innate and cellular immunity to humoral immunity (Panina-Bordignon et al., 1997) and occurs, in part, through β-adrenergic mechanisms (Hasko, Elenkov, Kyetan, & Vivi, 1995; Hasko, Nemeth, Szabo, Salzman, & Vizi, 1998).

Proliferation

Impairment of the ability of lymphocytes to proliferate in response to challenge also appears to be caused by exposure to catecholamines or other β-adrenoreceptor agonists. Here again, the accumulation of cAMP is a likely mechanism. Several studies have shown that proliferation in response to mitogens, measured as the number of replicates produced when memory cells are stimulated, is influenced by acute stress. Laboratory stress lasting minutes has produced reductions in the number of replicates produced during cell proliferation. Expression and activation of β-adrenoreceptors and the increase in cAMP that follows appear to inhibit T cells (Hadden, Hadden, & Middleton, 1970; Ledbetter et al., 1986) and NK cells (Van Tits et al., 1990).

One explanation for this is that the accumulation of cAMP interferes with the production/release of mitogen-activated protein kinase (MAPK), which plays an important role in the regulation of gene expression for many cellular processes, including cell growth (Schaeffer & Weber, 1999). As intracellular cAMP increases, proliferation to mitogens (e.g., phytohemaglutinin; Smith, Steiner, Newberry, & Parker, 1971) decreases, as does proliferation to anti-CD3 antibody (Bartik, Bauman, Brooks, & Roszman, 1994). Increases in cAMP also interfere with lymphocyte proliferation by antagonizing IL-2, which is necessary for proliferation, at an early stage of the G1 phase when uptake of growth factors and activation of protein kinases for DNA replication is necessary (Johnson, Davis, & Smith, 1988). The increases in intracellular cAMP disrupt transcription of the *jun* gene, which interferes with production of the *jun* protein that is necessary for binding to DNA at the IL-2 promoter site, resulting in suppression of IL-2 expression (Tamir & Isakov, 1994). Inhibition of IL-2 halts cell maturation and weakens proliferation (Boudard & Bastide, 1990), which is consequential for subsequent immune challenge.

Activation-Induced Cell Death

Activation-induced cell death (AICD) is cell death (typically from apoptosis but sometimes from necrosis) that occurs as a result of T-cell receptor activation. AICD is dependent upon several events including some that cause production of reactive oxygen species (ROS), or oxygen molecules that have lost an electron (Finco, Kadlecek, Zhang, Samelson, & Weiss, 1998; Kaminski, Kiessling, Suess, Krammer, & Gulow, 2007). These ROS play a role in intracellular signaling and are involved in many cellular processes (Nagy, Konz, & Pearl, 2003), some of which will be described later in this chapter. Apparently, cells can reach a point when they either proliferate or undergo programmed death upon exposure to a pathogen. This process is affected by the metabolic activity of the cellular mitochondria. Production of cytokines such as IL-2 and the activation of specific pathways, help to explain major influences of metabolic activity.

Peripheral lymphocytes often undergo apoptosis in response to an immune challenge when endogenous IL-2 is not available (Rosenberg et al., 1988). Failure of T cells to produce sufficient levels of IL-2 during T-cell activation is associated with more apoptosis in CD8 T cells (Laux et al., 2000). In another study, melanoma-reactive CD8 cells that were genetically engineered to express IL-2 proliferated without endogenous IL-2 and were able to survive for 8 weeks. However, clones that did not express IL-2 failed to proliferate (Colombo et al., 1996; Geizman-Smitz et al., 2000; Liu & Rosenberg, 2001).

Activation of lymphocytes with IL-2 is normally marked by an increase in adenosine triphosphate (ATP), a molecule that plays a major role in the storage and transfer of energy within the cell (Kaplan, Aebersold, & Cohen, 1989). Further, IL-2 is a regulator of glucose and nutrient uptake in lymphocyte metabolism (Vander Heiden et al., 2001), a process that is basic to lymphocyte survival and function (Maclver et al., 2008). Indirect evidence for a role for stress in these key metabolic processes comes from work indicating that incubation of lymphocytes with a glucocorticoid agonist for 1 hour decreased pyruvate metabolism (important for supporting oxidative phosphorylation) by 46% (Serrano, Curi, Parry-Billings, Williams, & Newsholme, 1993). Similarly, catecholamines have been demonstrated to alter production of cAMP and thereby inhibit IL-2 production (Boudard & Bastide, 1990).

There are many pathways that influence mitochondria metabolism, which in turn affects proliferation. One study showed that A-kinase anchor proteins (AKAPs), specifically AKAP121, increased cytochrome c oxidase activity, a measure of mitochondrial synthesis of ATP (Livigni et al., 2006). AKAP121 regulates mitochondrial metabolism by acting as an anchor for cAMP and tyrosine kinase, an enzyme with an important role in the phosphorylation of proteins. Additionally, Lee and colleagues (2005), who found evidence of interplay between kinases, cAMP, and cytochrome c oxidase, reported that, under certain conditions, increased levels of cAMP inhibited cytochrome c oxidase activity. Taken together, these studies demonstrate how intertwined the units in this pathway are, and illustrate how stress-related activity of cAMP may increase or decrease mitochondrial metabolic activity.

OXIDATIVE DAMAGE AND IMMUNITY

Another series of integrated pathways that may contribute to immune system dysfunction, aging, and disease are reflected in the concept of genomic stability or cell defense. Cellular defense refers to processes that occur within cells that minimize or repair damage to DNA in cell nuclei or otherwise prevent transmission of damaged DNA. Among the elements that characterize the molecular environment for immune cells and can contribute to their dysfunction are oxygen species such as ROS. These

ROS are capable of binding with and damaging proteins, lipids, and DNA in cell nuclei. As described earlier, transcription and cell signaling processes permit or facilitate cell replication, and any "errors" or mutations that are not eliminated by cellular repair can become part of the "permanent" genome.

This concept is broad, with several implications for research on stress and immune activity. It is also pertinent to consideration of cancer and cancer surveillance, based largely in molecular events and markers. Central aspects of cellular defense include the effect of DNA damage and repair processes, and the effects of stress on these processes. Although still in early stages, research on stress and DNA damage and repair is accumulating and available evidence suggests several potentially important relationships. The extent to which these processes affect larger systemic activities and/or health is not yet known, and mechanisms underlying these effects are not established.

DNA Damage and Disease

DNA damage can alter or disrupt genes that direct most activities within cells and in the body. Unprogrammed changes in these genes can alter cell function. Damage to the DNA that makes up these genes can result in mutations that then increase the possibility of permanent changes in cellular activity. This may cause real effects on health and illness. For example, repeated mutation or other DNA damage in areas of a gene that regulate control of proliferation can produce cells that cannot control their growth and have the capacity to become malignant. The likelihood of developing cancer also may increase when DNA damage and subsequent genomic instability occurs in precancerous cells or in tumor-suppressor genes in other cells. When DNA damage occurs in immune cells, it may cause dysfunction that opens a window of vulnerability that compromises the capacity of immune cells to complete their many missions, including fighting infections. By better understanding the ways in which stress affects oxidative damage, repair, and genomic instability, we may learn a good deal about several pathways to illness.

DNA damage can be caused by many kinds of insults, including radiation, exposure to toxic substances, and smoking. One of the major sources of DNA damage is oxidative stress, typically defined in terms of the balance between ROS and antioxidant compounds. Several basic properties of ROS are relevant, among them the fact that ROS are inevitable, normal products of cellular activities needed for survival and function. They are unstable and bind to cells or molecules that also have unpaired electrons, altering their DNA by causing strand breaks. Antioxidants interfere with this binding and reduce the effects of ROS cells. The balance between these agents results in manageable activity but, when ROS increase sharply and antioxidants do not, or when antioxidant levels are suppressed, oxidative stress results and the potential for DNA damage is increased.

Stress Effects on DNA Damage/Repair

There is some evidence that behavioral stress increases oxidative damage to cell nuclei and affects the cell's capacity to repair such damage (Cohen, Marshall, Cheng, Agarwal, & Wei, 2000; Forlenza, Latimer, & Baum, 2000; Wu, Chiou, Chang, & Wu, 2004). Studies have measured levels of 8-hydroxy-deoxyguanosine (8-OH-dG), which is produced during nuclear repair and is detectable as a stable correlate of DNA damage in urine or blood samples. This biomarker for DNA damage has been linked to biobehavioral factors such as stress (Irie, Asami, Ikeda, & Kasai, 2003; Irie, Asami, Nagata, Miyata, & Kasail, 2001, 2002). For example, Irie and his colleagues (2001) found that, among Japanese workers, greater stress related to workload was associated with higher levels of 8-OH-dG predominately in women. These findings remained after controlling several confounding and/or moderating conditions, though they varied as a function of reported coping strategies (Irie et al., 2001). Depression also was linked to 8-OH-dG levels and damage associated with neutrophil activity (Irie et al., 2003). In addition, individuals who manifest indications of hostility appear to show elevated 8-OH-dG levels (Carroll, 2004).

Thymidylate synthetase, a protein used in DNA replication and repair, has also been linked to stress, suggesting more extensive damage as well as greater repair (Ehrnrooth et al., 2002). Additionally, prolonged stress increased susceptibility to damage in peripheral blood lymphocytes (Dimitroglou et al., 2003). These results are consistent with animal research, linking stressors such as rotation or restraint with damage and repair of nuclear material. Conditioned emotional stress also produced DNA damage in rats, though this effect depended on the dose and duration of emotional responding (Adachi, Kawamura, & Kazuo, 1993). Stressful conditions also produced increases in the rate of chromosomal aberrations and sister chromatid exchanges in rats (Fischman, Pero, & Kelly, 1996) and promoted unscheduled DNA synthesis (Fischman et al., 1996; Fischman & Kelly, 1999).

Although some of the research described earlier interpreted elevations in repair markers as an indication of greater DNA damage, Glaser and colleagues' initial study in this area reported that stress *reduced* repair of DNA damage in rats (1985). Rather than an indication of reduced DNA damage, this was taken to suggest a mechanism whereby stress might increase susceptibility to cancer. A study in humans used an academic stress model, examining levels of DNA synthesis during higher stress examination periods and "routine" lower-stress periods of the academic year (Tomei, Kiecolt-Glaser, Kennedy, & Glaser, 1990). Blood drawn from students at each time point was exposed to radiation that induced apoptosis and/or to a phorbol ester, which inhibits apoptosis.

Radiation decreased DNA content regardless of stress but, when the chemical was added, stress increased DNA synthesis and the antiapoptotic effects of the chemical stimulus (Tomei et al., 1990). Other studies using academic stress models have also found evidence of stress-related damage, but their methodology is complicated by the need to separate these effects from modulation of repair, making interpretation of these studies more difficult (Cohen et al., 2000; Forlenza et al., 2000).

Separating Stress Effects on DNA Damage and Repair

A more recent study in our laboratory suggests that stress hormones may affect repair as well as damage (Flint, Baum, Chambers, & Jenkins, 2007). Stress hormones cortisol, NE, and E were expected to increase oxidative stress and DNA damage and/or decrease the ability of cells to repair damaged DNA. We first measured DNA damage in precancerous 3T3 cells induced by addition of stress hormones in vitro. To determine if stress hormones decreased the ability of the cell to repair damaged DNA, we measured gene expression levels of the genes involved in the DNA repair pathways. More specifically, we measured the expression levels of genes specifically involved in DNA damage signaling pathways, especially those associated with a key signaling network in a cell cycle arrest process that permits DNA repair prior to mitosis.

To accomplish this, we chose to grow a particular cell line (NIH 3T3 fibroblasts) that is considered to be easily transformed and has verified utility in studying DNA damage (Chen et al., 2004; Lin et al., 2004, Sheppard, 1977). The cells were synchronized in the G1 phase of the cell cycle. The cells were untreated or were stimulated with either cortisol (10^{-6} M), NE (10^{-7} M), or E (10^{-7} M) either singly or in combination. These concentrations mimic the physiological increase in stress hormones generated during acute stress (Rupprecht et al., 1991). In some experiments, key surface receptors were blocked by addition of mifepristone (RU486; 10^{-6} M) and/or propranolol (10^{-6} M) 30 minutes before addition of stress hormones. Exposure to cortisol, NE, or E for 10 minutes induced significant DNA damage in 3T3 cells, with NE causing the most damage. Incubation with either the glucocorticoid receptor antagonist RU486, or the beta receptor antagonist propranolol, 30 minutes prior to hormone treatment, blocked the effect of the hormones, indicating that damage was specifically related to each hormone. Only E affected cell proliferation.

We also cultured cells for 30 minutes to determine the effect of longer hormone exposure. We observed significant increases in DNA damage with all three hormones, and this effect was again mitigated when receptor antagonists were applied. Exposure of 3T3 cells simultaneously to all three hormones resulted in damage comparable to damage caused by each hormone alone. As another means of assessing stress hormone effects, 3T3 fibroblasts were incubated with serum isolated from laboratory mice (from the BALB/c strain) that were either stressed for 2 hours or remained in their home cages, which induced a 2.5-fold increase in DNA damage compared with serum isolated from control mice. When these 3T3 cells were incubated with either RU486 or propranolol before application of serum, we observed a 50% blocking effect. However, when RU486 and propranolol were added together, the effects of the serum taken from stressed mice were fully blocked.

The ability of 3T3 cells to repair oxidative DNA damage was examined by incubating cells in a growth medium for 4 hours to allow the DNA to be repaired after initial incubation with hormones (30 minutes). The extent of remaining DNA damage (the inverse of the amount of repair) was compared to control groups using the Comet assay. Results suggested that both cortisol and NE, but not E, interfered with repair of DNA damage.

Another hint that these oxidative processes reflect hormonal influences on transformation of 3T3 cells can be found in some unpublished data from our laboratory. Normal cells must be anchored to a substrate to survive and grow, but tumor cells do not usually require anchorage and can grow in suspension. The Soft Agar assay measures a transformed phenotype by examining the capacity of treated cells to grow without anchorage. Enhanced anchorage-independent growth reflects cell transformation. For this assay, 3T3 cells were incubated with stress hormones and anchorage-independent growth was observed.

Discussion

The research above earlier suggests that stress influences oxidative cellular and genetic damage. As noted earlier, the relationship between damage and repair needs further attention: Regular monitoring of genomic integrity and DNA damage and the existence of several different repair pathways complicate the processes governing cell proliferation and apoptosis. Maintenance of cell homeostasis requires repair of DNA damage and the type of repair depends on the nature of the damage detected. Some studies have found increased repair in stressed subjects, presumably because of greater damage produced in "stress groups" than was found in control participants (Cohen et al., 2000; Forlenza et al., 2000). Kiecolt-Glaser, Stephens, Lipetz, Speicher, and Glaser (1985) found the opposite, noting that participants experiencing greater chronic distress exhibited poorer lymphocyte DNA repair. Glaser and colleagues (1985) found that stress reduced the amount of methyltransferase activity in the spleen of rats, also suggesting curtailed repair capacity. Inconsistencies in these data have been attributed to different methods of measuring repair or to differences in the duration of stress exposure and to other factors specific to particular studies.

The pathways by which these effects are accomplished and their impact on cellular or systemic function

also remain to be specified. A few studies have looked at the HPA axis and the effect of pituitary surgery on DNA damage or the effects of acute stressors on oxidative stress (Fischman & Kelly, 1999; Yamaguchi, Kunitomo, & Haginaka, 2002). Their findings are not clear enough to allow identification of mediators of stress effects on DNA damage or repair. However, increases in some proinflammatory cytokines appear to be related to stress and oxidative stress (Maes et al., 1998). Another level of genomic defense centers on the capacity of cells to undergo apoptosis, a process that occurs throughout development, during lymphocyte repertoire selection, and as part of an immune response to infection or tumors. Relatively few studies have considered stress effects on this process, which prompt cells to undergo programmed death. Tomei and colleagues (1990) found that academic stress reduced apoptosis induced by radiation damage. This finding is inconsistent with more recent investigation of stress and apoptosis in animals that report stress-related increases in apoptosis (Hatanaka et al., 2001). Again, differences in species, measures, and stressors make interpretation of these inconsistent findings difficult.

Stress and T-Cell Priming

In a recent study from our laboratory (Flint et al., 2005), we examined the effects of acute stress on DNA damage and transcriptional changes in mouse T lymphocytes in vivo. We compared cells from mice that had been exposed to a 2-hour restraint stressor and cells from control animals, measuring molecular changes in these cells to better understand how stress affects immune response at a genetic level. Following the restraint stressor, mice were sacrificed at 0, 15, 30, and 120 minutes. Corticosterone was measured in peripheral blood as a check on the effectiveness of the stressor. DNA damage in isolated splenic CD3+ T cells was analyzed using the Comet assay (Giovannelli, Pitozzi, Riolo, & Dolara, 2003; Singh, McCoy, Tice, & Schneider, 1988), in which nucleoid DNA extends under electrophoresis to form "comet tails" and the relative intensity of DNA in the tail reflects DNA break frequency.

For genomic analysis, complementary DNA (cDNA) was synthesized from total RNA isolated from T cells and used as a molecular probe. Experiments were performed to examine changes in gene expression in T lymphocytes isolated from stressed mice compared to control mice at 30 minutes and 120 minutes. Results showed that the stress manipulation was effective and that it had effects on several processes. Restraint produced increases in corticosterone levels: At the end of the 120-minute stressor, we observed a 6.5-fold difference in serum corticosterone between stressed and control mice, and these levels remained significantly elevated compared to controls at 15 and 30 minutes after the stressor and declined thereafter.

To determine if restraint stress induced DNA damage in leukocytes, we evaluated the degree of DNA damage by the Comet assay. Consistent with previous human data (Dimitroglou et al., 2003), we could not detect any significant effects of the 120-minute restraint stress on DNA damage within polymorphonuclear and mononuclear leukocytes. However, restraint stress significantly altered gene expression in mouse T lymphocytes. Using mouse DNA damage and signaling pathway cDNA arrays, we measured differences in gene expression between stressed and control mice, selecting only those genes that were expressed in each of the mice. At 30 minutes following stress, T cells exhibited higher levels of transcription of 15 genes involved in DNA damage signaling pathways, as well as 10 genes involved in genomic stability and repair.

These genomic analyses indicated that restraint stress altered expression of several genes involved in cell cycle arrest, apoptosis, and DNA damage/repair pathways in mouse T lymphocytes. Taken together, the findings suggest "priming" of T lymphocytes by a psychological stressor. First, stress was associated with induction of genes specifically viewed as "DNA damage sensors." Second, stress was associated with rapid alteration of expression of several genes involved in the control mechanisms that ensure the fidelity of cell division ("cell cycle checkpoint"), particularly the key phase after which mitosis is initiated. Stress also affected expression of genes involved in cell signaling, regulation of apoptosis, and proliferation. Overall, the data suggest that stress specifically upregulates several genes that are critical for T-cell responsiveness. The response was transient, as many of the altered genes were downregulated to baseline within 120 minutes. The findings suggest the hypothesis that, at the molecular level, stress activates genes responsible for priming the T cell to undergo either apoptosis or proliferation. Presumably, subsequent signaling initiated by a second biological event would then switch on genes that induce either an apoptotic or proliferative response.

TELOMERES AND MARKERS OF CELLULAR AGING

For years, many experts from many disciplines have described the effects of stress on aging as "wear and tear." An early description of this process was described by Selye (1956) but many versions of this general approach can be found. Essentially, stress is seen as adding to or multiplying the burden an organism carries as he/she struggles to survive. Allostatic load also captures the essence of this notion, suggesting that this burden wears on the organism and in a very real sense makes it "older." Stress strips away capacity to cope just as the road wears the tread off a tire. The accumulation of this burden also adds to "normal" wear and tear on organs and organ systems, accelerating deterioration associated with age and use. Stress appears to increase the incidence or virulence of diseases that are associated with advancing age and that one might

expect to be produced by the cumulative burden that is carried. There are several anecdotal accounts that support this notion, and many lay, clinical, and scientific observers make assumptions based on this relationship.

Data providing direct support for these ideas are rare, but there is considerable indirect or circumstantial evidence. There are a number of reasons for this with human data. One of the most important has been the lack of good measures of "real aging." If stress affects the speed at which one ages, then measures of chronological age (how many years or days one has lived) should not be accurate reflections of one's age-related functions. Biological and/or psychological markers of how "old" a system is, and how resilient it is, are needed as better estimates of aging. Measured simultaneously, these markers could become indicators of how much aging has occurred due to several sources of burden that interact over time. How can one operationalize the cumulative effects of this wear and tear, punctuated by occasional major stressors?

Epel (2009) has argued that telomeres may represent the kind of measure we have been looking for, reporting evidence that stress is related to the rate of telomere shortening (Epel et al., 2004; Griffiths et al., 2002). A telomere is a region of DNA at the end of a chromosome that protects it from deterioration. At a cellular level, aging is represented in several ways, some of which are related to the number of times that cells have divided. This is one way to characterize aging; the more division a cell has experienced, the older it is (and perhaps the more "brittle" it has become). The length of telomeres reflects the number of cell divisions: They are points of contact between chromosomes separating during cell division. Each replication costs some length and the more divisions a cell has undergone, the smaller the "cap" that is found at all the end of chromosomes. Telomeres are also important in preventing mutations or recombinations of cells or cell fragments, which is associated with cancer (Epel, 2009). Since the major risk factor for cancers is age, it is likely that the cumulative stress load to which people are exposed can affect telomeres that protect against some of the negative effects of aging. In fact, "telomeres that are shortened past a critical length cause the cell to enter a state of arrest (cell senescence) when cells can no longer divide" (Epel, 2009, pg. 6). These and other processes have been described as mechanisms for telomere length's impact on disease and early mortality (Epel et al., 2004; Fuster & Andres, 2006).

As is typically the case, the value of telomeres as a marker of aging is complicated by a bewildering array of other factors and interactions among elements in several systems. Among the pathways by which stress or life's cumulative burden may influence telomeres are oxidative damage, gene effects, immunological activity, and hormonal changes. Telomere length is associated with socioeconomic status (SES; lower SES associated with shorter telomeres; Cherkas et al., 2006) and is highly variable in the general population (Aviv, 2008). Regardless, there seems to be converging evidence that the frequency of cell division is the main determinant of telomere length and that the frequency of cell division will be increased by oxidative damage to cells (requiring that more undamaged "new" cells be produced; Ito et al., 2006; Proctor & Kirkwood, 2002). Inflammation and oxidative stress appear to be key aspects of these processes and are assumed to be primary sources of telomere length and of aging as well (Balaban, Nemoto, & Finkel, 2005; Finch & Crimmins, 2004). At the same time, the duration of a chronic stressor and its perceived impact also have been linked to telomere length and may be central to understanding aging (Epel et al., 2004).

CONCLUSION

We have considered a number of different molecular processes as they may relate to stress, developing a matrix for extending the study of stress to new levels of analysis. Learning more about how stress operates at cellular and subcellular levels will better inform research driven by evaluation of one or another pathway by which behavior or behavior–environment interactions influence health and illness. In particular, these processes are important in the regulation of effector systems involved in immunity, in the ongoing sensory processes and regulatory functions of the nervous and endocrine systems, and in the aging of cells, tissues, and organisms. Further study of these issues and their incorporation into ongoing stress research appears warranted.

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8 Social Responses to Stress: The Tend-and-Befriend Model

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For decades, the scientific study of stress has been guided by the theory of "fight-or-flight" (Cannon, 1932). From this standpoint, animals and humans exhibit two typical responses to external threats. If the threat is one that will yield to aggressive action, then "fight" responses will be seen. In animal studies, the fight response typically assumes the form of physical aggression, whereas in humans, the fight response may assume any of multiple forms, including physical aggression, verbal aggression, or other approach-based coping responses such as active problem solving. Likewise, the "flight" response usually assumes the literal form of fleeing in animals, but in humans, fleeing can take on additional forms, such as social withdrawal or withdrawal through substance use such as alcohol or drugs.

Although this viewpoint is consistent with most animal research, it ignores one of human beings' most basic ways of fending off threats, namely, the fact that they live in small groups that afford joint protection. To characterize these affiliative responses to stress, we have developed a model of "tend-and-befriend" (Taylor, 2002; Taylor et al., 2000). Tending involves nurturant activities designed to protect the self and offspring that may promote safety and reduce distress. Befriending is the creation and maintenance of social networks that may aid in this process. Especially under conditions of stress, people protect their offspring and affiliate with others for protection and comfort. In this chapter, we review the evidence for tending and befriending under stress, explore the neural and neuroendocrine underpinnings of these responses, discuss gender differences in tend-and-befriend responses, and suggest clinical implications and directions for future work.

STRESS AND AFFILIATION

Social relationships are a significant part of life, and perhaps never more so than under conditions of stress. A large and growing body of research provides evidence that the perception or use of social support under stressful conditions is associated with positive effects on an array of mental and physical health disorders, such as cardiovascular disease (e.g., Grace et al., 2002; Lett et al., 2005), depression (e.g., Sayal et al., 2002), systemic lupus erythematosus (Bae, Hashimoto, Karlson, Liang, & Daltroy, 2001), and progression of HIV infection (Lesserman et al., 2002). Importantly, both the quantity and quality of social relationships have also been reliably related to mortality (e.g., House, Landis, & Umberson, 1988).

The beneficial biological effects of social support are likely heavily mediated by two interacting bioregulatory systems, the sympathetic nervous system (SNS) and the hypothalamic pituitary adrenal (HPA) axis. Together these systems mobilize an organism for concerted efforts to combat or escape from threat, and, as such, these biological systems are protective. However, over the long term, repeated or prolonged engagement of these systems can lead to accumulating damage to the underlying stress systems. These changes can reduce the resiliency of stress systems, and the resulting wear and tear on the body's physiological systems has been termed allostatic load (McEwen, 1998). Alterations in the functioning of other systems, such as the immune system, are also implicated (Uchino, 2006). In interaction with genetic risks, accumulating allostatic load may enhance one's prospects for an array of chronic diseases. Tend-and-befriend is conceived of as affiliative responses to stress that may protect against the buildup of allostatic load.

TENDING

Tending to offspring in times of threat, we argue, is a primary frontline response for ensuring survival of the species. In addition, in the short term, tending responses to stress are beneficial because they reduce biological reactivity to stress in parent and offspring. Over the long term, tending helps offspring to develop socioemotional skills for managing stress, and it shapes their biological stress regulatory systems. Evidence from both animal and human studies suggests that the beneficial effects of tending on physical and mental health begin with supportive familial contacts in early life.

The earliest evidence for the benefits of tending comes from Harlow and Harlow's (1962) studies with monkeys

that were raised with an artificial terrycloth mother and who were isolated from other monkeys during the first 6 months of life. These monkeys showed disruptions in their adult social contacts, they were less likely than those raised by their mothers to engage in normal social behaviors such as grooming, their sexual responses were inappropriate, mothering among the females was deficient, and they often showed highly fearful or abnormally aggressive behavior toward their peers. Furthermore, monkeys who experienced total social isolation and had no surrogate mother for the first 6 months of life (or more) subsequently had severely damaged or destroyed social and sexual behavioral capabilities (Harlow, Dodsworth, & Harlow, 1965).

Building on work like this, Meaney and colleagues (Francis, Diorio, Liu, & Meaney, 1999; Liu et al., 1997) explicitly demonstrated the relationship between early nurturant contact and the development of stress responses in offspring and showed that maternal contact influences affective and neuroendocrine responses to stress across the lifespan. In their paradigm, infant rats are removed from the nest, handled by a human experimenter, and then returned. The response of the mother to this separation and reunification is intense licking and grooming and arched back nursing, which provides the pup with nurturant and immediate soothing stimulation. In the short term, this contact reduces SNS and HPA axis responses to stress in the pup (and in the mother as well). Over the long term, this maternal behavior results in a better regulated HPA axis response to stress and novelty and to better regulation of somatic growth and neural development. This compelling animal model suggests that nurturant maternal stimulation modulates the responses of offspring to stress in ways that have permanent effects on the offspring's behavioral and biological stress reactivity (Meaney, 2001).

Cross-fostering studies in which highly reactive or less reactive rat pups are cross fostered to exceptionally nurturant or normal mothers indicate that the maternal style of the foster mothers can be adopted independent of the rat pups' temperamental reactivity (e.g., Francis et al., 1999). Highly reactive females raised by especially nurturant mothers not only show lower reactivity themselves but learn nurturant parenting behaviors, which they then pass on to their offspring. Genomic factors contributing to these effects include glucocorticoid receptor expression (with respect to stress reactivity) and oxytocin receptor expression (with respect to maternal behavior) (see Meaney, 2001, for a review), but nongenomic pathways are also involved; that is, there is evidence of intergenerational transfer of nurturing over and above genetic predispositions (Francis et al., 1999). Tending behavior, thus, is critical not only for modulating immediate responses to stress in both mother and offspring but also for crafting the psychosocial and biological stress reactivity systems that will serve offspring across the lifespan. These tending skills appear to be transferred intergenerationally through both genomic and nongenomic pathways.

Warm, nurturant, and supportive contact with parents affects physiological and neuroendocrine development in human infants and children as well (Repetti, Taylor, & Seeman, 2002). Families characterized by unsupportive relationships have damaging consequences for the mental, physical, and social health of their offspring, not only in the short term but across the lifespan. Neglect of offspring, overt family conflict, and/or relationships that are cold and unsupportive have been tied to a broad array of adverse physical and mental health outcomes long into adulthood (Repetti, Taylor, & Saxbe, 2007). The chronic stress of an unsupportive early environment produces repeated or chronic stimulation of stress responses. Over time, such alterations may lead to pathogenic changes in the functioning of these systems that permanently alter the neuroendocrine responses and the stress-related behavior of offspring. Indeed, as reviewed by Sanchez (2006), in nonhuman primate infants, early disruptions in the mother–infant relationship are stressful for the infants, and the chronicity and intensity of these experiences appear to have long-term effects on the infants' biological stress responses and socioemotional behavior. For instance, it was found that sustained HPA axis activations early in life resulted in below average functioning of the axis over development. Evidence was also reviewed, however, showing that nurturant caregiving (responsive and sensitive mothering) can buffer against these adverse effects of early adversity. Thus, early nurturant contact, or lack thereof, shapes biological stress responses and lays the groundwork for future mental and physical health and for the development of social competencies.

BEFRIENDING

Affiliation with others, "befriending," is vital for managing threatening circumstances. Social interaction is critical for health across the lifespan, and social isolation has been found to be a risk factor for mortality in both animals and humans. For instance, House et al. (1988) reviewed evidence from six large prospective studies indicating that mortality is higher among more socially isolated individuals, even when controlling for biomedical risk factors for mortality. They have argued that the data on social support suggest that insufficient social support is an important risk factor for morbidity and mortality, with an effect size similar to that for more well-known risk factors such as cigarette smoking, obesity, physical activity, cholesterol, and blood pressure. The beneficial effects of social support on both mental and physical health are well established (see Taylor, 2007; Uchino, 2006, for reviews), which is due in part to the ability of social support to mitigate the negative impact of stressors (see Uchino, Cacioppo, & Kiecolt-Glaser, 1996, for a review).

GENDER DIFFERENCES IN TEND AND BEFRIEND

There appear to be significant gender differences in tending and befriending, which may reflect, in part, a robust and biologically based difference in how men and women cope with stress. Although the behaviors of fight-or-flight may be especially characteristic of men's responses to stress, tending to offspring and befriending of others may be more characteristic of women's responses to stress (Taylor et al., 2000). This argument is based on the assumption that during early human prehistory, men and women faced somewhat different adaptive challenges and, as a result, developed different stress responses to meet these different challenges. Specifically, females of most species, including humans, have the primary responsibility for the early nurturing of offspring through pregnancy, nursing, and care in early life. Stress responses in females, then, are likely to have evolved in such a way as to simultaneously protect both self and offspring, such as by tending to offspring and befriending others in the social group.

Consistent with this perspective, research indicates that women draw on socially supportive networks more in times of stress than do men, women may be more benefited by social support than are men, and women provide more frequent and effective social support to others than men provide (Taylor, 2002; Thoits, 1995). Although men typically report larger social networks than women do, in part because of their historically greater involvement in employment and community organizations, studies indicate that women are more invested in their relationships and see their relationships with others as more intimate (e.g., Belle, 1987). Adolescent girls, college-age women, and adult women all maintain more same-sex close relationships than men do, and they turn to their female friends more than men turn to their male friends (Taylor, 2002). Two meta-analyses (Luckow, Reifman, & McIntosh, 1998; Tamres, Janicki, & Helgeson, 2002) have also found that women were significantly more likely than men to seek and use social support to deal with a broad array of stressors. Women also appear to be more benefited by social contacts in times of stress than are men. For example, a meta-analysis of the social support and health literature conducted by Schwarzer and Leppin (1989) found that the correlations between social support and good health were consistently higher for women than for men. In fact, the gender differences in the relationship between social support and health were the most reliable findings of this meta-analysis. Finally, studies of caregiving have found that women are more likely to be support providers than are men. More than 80% of care to disabled children, parents, and spouses is provided by mothers, daughters, and wives. Men, by contrast, appear to be more likely to institutionalize their wives in response to the most common causes of caregiving such as stroke or Alzheimer's disease (e.g., Freedman, 1993).

PROVIDING SOCIAL SUPPORT

Is tending and befriending inherently costly, potentially undermining any benefits? In the past, the receipt of social support has been thought to be highly beneficial both biologically and psychologically, but providing social support has been thought to be inherently costly to the provider. On the surface, this is a reasonable concern. The provision of advice, emotional support, or tangible assistance can be costly to a support provider in time and resources. Some evolutionary perspectives on altruism also suggest that altruistic acts can put the provider at risk (Hamilton, 1963). The idea that providing social benefits to others is inherently costly is also given credence by the research on caregiving. Caregiving can be a harmful, even fatal undertaking, as caretakers are at high risk for physical and mental health disorders. Evidence of immunocompromise is often present in caregivers, which can leave them vulnerable to disease (e.g., Kiecolt-Glaser, Glaser, Gravenstein, Malarkey, & Sheridan, 1996; Newsom & Schulz, 1998). Caregiving can have adverse effects on wound repair (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995), on the regulation of SNS responses to stress (Mills et al., 1997), and on natural-killer cell function (Esterling, Kiecolt-Glaser, & Glaser, 1996), among other adverse effects. Although evidence such as this would seem to bear out the viewpoint that giving social aid is costly, the majority of these studies have focused on populations that involve particularly burdensome caregiving.

In recent years, the benefits of giving social support have become better understood, and research now suggests that providing social aid to another may be stress-reducing for the provider as well as the recipient. For example, Trivers' (1971) reciprocal altruism perspective suggests that providing aid to others increases the likelihood that there will be others there for you when your needs arise. Giving support to others may cement a personal relationship, provide a sense of meaning and purpose, and signify that one matters to others, all of which promote wellbeing (Batson, 1998; Taylor & Turner, 2001). Helping others may also reduce psychological distress (Midlarsky, 1991) and contribute to good health and longevity (Brown, Nesse, Vinokur, & Smith, 2003; Luoh & Herzog, 2002; Schwartz & Sendor, 2000).

Although the exact mechanisms underlying the benefits of giving support to others are not fully understood, the animal studies on the impact of nurturing behavior on offspring may represent a useful model. That is, not only are offspring soothed by nurturant contact, but the animal providing the nurturant contact, namely the mother, is benefited as well, in the form of reduced sympathetic arousal and signs of reduced agitation, among other benefits (Coplan et al., 1998; Liu et al., 1997). Thus, it is possible that the benefits of providing support to others operate through some of the same physiological

and neuroendocrine pathways through which the receipt of support from others achieves its benefits.

BIOLOGICAL BASES OF TEND AND BEFRIEND

The tend-and-befriend system is conceived of as an affiliative neurocircuitry that may piggyback onto other basic drives such as hunger, thirst, sexual drives, and other appetites. Fundamentally, tend-and-befriend is a behavioral approach system that may be chronically in place but that becomes especially important in times of threat or stress. As occurs for other appetites, we suggest that there is a biological signaling system that comes into play if one's affiliative contacts fall below an adequate level. Once signaled, the appetitive need is met through purposeful social behavior. If contacts are hostile, unsupportive, or also under threat, then psychological and biological stress responses may increase, but if social contacts are supportive and comforting and provide protection, then stress responses are likely to decline. Such positive contacts, in turn, should lead to a decline in the need and a decline in stress responses.

Biological underpinnings of tend-and-befriend responses appear to be based at least in part on oxytocin and on the endogenous opioid peptide system. Oxytocin and opioids are both released in response to at least some stressors, and oxytocin, potentially in consort with opioids, attenuates biological stress responses. Additionally, because biological neurocircuitries tend to be efficient, the dopamine and opioid systems that are recruited for other reward-based systems are likely to be recruited for the satisfaction of affiliative needs as well (see Depue & Morrone-Strupinsky, 2005). Indeed, affiliation, including affiliative activities related to stress reduction (Depue & Morrone-Strupinsky, 2005), and cues of loved ones (e.g., Aron et al., 2005), can activate the dopamine-mediated reward system in the brain.

ROLE OF OXYTOCIN

Oxytocin is a neural hormone that is produced in the paraventricular (PVN) and supraoptic nuclei of the hypothalamus and is released into circulation from the magnocellular neurons which extend down to the posterior pituitary. Oxytocin is additionally released by parvocellular neurons within the PVN that may project to many other areas within the brain including the hypothalamus, amygdala, locus coeruleus, the dorsal motor nucleus of the vagus nerve, the periaqueductal grey matter, and the nucleus raphe magnus (Millan, 2002; Sofroniew, 1983). Oxytocin is most widely known for its roles in childbirth, lactation, pair bonding (e.g., mother–infant, female–male), and sexual behavior. Positive social contact, such as affectionate contact, can also induce the flow of oxytocin (e.g., Uvnas-Möberg, 1999). As previously mentioned, oxytocin has consistently been found to reduce anxiety and biological stress responses. Because the impact of oxytocin is modulated by estrogen (see Insel, 1992), oxytocin's effects are thought to be stronger in females than in males and may be implicated in the maternal tending of offspring seen in response to stress.

Biological Signaling System

Because affiliation is vital to the survival of human beings, there are likely to be biobehavioral mechanisms that are sensitive to social threats or loss of social contact. Evidence for this idea comes from research on separation distress. In a variety of species, when the young are separated from the mother, separation distress in offspring can result, leading to distress vocalizations which may prompt the return of the caregiver. This system appears to be dependent, in part, on oxytocin and brain opioids (Panksepp, 1992).

Adults experience separation distress as well, and oxytocin may act as a signal prompting affiliative behavior. Research from our laboratory examined the relation of plasma oxytocin levels to reports of relationship distress in adult women and found that women who were experiencing gaps in their social relationships had significantly elevated levels of oxytocin (Taylor et al., 2006). Specifically, women with high levels of oxytocin were more likely to report reduced contact with their mothers, their best friends, a pet, and the social groups of which they were a part. In addition, the women with significant others were more likely to report that their partners were not supportive, did not understand the way they felt about things, and did not care for them, compared to women with lower levels of oxytocin. Poor quality of the marital relationship and infrequent displays of affection by the partner were also associated with higher levels of plasma oxytocin. Plasma oxytocin was unrelated to general psychological distress, only to gaps or problems in positive relationships, and whereas oxytocin appeared to signal gaps in relationships, cortisol levels were not similarly elevated. These points suggest discriminant validity for the relation of oxytocin to relationship distress. Similar findings have been reported by Turner, Altemus, Enos, Cooper, and McGuinness (1999), who found that elevated plasma oxytocin was associated with anxiety over relationships, perceived coldness or intrusiveness in relationships, and not being in a primary romantic relationship. Thus, elevated levels of plasma oxytocin appear to signal relationship distress, at least in women.

Relation of Oxytocin to Affiliation

If oxytocin is related to social distress, then as an affiliative hormone, oxytocin may provide an impetus for social contact to ameliorate stress. There is manifold evidence

that oxytocin promotes affiliation, much of which has come from animal studies (e.g., Panksepp, Nelson, & Bekkedal, 1999; see Insel, 1997, for a review). Exogenously administered oxytocin has been related to increases in physical proximity, increased maternal behavior, grooming, and preferences for members of one's own species in whose presence elevated oxytocin was experienced (see Panksepp, 1998; Taylor, 2002, for reviews). Oxytocin is thought to underlie affiliative activities in humans as well, including maternal behavior and social bonding more generally (e.g., Carter, 1998; Carter, Lederhendler, & Kirkpatrick, 1999; Taylor, 2002). Thus, it appears that affiliative behaviors may be subserved by oxytocin.

Relationship of Oxytocin to Stress Responses

Oxytocin can reduce the magnitude of stress responses and, as such, may be a proximal hormonal stimulus for the beneficial effects of social contact during stress. Animal studies have shown that exogenous administration of oxytocin or stimulation of oxytocin secretion results in enhanced sedation and relaxation, reduced anxiety, decreased sympathetic activity, decreased activity of the HPA axis, and elevated vagal nerve tone (associated with parasympathetic functioning), among other effects suggestive of reduced biological reactivity (Carter, 1998; Uvnas-Möberg, 1997; Uvnas-Möberg, 1998a). Oxytocin also has analgesic effects that may aid in combating certain kinds of stressors (e.g., Petersson, Alster, Lundeberg, & Uvnas-Möberg, 1996).

Research with humans, although more sparse, suggests similar effects. For example, in breastfeeding women (Light et al., 2000) and women reporting more frequent hugs from partners (Light, Grewen, & Amico, 2005) (both of which are populations in which oxytocin levels have been found to be elevated), and in men receiving exogenous administration of oxytocin (Heinrichs, Baumgartner, Kirshbaum, & Ehlert, 2003), psychological and biological stress responses are lower. Breastfeeding women report less anxiety than do bottle-feeding mothers, show lower blood pressure, lower vascular resistance level, and higher cardiac output both before and during stress (e.g., Altemus et al., 2001; Grewen & Light, 2006; Mezzacappa & Katkin, 2002). The level of calm reported by breastfeeding mothers is highly correlated with their plasma oxytocin levels (Uvnas-Möberg, 1996). Overall, the evidence that naturally elevated levels of oxytocin or exogenously administrated oxytocin attenuate stress responses is strong in both animal and human studies.

DOES OXYTOCIN UNDERPIN TEND AND BEFRIEND?

Oxytocin appears to be importantly implicated in the dynamics of the tending and befriending response to stress. Oxytocin is at high levels following the birth of offspring and appears to promote bonding (Feldman, Weller, Zagoory-Sharon, & Levine, 2007). Also, oxytocin levels increase in response to physical social contacts such as touch and grooming (Stock & Uvnas-Möberg, 1988; Uvnas-Möberg, Bruzelius, Alster, & Lundeberg, 1993) and from massage-like stroking in both infant and adult mammals, including humans (Turner et al., 1999; Uvnas-Möberg, 2004). The physical contact that may result from affiliation may reduce anxiety and SNS and HPA axis responses to stress (e.g., Uvnas-Möberg, 1998b).

Is oxytocin implicated in befriending processes? Animal research suggests that it may be. In a study by Detillion, Craft, Glasper, Prendergast, and DeVries (2004), Siberian hamsters received a cutaneous wound and were then exposed to immobilization stress. The stressor increased cortisol concentrations and impaired wound healing, but only in socially isolated and not in socially housed animals. Thus, social housing acted as a stress buffer. Removing cortisol via adrenalectomy (removal of the adrenal glands) eliminated the impact of the stressor on wound healing, thereby implicating the HPA axis in the healing process. Of particular interest, treating the isolated hamsters with oxytocin eliminated stress-induced increases in cortisol and facilitated wound healing; treating socially housed hamsters with an oxytocin antagonist delayed wound healing. These data imply that, consistent with the tend-and-befriend perspective, social contacts can protect against the adverse effects of stress through a mechanism that implicates oxytocin-induced suppression of the HPA axis.

OPIOID MECHANISMS

Opioids are known for their rewarding, analgesic, and addictive properties. Numerous studies also suggest an important contribution of endogenous opioid peptides in the modulation and regulation of stress responses. Endogenous opioids are released in the brain during stress, and they are believed to be involved in the blunting and termination of cardiovascular and neuroendocrine stress responses (Drolet et al., 2001; McCubbin, 1993). Thus, the release of opioids during stress may serve as an inbuilt defense system that balances the response that stressors place on the organism against the potential detrimental effects that sustained stress responses may produce.

Opioids are also believed to influence affiliative and social responses to stress (see Taylor, Dickerson, & Klein, 2002, for a review) and have been found to play an important role in social attachment (Nelson & Panksepp, 1998). For instance, exogenous and endogenous opioids have been found to alleviate separation distress (as measured by isolation cries) in dogs, guinea pigs, chicks, rats, and primates (Panksepp, 1998; Panksepp, Herman, Vilberg, Bishop, & DeEskinazi, 1980). Behavioral quieting in response to social contact may also be opioid based (Panksepp et al., 1980). In addition, opioid levels are elevated following bouts of allogrooming in monkeys

(Keverne, Martensz, & Tuite, 1989), social contact can have analgesic effects at least partially mediated by opioid release in mice (D'Amato & Pavone, 1996), and social interaction with the mother can induce release of opioids in rats (Blass & Fitzgerald, 1988; Carden & Hofer, 1990). Thus, in terms of the tend-and-befriend framework, these findings suggest that opioids are involved in the benefits of "tending," as endogenous opioid release resulting from social contact may reduce the emotional and biological consequences of stress. In addition, opioids may play a role in "befriending," as they may mediate the rewarding properties of affiliative interactions, thereby promoting subsequent social interactions.

FUTURE DIRECTIONS

Several issues regarding the relationship of oxytocin and opioid mechanisms to tending and befriending processes and to stress responses require additional research. First, if affiliative efforts are unrequited or negative, heightened stress responses may occur. In a study consistent with this point (Taylor et al., 2006), women participated in a socially threatening laboratory challenge task, and their responses were assessed. Those with low levels of plasma oxytocin showed an increase in cortisol in response to the social threat and a decrease during recovery. By contrast, women with initially high plasma oxytocin levels had significantly higher cortisol levels initially, which decreased early on in the laboratory procedures, but then again became elevated during the threat tasks. These findings suggest that women with high levels of oxytocin may be especially attuned to social features of the environment, and their levels of stress may be exacerbated by unsupportive social contacts. Thus, quality of social contacts during stressful times may be an important variable for understanding the relation of oxytocin to stress responses.

The fact that high levels of oxytocin can be associated both with relationship distress and with reduced stress responses also represents an issue on which further research is needed. One hypothesis is that bursts of oxytocin, as may occur in response to anticipated or actual social contact or exogenous administration of oxytocin, reduce stress responses, but levels of oxytocin in the plasma, which likely represent trace evidence of some preceding process, are associated with relationship distress (Turner et al., 1999; but see Grewen, Girdler, Amico, & Light, 2005). Turner et al. (1999) have also suggested that chronically elevated levels of basal oxytocin may be indicative of poor oxytocin regulation in response to social stimuli.

Another possible resolution stems from the fact that most studies documenting the stress-reducing qualities of oxytocin have not disentangled the effects of oxytocin from affiliation itself or its anticipation. It may be that affiliation and its biological consequences produce some of the effects that have been attributed to oxytocin. At least some of the stress-reducing properties associated with affiliation appear to be mediated by a downstream opioid pathway. Whether unrequited social contact implicates this opioid pathway is unclear.

Much of the preceding discussion has focused on women's responses to stress, because there is considerable evidence that women both seek and provide more social support than men do under stressful conditions. Although these gender differences are very consistent, they are relatively modest in magnitude, which means that men also typically affiliate in response to stress. Whether there are biological underpinnings of men's affiliative responses to stress is largely unknown. One possibility is that oxytocin underlies affiliative tendencies in men as well as in women. Exogenous administration of oxytocin has stress-reducing properties in men just as it does in women (e.g., Heinrichs et al., 2003), and recent research has shown that exogenous administration of oxytocin can enhance feelings of trust and cooperative behavior in men (e.g., Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). Nonetheless, because oxytocin is strongly regulated by estrogen and antagonized, at least in some species, by androgens, some researchers have speculated that oxytocin is a more potent influence on affiliative behavior in women than in men (Taylor et al., 2000).

A hormone very similar to oxytocin in molecular structure is vasopressin, and in certain respects, vasopressin may be a male counterpart to oxytocin in women (see Insel, 1997). Animal studies, for example, have found that vasopressin is related to mate guarding and other social activities in male prairie voles (Carter, 1998), and research implicates the vasopressin receptor gene in empathetic responses to others in men (Keverne & Curley, 2004). In summary, men clearly engage in affiliative activities of many kinds under stressful conditions, and although the biological underpinnings of such behavior are not yet fully known, it appears that both oxytocin and vasopressin may be involved.

CLINICAL IMPLICATIONS

If the tend-and-befriend model represents a viable perspective on human responses to stress and to gender differences in these responses, then there should be predictable mental and physical health consequences. A first and obvious point is that if tending and befriending with others is an adaptive response to stress, then those who draw on affiliative contact to combat stress should experience better mental and physical health outcomes than those who do so less. The literature on social support makes precisely these points (see Taylor, 2007, for a review). In terms of clinical disorders, one would expect to see men somewhat overrepresented in disorders related to fight-and-flight, and this is also the case. For instance, men are more likely to die of homicide and suicide and of complications related to substance abuse

than are women (Verbrugge, 1983). Although women are closing the gender mortality gap as their lifestyles have changed, the female propensity to use social support for dealing with stressful events as opposed to responses indicative of fight-or-flight may be reflected in women's consistently longer lifespan throughout the world.

Still, just as disorders related to fight-or-flight may be experienced disproportionately by men, might we expect to see that vulnerabilities related to the social network are experienced disproportionately by women? The answer appears to be yes. Women report more stressful events in their social networks than men do and report being more involved in them (see Taylor, 2002, for a review). Indeed, in a longitudinal study with adult opposite-sex twin pairs, it was found that women were more sensitive than men to the depressogenic effect of low levels of social support, suggesting that difficulties in social relationships may play a larger role in the etiology of major depression in women than in men (Kendler, Myers, & Prescott, 2005). As noted earlier, women's caregiving activities often expose them to mental and physical health risks. Women also show a greater vulnerability to posttraumatic stress disorder (PTSD) than men do, which appears to be tied to the fact that their PTSD-related traumas are often social in nature, such as abuse and rape (Olff, Langeland, Draijer, & Gersons, 2007).

On a more positive clinical note, women may be especially benefited by social interventions to reduce stress. Women are more likely to participate in social support groups than men are. Indeed, one study found that women were more likely than men to use supportive social services of all kinds (Taylor, Falke, Shoptaw, & Lichtman, 1986). There are both good and lamentable aspects of this pattern. On the one hand, women appear to be served well by socially supportive services, but on the other hand, men may choose not to use such services. Women, though, are generous support providers, and the literature clearly indicates that men, children, and other women are benefited by women's propensity to give social support. Except for extreme examples such as caregiving noted earlier, women may profit both psychologically and biologically from their caregiving as well as their care seeking.

CONCLUSIONS

Human being's basic mode of coping with stress and threatening circumstances is affiliation with others. Since early human prehistory, group living and banding together to combat joint threats have been the major ways that humans have ensured their survival. We have termed such affiliative responses "tend-and-befriend," referring to the fact that in stressful times human beings tend to their offspring to protect them from harm and affiliate with others for successful joint efforts against threats. The evidence suggests that women are more likely to tend-and-befriend in response to stress, whereas men may be more likely to engage in the fight-or-flight response in stressful circumstances. Clinical observations regarding these hypothesized differences tend to support the existence of these gender patterns. However, the difference in magnitude in affiliative responses to stress between men and women is relatively small, and clearly men's survival has been beneficially affected by affiliative responses to threat, just as women's survival has.

Issues for future research include the fact that the biological underpinnings of affiliative responses to stress are still uncertain. There is evidence that oxytocin, vasopressin, endogenous opioid peptides, and the dopamine system may underlie affiliative activities and induce lower arousal to threatening circumstances as well. Progress on a biobehavioral model underlying social responses to stress can be expected within the next decades.

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9 Stress and Support Processes

Bert N. Uchino and Wendy Birmingham

INTRODUCTION

There is a large body of epidemiological research suggesting that individuals who lack social support are at greater risk for mental and physical health problems (Barrera, 2000; Berkman, Glass, Brissette, & Seeman, 2000; Cohen, 2004; House, Landis, & Umberson, 1988; Uchino, 2004). For instance, low social support is related to higher levels of depression, anxiety, and life dissatisfaction (Barrera, 2000). Social support is also linked to lower all-cause mortality—especially from cardiovascular disease (Uchino, 2004). This impressive body of research highlights the importance of support processes in health and well-being.

Although many factors play a role in such complex associations, it is thought that the interface between social support and stress-related processes is crucial to understanding these epidemiological links (Cohen, 1988; Gore, 1981; Lin, 1986). Of course, not all models of social support highlight a role of stress (e.g., direct effects model; Cohen & Wills, 1985), but even in such cases stress may play an indirect role (Uchino, 2004). In this chapter, we review the current status of support–stress models and highlight promising areas of future research. We begin with a brief conceptual overview of social support.

THE CONCEPTUALIZATION OF SOCIAL SUPPORT

Most recent work on social support conceptualizes it as the functions that are provided by social relationships. These functions may be separated into perceived and enacted (received) dimensions (Tardy, 1985). Perceived support refers to one's potential access to social support, whereas received support refers to the actual utilization or exchange of support resources (also see Barrera, 1986; Dunkel-Schetter & Bennett, 1990). These two dimensions do not appear to be interchangeable as beneficial effects of perceived support may be obtained in the absence of any actual support being provided (Cohen, 1988; Sarason & Sarason, 1986).

So what exactly is made available or provided by supportive individuals? Sidney Cobb (1976) defined these social resources as information that one is cared for, loved, esteemed, and part of a mutually supportive network. Other researchers have taken a broader approach to defining support. For instance, tangible aid (e.g., providing money) is sometimes conceptualized as a form of social support (Barrera, Sandler, & Ramsey, 1981; Cohen, Mermelstein, Kamarck, & Hoberman, 1985). Many researchers argue that the types of support that may be perceived or received are what can be termed emotional (e.g., expressions of caring), informational (e.g., information that might be used to deal with stress), tangible (e.g., direct material aide), and belonging (e.g., others to engage in social activities) (Cohen et al., 1985). These distinctions are important because of models that specify the importance of specific support dimensions in fostering adjustment to stress (Cutrona & Russell, 1990).

Finally, support can be defined in terms of its level of specificity. It can be operationalized at the level of the specific network member or in terms of more global evaluations of support (Cohen et al., 1985). However, research suggests that these different ways of measuring support are not highly related and that support from specific network members may uniquely predict adjustment even after considering general perceptions of support (Davis, Morris, & Kraus, 1998; Pierce, Sarason, & Sarason, 1991). In addition, research suggests that certain network members tend to be characterized by the provision of many different support types (e.g., strong ties, parents), whereas others tend to be limited to the provision of one kind of support (Wellman & Wortley, 1990). These data suggest the potential importance of separating specific sources of support depending on the person's life circumstance and the social-cultural context (Dressler & Bindon, 2000; Wills, Gibbons, Gerrard, & Brody, 2000).

MAJOR MODELS LINKING SUPPORT AND STRESS

There are a number of models that postulate a direct role for stress in support processes. Of these, the buffering model of support has been the most widely researched

(Cobb, 1976; Cohen & Wills, 1985). However, another important model that has received much less attention focuses on the possibility that support may reduce one's actual exposure to stressful events (stress prevention model; Gore, 1981). We review these and other closely related models in the following text and evaluate their current status in explaining links between social support and health.

STRESS-BUFFERING MODEL

The buffering model has received considerable attention (Barrera, 2000; Cohen & Wills, 1985). As shown in Figure 9.1, this model posits that social relationships are beneficial because they can decrease the negative effects of stress on both mental and physical health (Cohen & Herbert, 1996), and that this buffering is more apparent when examining functional social support measures (Cohen & Wills, 1985; but see Barrera, 1986). Cohen (1988) has postulated that buffering occurs through an appraisal process and subsequent coping responses (see Figure 9.1). That is, support can influence one's initial appraisal of stress so that its harmful effects are buffered. In addition, after the appraisal process, support can serve as a coping resource to foster adaptation to stress. It should be noted, however, that very little research separates these distinct points as most studies on support examine more general perceptions of stress that likely reflect appraisal, reappraisal, and in some cases coping processes as well.

Overall, there is strong evidence for a buffering effect of support on adjustment to stress (Cohen & Wills, 1985; Cutrona & Russell, 1990). Even when faced with extremely stressful events (e.g., death of a spouse), the perceived adequacy of support is inversely related to the intensity of the stress response and can facilitate coping over the long term. In fact, social support has been shown to decrease the negative mental health effects associated with a wide range of stressors, such as unemployment, bereavement, and serious medical problems (Cutrona & Russell, 1990). This perspective has also been tested in a number of well-controlled laboratory studies and results suggest that the receipt of social support is associated with lower cardiovascular reactivity to stressors (Lepore, 1998; Thorsteinsson & James, 1999). Epidemiological studies are also consistent with this buffering framework (Falk, Hanson, Isacsson, & Östergren, 1992; Johnson, Stewart, Hall, Fredlund, & Theorell, 1996; Rosengren, Orth-Gomer, Wedel, & Wilhelmsen, 1993). For instance, Falk et al. (1992) examined a random sample of 621 men (aged 78–79 years) in Malmo, Sweden. These researchers found that the combination of high job strain and low support was associated with the highest mortality rate over the subsequent 7 years.

Despite these findings, one important critique of the stress-buffering model of support is that although measures of perceived support often detect such associations, measures of received support sometimes do not (Helgeson, 1993). The issues involved in the actual receipt of support are complex but a number of explanations are currently receiving empirical attention (Barrera, 2000; Bolger & Amarel, 2007; Uchino, 2004). One possible explanation is based on the finding that stressful circumstances are usually associated with increased support-seeking. As a result, those who report greater levels of received support are actually under more severe stress (Barrera, 1986). One implication of this argument is that researchers may need to follow the effects of received support in stressed populations over longer periods of time because initially it may represent an individual's attempt to mobilize support, with received support eventually helping one resolve the stressor only over time.

A second reason why received support might not be as effective during stress is due to the quality of the support that is received. Lehman, Ellard, and Wortman (1986) tested this possibility in a sample of bereaved individuals. These researchers found that bereaved participants were readily able to recall support attempts that were both helpful and unhelpful. Actions such as expressing concern and contact with similar others were viewed as helpful, whereas giving advice and encouraging recovery were seen as unhelpful. They then asked a separate group of nonbereaved participants what they would do to support an individual in such a situation. Contrary to the possibility that potential support providers do not know what to do or say, participants' reports of what they would do to be supportive matched quite well with the reports of what was helpful in individuals

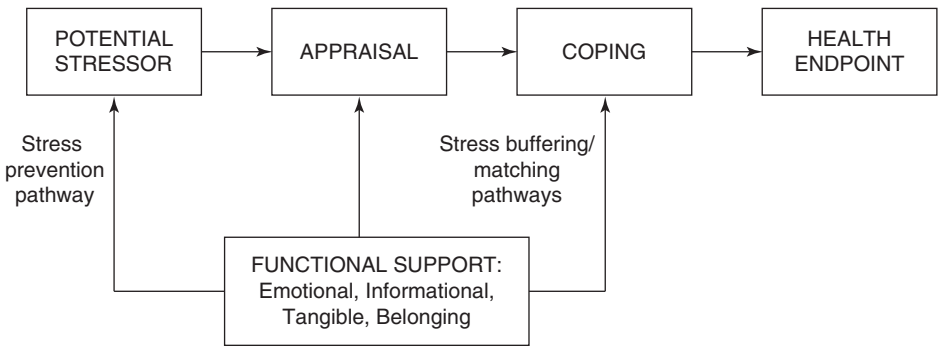

Figure 9.1 ■ Existing models linking support to stress and coping processes.

who had experienced bereavement. If people know what to do then why did so many individuals report unhelpful support attempts by individuals in their network? The authors hypothesized that people interacting with someone undergoing a stressful event feel anxious about these interactions. They would not want to do or say anything that would upset the individual at such a time of vulnerability. Ironically, this anxiety may make it difficult to be an effective support provider as individuals slip into more automatic or casual responses (e.g., "I'm sure you will be fine") that may then be viewed as insensitive and stressful in their own right (also see Coyne, Wortman, & Lehman, 1988).

A final explanation for why received support may not be beneficial is related to the possibility that asking for or receiving support may be associated with a drop in self-esteem (Nadler & Fisher, 1986). This decrease in self-esteem may in turn offset any benefits of received support and/or operate as a source of stress on its own. Because of this possibility, Niall Bolger and his colleagues (Bolger, Zuckerman, & Kessler, 2000) have argued that the best form of received support may be those acts that are not actually noticed by the recipient as supportive. In one intriguing study of "invisible support," Bolger and his colleagues followed couples where one member was preparing to take the stressful New York State Bar Exam. Diary measures of received support were completed over a 1-month period. Results of the study revealed that there were many instances in which the partner reported providing support but the recipient did not notice. Further, the provision of invisible support was associated with the lowest levels of depression during the study period (also see Bolger & Amarel, 2007; but cf. Gable, Reis, & Downey, 2003).

Recent research on invisible support is starting to clarify the links between received support and stress. In a series of well-controlled laboratory studies, Bolger and Amarel (2007) found that invisible support (operationalized as support from a confederate that was expressed indirectly to the experimenter instead of being directly provided to the participant) was associated with smaller increases in distress. Consistent with the potential negative influences of visible support on self-esteem, they also found that these effects were mediated by individuals communicating a sense of inefficacy to the person about to undergo stress. These studies are also important because, as Bolger and Amarel (2007) propose, the potential negative influences of received visible support may operate primarily at stages before actual requests for support (e.g., appraisal). This underscores the significant role played by the time course associated with support–stress processes.

Because not all studies have found received support to have negative/null effects during stress, it has been argued that we need to be careful in accepting this proposition too generally (Barrera, 1986). More specifically, received support can be of several types (e.g., informational, belonging, emotional) and few studies have looked at how specific dimensions of received support predict adjustment during stress. There is good reason to take a closer look at specific dimensions because research suggests that the receipt of informational and tangible support tends to be viewed as less nurturant and more controlling than either emotional or belonging support (Trobst, 2000). In one study it was found that received tangible and informational support predicted increased depressive symptoms, whereas received emotional support did not predict depressive symptoms (Finch et al., 1997). However, received positive interactions (belonging support) predicted lower levels of depression, a finding that was obscured if one only looked at total received support. Other research in chronic disease populations suggests a detrimental influence of received tangible support on depression but a beneficial influence of received emotional support (Penninx et al., 1998).

Researchers have also tried to reconcile the mixed influence of received support during stress by arguing for a more complex view of how received support is related to perceived available support (Krause, Liang, & Keith, 1990; Wethington & Kessler, 1986). One perspective consistent with this view is the support deterioration deterrence model (Norris & Kaniasty, 1996). According to this model, stressful events can undermine an individual's perceived availability of support from others. This may occur because stressful events can challenge one's basic beliefs. In addition, if the stressor is widespread enough, immediate support providers may also be coping with the event, which would curtail their ability to provide support. Received support may then be beneficial because it prevents the deterioration of perceived support from others. Results from two large studies of victims of hurricanes Hugo and Andrew were consistent with this model as received support was a predictor of greater perceived support over time, which in turn predicted lower levels of distress (Norris & Kaniasty, 1996). An important implication of this perspective is that received and perceived support may be related in fundamental ways that can be modeled under the appropriate context.

Finally, it should be noted that studies finding received support to have no effect, or even a detrimental influence on adjustment, stand in stark contrast to laboratory studies described earlier that have found received support to lower cardiovascular reactivity during acute stress (Gerin, Pieper, Levy, & Pickering, 1992; Lepore, Allen, & Evan, 1993; see meta-analysis by Theorenstein et al., 1998). The most common form of support provided has been emotional support conveyed in a nonthreatening manner. These laboratory studies suggest that there is nothing about received emotional support per se that precludes it having a stress-buffering influence. It is also important to note that, due to random assignment, the laboratory studies linking received support to better physiological adjustment during acute stress are able to disentangle received support from current levels of stress. In more naturalistic settings, the mobilization of support during stress can present difficulties in disentangling the harmful effects of stress versus the beneficial effects of support (Barrera, 2000).

Overall, there is consistent evidence for the stress-buffering model using perceived support assessments (Barrera, 2000; Cohen & Wills, 1985). However, there is considerable research suggesting that measures of received support show less consistent stress-buffering influences. Modeling the factors responsible for this discrepancy is one of the most important areas for future research in this area.

MATCHING HYPOTHESIS

A major variant of the stress-buffering model is what has been called the matching hypothesis (Cohen & McKay, 1984; Cutrona & Russell, 1990). The matching hypothesis predicts that stress-buffering is most effective when the type of support matches the needs or challenges of the stressful event. More specifically, the matching hypothesis predicts that informational and tangible support should be most effective for controllable events (e.g., preparing for a job interview), whereas emotional and belonging support should be most effective for uncontrollable events (e.g., job layoff; Cutrona & Russell, 1990).

The research evaluating the matching hypothesis has yielded mixed findings (Barrera, 2000). For instance, in one study consistent with the matching hypothesis, researchers found that financial stress was associated with an increased risk for alcohol involvement (Peirce, Frone, Russell, & Cooper, 1996). They next examined whether different types of support would help individuals cope better with their current financial situation. Of the different types of support measured, it was found that only tangible support consistently decreased the association between financial stress and alcohol involvement. However, other studies looking specifically at individuals with low financial resources have not found tangible aid to be the most effective form of support (e.g., Krause, 1987).

Several possible reasons for these discrepancies represent difficulties in conducting a clean test of the matching hypothesis. One issue is that many stressful events are not easily classified as either controllable or uncontrollable and these classifications may change over time. A second problem is that many of the components of support are often highly related to each other, presenting statistical difficulties in teasing apart their independent effects. In addition, there is evidence that some types of social support are helpful across many different stressful life events and effects. Cohen and colleagues (1985) have found that emotional and informational support had the most consistent effects on varied outcomes such as depression, physical symptoms, and smoking cessation. As suggested by these authors, emotional and informational support may be particularly beneficial because people can almost always benefit from useful information or reassurances of their worth.

Despite these difficulties in testing the matching hypothesis, research continues to favor this approach for several reasons. First, studies that statistically model specific forms of functional support suggest that they are distinct lower-order processes that together make up the higher-order concept of social support (Cutrona & Russell, 1987). Second, the use of specific functional measures of support tells us more about why social support is beneficial. For instance, an association between emotional support and mental health gives researchers more specific guidelines in attempting to develop an effective support intervention. Future research will be necessary to evaluate, and perhaps modify, the matching hypothesis, in ways that take into account the complexities noted earlier.

STRESS PREVENTION MODEL

One model linking stress to support that has received much less attention is the stress prevention model (Gore, 1981; Lin, 1986). As shown in Figure 9.1, this model suggests that social support is beneficial because network members may provide us with the resources to avoid or reduce our exposure to some types of negative life events. In one early study, researchers found that the combination of community level and individual support was associated with less exposure to negative life events during the 1-year study period (Lin, 1986). In addition, a longitudinal study of older adults found that individuals with higher social support experienced a lower number of daily hassles over a subsequent 11-month period (Russell & Cutrona, 1991). Although much less research exists that specifically tests the stress prevention model, in actuality some studies examining stress reduction as a mediator of support influences may be relevant because general perceptions of stress likely reflect both stress exposure and stress reactivity (e.g., Bonds, Gondoli, Sturge-Apple, & Salem, 2002).

Consistent with the stress prevention model, existing longitudinal studies tend to find support to be related to lower stress exposure (McFarlane, Norman, Streiner, & Roy, 1983; Russell & Cutrona, 1991; but see Mitchell & Moos, 1984). Moreover, results of a few other studies are consistent with the putative role of reduced stress exposure in mediating links between support and health. In one cross-sectional study of adolescents, stress exposure was one "downstream" mediator of the relationship between parental support and drug abuse (Wills & Cleary, 1996). In addition, longitudinal data suggest that reductions in daily hassles were partially responsible for associations between social support and depression in an older adult sample (Russell & Cutrona, 1991). Nevertheless, more direct evidence is needed for the meditational role of stress prevention in explaining support–health links.

One important question is why more research has not been dedicated to examining this model (Barrera, 2000). There are several potential reasons. First, the long-standing emphasis on the stress-buffering model has led

to a focus on stress reactivity as the important outcome associated with social support. In addition, some stress measures do not draw an explicit distinction between stress reactivity and exposure. More recent models are starting to emphasize stress component processes (e.g., reactivity, exposure, recovery, restoration; Cacioppo & Berntson, 2007; Rook, 2003) and should serve to inform such issues.

Despite the paucity of relevant research, there are a number of intriguing pathways by which social support may reduce exposure to stress (Uchino, 2004). One possibility is that social support may act to influence cognitive processes such that more benign appraisals occur (Cohen, 1988). For instance, a tuition increase may not produce any stress for individuals who have adequate tangible support from their parents. Second, social support (e.g., informational support on planning for a rainy day) can help individuals make informed decisions that minimize their subsequent stress exposure via proactive coping (Aspinwall & Taylor, 1997). In fact, more broadly, social support may enhance self-esteem and personal feelings of control, which are important antecedents of proactive coping (Aspinwall & Taylor, 1997). Finally, adequate social support may help decrease exposure to "secondary stressors" (Pearlin, 1989). Negative events usually do not occur in isolation, and stressors often beget exposure to other stressors in related or "spillover" domains. A relevant example is how stress at work can lead to conflict at home (Bolger, DeLongis, Kessler, & Schilling, 1989; Repetti, 1989). However, if spousal support reduces the stress of work, it may effectively eliminate potential spillover into marital interactions and reduce exposure to such secondary stressors (Pearlin, 1989).

In our opinion, the scarcity of research on the stress prevention model represents a significant gap in our understanding of links between social support, stress, and health. We would encourage researchers to consider specific tests of this perspective using relevant methodologies (e.g., longitudinal designs; see Barrera, 2000). An adequate consideration of this perspective, in combination with the stress-buffering model, highlights the complexity of support–stress links, and how they unfold over time. This stands in contrast to the more static approach typically seen in most social support research in which support and stress are measured and related at one point in time. Such general issues and critiques of the models discussed earlier are highlighted next.

GENERAL CRITIQUE OF MAJOR SUPPORT–STRESS MODELS

The support–stress models reviewed earlier are elegant in their simplicity and parsimony. However, this simplicity may also be a weakness as it leaves unexamined key processes that the models imply. One of these processes highlighted earlier is that in which support events unfold and change over time, especially in response to stressors. This issue is evident when examining potential limitations of support in relation to certain life events. For instance, there are some stressors that not only have an effect on the person under stress but also on his or her social network. This "support deterioration" process can deplete critical support during times of need. In one study, Bolger, Foster, Vinokur, and Ng (1996) found that although support was initially mobilized in response to a breast cancer diagnosis, the patients' distress was related to a decrease in received support from the spouse over time. Consistent with a support deterioration model, experimental studies also suggest that individuals exposed to crowding stress are less likely to seek, offer, and value support during laboratory stress (Evans & Lepore, 1993). Moreover, such changes in social support during stress appear to mediate subsequent distress (Evans, Palsane, Lepore, & Martin, 1989; Quittner, Glueckauf, & Jackson, 1990).

Examining how stressors influence support is important, because in other contexts, stressful life events may not erode support but instead provide an important opportunity to foster the growth of personal relationships (Holahan & Moos, 1990). For instance, the experience of stress may lead to appropriate self-disclosure and facilitate the development of a person's social ties (Altman & Taylor, 1973). Such a process may, in turn, foster better adjustment during the course of a long-term stressor or subsequent stressful circumstances, as it increases a person's comfort level in receiving support from these individuals (Burleson & Goldsmith, 1998). By strengthening a person's social support network, this process may also be associated with stress prevention effects over time.

The complexity of the stress response also needs greater consideration in these models. Recent models of stress are starting to separate out its component processes and, of these components, reactivity and exposure are currently being modeled in social support work. However, other relevant processes include stress recovery and stress restoration (Cacioppo & Berntson, 2007). A consideration of these component processes is important for identifying potential mediators of support effects. For instance, consideration of stress recovery highlights the role of rumination in exacerbating the stress responses (Brosschot, Pieper, & Thayer, 2005). It is possible that received support in the short-term is associated with stress-enhancement effects because it leads to greater rumination about the experience which is eventually resolved over time. Considering these issues can inform current support–stress models and highlight relevant mechanisms in need of modeling.

The complexity of the stress response is also reflected by work highlighting the differential effect of distinct sources of stress. The matching hypothesis does take this into account at a broad level by specifying links to sources of controllable and uncontrollable stress. However, there are other stressor categorizations that are important to consider. For instance, Bolger and colleagues (1989) found that only social sources of stress were associated with

"carryover" effects on mood the next day. The larger stress field highlights the particularly harmful influences of social stress on outcomes such as immune-mediated diseases (Cohen et al., 1998; Kiecolt-Glaser & Newton, 2001; Padgett et al., 1998). It may also be the case that, among social stressors, conflict within close relationships is especially impactful (e.g., marriage, family; Kiecolt-Glaser & Newton, 2001; Rook, 2003).

The support–stress models predict what happens once support is perceived or received by the recipient. This focus ignores another important issue: Why and when will individuals seek support in the first place? This is a complicated question as persons under stress must decide to seek support based on their emotions (Do they feel embarrassed about the problem?), thoughts (Can they handle the problem on their own?), and the quality of their existing relationships (Is there someone that they can turn to about this problem?) (Barbee, Gulley, & Cunningham, 1990). Clearly stress is not related to seeking support in a simple fashion and this complexity needs stronger consideration in these models.

People may also be motivated to seek out support during stress on the basis of preferences for a particular type of support. Such motivations may influence when social support is effective because, all else being equal, getting the preferred types of support should be associated with a more beneficial outcome. As an example, it has been argued that socialization processes result in women both preferring and benefiting more from emotional support than other support types. To test this proposition Flaherty and Richman (1989) examined psychological adjustment in women and men during the first year of medical school. Results suggested stronger associations between emotional support and well-being in women compared to men. Future research will be needed to more directly incorporate these motivational processes within support–stress models.

Another issue relevant to support–stress models is personality processes that can influence whether or not individuals seek support in the first place, as well as the benefits that they receive from support transactions. Hostile individuals, for instance, are less likely to seek support because of their mistrustful nature (Smith, 1992). In addition, researchers have found that hostile individuals did not appear to benefit from received support as evidenced by their high levels of physiological reactivity during stressful tasks (Christensen & Smith, 1993; Lepore, 1995). Of course, the number of potential personality processes or individual difference factors that can influence support processes is daunting. Within the physical health domain, one strategy is to examine personality factors that predict health outcomes (e.g., hostility, optimism, neuroticism). Overall, a more sustained analysis at the interface of conceptually relevant personality factors and stress-related support processes is needed in future research (see Pierce, Lakey, Sarason, Sarason, & Joseph, 1997, for a discussion of such issues).

It is also important to note that support–stress models do not explicitly take into account how the type or quality of relationship may influence the effectiveness of social support. The importance of this point is made by a study from Christenfeld and colleagues (1997) who had participants perform a stressful task while either a friend or stranger provided them with standardized supportive behaviors. Despite the fact that the same objective supportive behaviors were performed, blood pressure reactions to the stressful task were lower for participants who were given support from a friend versus a stranger (Christenfeld et al., 1997).

Even among friends there are differences in relationship quality that may have an effect on the effectiveness of support. We have argued more generally that the quality of individuals' social networks can be heuristically categorized based on their underlying positivity and negativity in the support process (see Uchino, Holt-Lunstad, Uno, & Flinders, 2001). This interest is fueled by research showing that positive and negative aspects of relationships tend to be separable dimensions, and both predict important health outcomes (Finch, Okun, Barrera, Zautra, & Reich, 1989; Friedman et al., 1995; Kiecolt-Glaser & Newton, 2001; Newsom, Nishishiba, Morgan, & Rook, 2003; Rook & Pietromonaco, 1987). A unique aspect of this conceptualization for the social support and health literature is represented by network members that are relatively high in *BOTH* positivity *AND* negativity during support. We label such a network member as an ambivalent network tie (e.g., overbearing parent, volatile romance). The implications of such ambivalent relationships have not been adequately considered as most prior research on social support has ignored the negative aspects that may co-occur with the positive aspects of relationships (Coyne & DeLongis, 1986; Uchino et al., 2001). Can individuals benefit from the positivity associated with ambivalent relationships? Or is negativity more salient, leading to harmful effects?

Our program of research is consistent with a detrimental influence of ambivalent ties. For example, we have found that older adults with higher numbers of ambivalent relationships within their network had higher levels of depressive symptoms and greater cardiovascular reactivity during stress (Uchino et al., 2001). In addition, ambulatory systolic blood pressure (SBP) was highest when participants were interacting with individuals they felt ambivalent toward, as compared to those toward whom their feelings were primarily positive, indifferent, or primarily negative (Holt-Lunstad, Uchino, Smith, Cerny, & Nealey-Moore, 2003). In one of our laboratory studies, we found that women provided with support from an ambivalent female friend (i.e., a friend they had both positive and negative feelings about) showed heightened cardiovascular reactivity during stress (Uno, Uchino, & Smith, 2002). Finally, these influences seem specific to a support-seeking context, as discussing a negative event (but not positive or neutral event) with an ambivalent

tie is associated with increased blood pressure reactivity (Holt-Lunstad, Uchino, Smith, & Hicks, 2007). These findings make it clear why not all relationships will result in stress-buffering or prevention effects. Relationships contain expectations for appropriate interactions and a personal history that can facilitate or hinder the support–stress process (Berscheid & Reis, 1998). These issues need greater consideration in current models.

Finally, an important aspect of these support–stress models that is often neglected is the effect of various "outcomes" on these models. Much research has documented the role of social support on stress-related differences in mental (e.g., depression) and physical health (e.g., morbidity). However, each outcome defines the health context and has unique implications for reciprocal links to support–stress processes. For instance, depression seems to influence one's interpretation of support and others' perception of that individual (Bolger & Eckenrode, 1991; Coyne, 1976). The chronic disease context is also important to consider as some conditions are more stigmatizing than others (e.g., HIV), a factor that can greatly impede the support process. These issues highlight the need for more dynamic process-oriented support–stress models that take into account changes over time appropriate to the particular health context.

Of course, these general critiques of support–stress models should not discourage their use in guiding research and relevant interventions. As noted earlier, some of these models (e.g., stress-buffering) have received substantial support for their basic tenets, whereas other models represent promising avenues for future work (e.g., stress prevention). However, due to their generality, we believe they represent important starting points and that greater attention to the relationship, stressor, and health context will be necessary.

A "revised" general framework for support–stress processes is depicted in Figure 9.2. Represented in this framework are the major models covered earlier, as well as basic processes that start to capture the complexity inherent in such links. The top half of the model represents basic stress and coping processes, including links to stress components that ultimately influence health outcomes (Cacioppo & Berntson, 2007). The bottom half depicts links between stress/coping and support-related processes (i.e., stress prevention, stress-buffering, matching), including support mobilization, deterioration, and a consideration of the source of support and type of stress matching (Uchino, 2004). Finally, the role of the specific health outcome of interest in the support process is also modeled. Such a broad framework can be used to guide relevant intervention because these complexities can determine the success or failure of intervention attempts. We now turn to a discussion of such intervention issues.

INTERVENTION ISSUES

Due in part to the potential role of social support in fostering adjustment to stress, there have been hundreds of support interventions in various populations aimed at helping individuals utilize their relationships for positive health outcomes (Hogan, Linden, & Najarian, 2002). Most of these interventions are based in chronic disease populations in an attempt to foster better mental and possibly physical health outcomes (Uchino, 2004). The source of support varies from a new relationship (e.g., physician) to established network ties. In addition, the intervention setting can include others (e.g., support groups) or involve a one-on-one interaction (Gottlieb, 1988). The implicit model driving these interventions appears to be the stress-buffering perspective, given the social, emotional, and cognitive challenges associated with managing chronic diseases.

We will not attempt to provide a comprehensive review of this large literature (see Hogan et al., 2002). However, we will discuss important issues for future support interventions based on the current status and issues

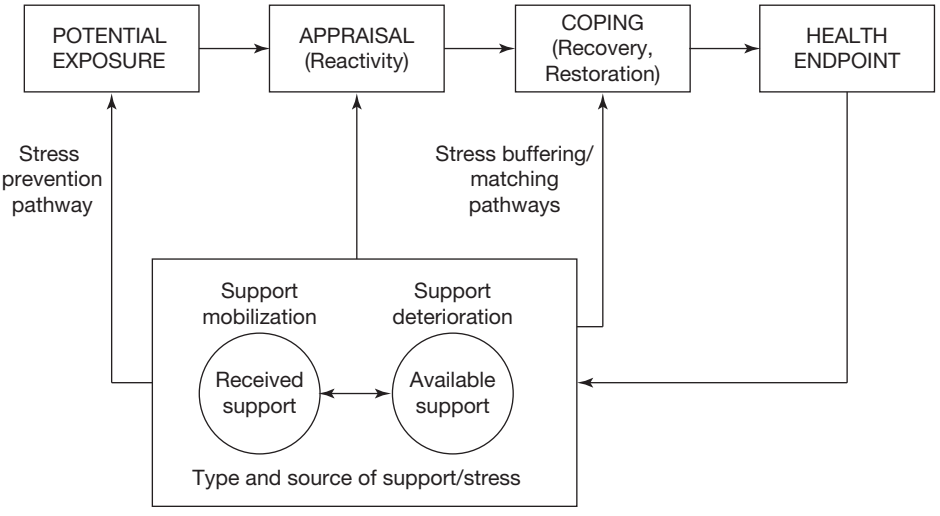

Figure 9.2 ■ Revised model linking support to stress and coping processes that emphasizes the importance of contextual factors.

inherent in the models discussed earlier. One of the most important issues is that sometimes measures of received support show no stress-buffering influences (Helgeson, 1993). This is quite important as support interventions attempt to foster received support from health care professionals, existing social networks, or peer support groups. Depending on the mechanism believed to be responsible for received support influences, interventions will need to take this into account. For instance, existing network ties can be trained to provide "invisible support" so as to not undermine the efficacy and esteem of the patient (Bolger et al., 2000). In peer support groups, the decision has already been made to seek support, and there is more reciprocal exchange of support, so such issues might be less salient compared to the actual nature and quality of the support provided (Bolger & Amarel, 2007).

At a more general level are issues related to the time course and context of the disease. As noted earlier, these factors can directly affect support–stress processes in ways that are not explicitly addressed in current models. In fact, one of the most basic questions to ask in attempting a support intervention is related to its appropriateness to the situation and population of interest. However, surprisingly few interventions appear to involve a thorough consideration of these issues (Gottlieb, 2000). In an attempt to highlight this problem, we have suggested that social support interventions can be comprehensively described by a variant of the question historically asked in the persuasion literature, "Who is saying what to whom and with what effect" (Smith, Lasswell, & Casey, 1946). For support interventions, the question becomes "Who is *providing* what to whom and with what effect" (Uchino, 2004).

This basic question makes salient the targets addressed by a well-designed support intervention (see Figure 9.2). At the "who" stage it may be important to address issues of who is available in the patient's network and what functions that person normally serves. If the patient's network is impoverished due to losses (e.g., bereavement), or if he or she is socially isolated, support from a new relationship may be required (Gottlieb, 2000). Of course, if an individual is socially isolated it also becomes important to address why this may be the case and to act accordingly (e.g., social skills training, anxiety reduction). In addition, "providing what to whom" will be highly context-specific (e.g., stressed caregivers or cardiac patients), and these contextual factors will need careful consideration in such intervention studies. One contextual consideration is the time frame for the interventions based on participant need. It may seem obvious but longer-term interventions appear to be associated with better outcomes (Cutrona & Cole, 2000). However, in some cases, long-term interventions may not be practical, and the use of "booster" sessions may be important.

Another important issue for these intervention studies revolves around the "with what effect" aspect of the question. Most support interventions target a set of defined outcomes such as well-being, behavioral change, or mortality. However, there are two other aspects of this question that are worth discussing. First, it is surprising that many support intervention studies fail to examine whether support levels change as a function of the intervention (Hogan et al., 2002). One exception is a recent stress-reduction intervention in caregivers of Alzheimer's Disease patients that demonstrated that reductions in caregiver depression were mediated by changes in satisfaction with support (Roth, Mittleman, Clay, Madan, & Haley, 2005). However, the relative lack of such support assessments can represent real problems in interpreting the results of an intervention. To be sure, in some cases it may be difficult to show changes in general perceptions of support availability as they tend to be quite stable and may have origins in early childhood interactions (Sarason, Sarason, & Shearin, 1986). Nonetheless, interventions can still address whether participants perceived that different support functions such as emotional or informational support were exchanged. This provides a support manipulation check that is firmly grounded in the intervention.

An emphasis on "with what effect" also makes salient the importance of examining the mechanisms by which the support intervention may be working. It is perfectly understandable why an intervention might be heavily focused on a primary outcome such as disease progression. However, intervention outcomes are a result of a process, and the need to understand this process is crucial to the reciprocal enterprise of theory building and practical application. For instance, the stress-buffering model highlights the importance of stress appraisals. Modeling such potential mechanisms is of importance to social support research more generally, and experimental interventions may provide a sensitive test of these pathways.

A final support intervention issue for consideration is that most focus on individuals who already have psychological, behavioral, or medical problems. An alternative way of thinking about support interventions is as a form of primary prevention that focuses on young, healthy individuals. Primary prevention refers to attempts to reduce the probability of a health problem developing (Kaplan, 2000) and would be consistent with stress prevention models. In a compelling analysis, Robert Kaplan argued for the promise of primary prevention efforts, especially in light of the more limited public health benefits that seem to arise from secondary prevention efforts that simply focus on the identification and treatment of disease.

Given that many chronic diseases have a long-term etiology and develop over decades (e.g., cardiovascular disease), primary prevention may be particularly important to consider in contemplating the development of appropriate social support interventions. For instance, it raises the interesting possibility that social support interventions may be usefully applied early in children and

adolescents to provide them with general social support skills. According to existing support–stress models, the cumulative effects of such an intervention, if successful, should produce improvements in both life quality and longevity over the lifespan.

CONCLUSION

In this chapter, we have reviewed the current status of support–stress models. Although such models have dominated research on social support and health, some remain in need of closer scrutiny (i.e., stress prevention model). The available evidence is reasonably consistent with these models, but further clarification of conflicting findings is warranted (e.g., effects of perceived versus received support). Priorities for future research include greater attention to the specific component processes implied by the general concept of psychological stress, and to issues that arise from consideration of the social and disease context and of temporal transitions in these factors. Relationships appear to have a tremendous potential to help those in need, and existing research is beginning to elucidate the complex but tractable associations linking social support, stress, and health.

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10 Social Network Functions and Health

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The idea that people who have few social ties are at risk for poor mental and physical health has been recognized since at least the time of Durkheim (1897/1951), and in the intervening 100+ years, an extensive scientific literature on the health effects of social networks has emerged. This literature—which spans multiple disciplines, including psychology, sociology, anthropology, epidemiology, medicine, and public health—provides strong evidence that social network involvement predicts morbidity and mortality (Berkman, Glass, Brissette, & Seeman, 2000; Cohen, 2004; House, Umberson, & Landis, 1988). In Berkman and Syme's (1979) seminal study, for example, people with more social ties (those who were married, had more family members and friends, and participated in more community organizations) were significantly less likely to die within a 9-year follow-up period. Links between social network involvement and mortality have since been replicated in many prospective studies, with more socially integrated individuals having a risk of mortality that is two to four times lower than that of less socially integrated individuals (House et al., 1988). This research is persuasive because it typically includes controls for baseline health status, health behavior, use of health services, and demographic characteristics that could potentially account for the association between social network involvement and mortality. The health-related risks of small social networks are comparable in size, moreover, to those of conventional risk factors, such as smoking and obesity (House et al., 1988; Rutledge et al., 2008).

Research has linked social network involvement not only to mortality but also to morbidity (Cohen, 2004; House, 2001). People with fewer social network ties have been found to be at elevated risk for infectious disease, cardiovascular disease and stroke, some forms of cancer, and possibly dementia (Cohen, 2004; Fratiglioni, Paillard-Borg, & Winblad, 2004; Rutledge et al., 2008; Uchino, 2006). Social network involvement has been linked to the course, as well as the onset, of chronic illness, including illness adjustment, postsurgical recovery, disability transitions, and survival (e.g., Avlund, Lund, Holstein, & Due, 2004; Cohen et al., 2007; Contrada et al., 2008; Seeman & Crimmins, 2001).

Not all people appear to benefit equally, however, from social network involvement. For example, research suggests that men may derive more health benefits from social integration than do women (Cohen, 2004; Seeman, 1996). In some studies, moreover, the benefits of social network involvement have emerged only in comparisons of the most socially isolated versus most socially integrated individuals (e.g., Brummett et al., 2001). Nonetheless, the generally robust evidence of links between social integration and health, coupled with parallel findings from animal studies (House et al., 1988), has generated great interest in understanding *how* and *why* social integration affects health (House, 2001; Uchino, 2010). House (2001) commented in this regard that our knowledge of "how and why social isolation is risky for health—or conversely—how and why social ties . . . are protective of health, still remains quite limited" (p. 273).

In this chapter, we seek to contribute to ongoing discussions of the "how" and "why" aspects of social network involvement by examining three broad domains of social network involvement that have been hypothesized to have distinctive effects on health and well-being: *support, companionship, and control.* Within each of these domains, both beneficial and detrimental aspects of social network interaction can be distinguished and linked to health consequences, some of which may be conceptualized in terms of the amelioration or generation of psychological stress, respectively. For example, support can be well timed and responsive to a stressed individual's needs, or it can be poorly timed, grudgingly rendered, or otherwise insensitive. Support that is not forthcoming in times of need can lead people to experience intensely distressing support letdowns. Being able to experience companionship with others can provide stimulation and kindle positive affect, but rejection by others can erode feelings of self-worth, arouse negative affect, and undermine self-regulation. Others' attempts to monitor and influence (or control) one's health behavior can reduce risky behavior, but they can provoke resistance and psychological distress. The psychological and physiological processes and health behaviors triggered by these different kinds of interactions with social network members, in turn, have the potential to affect morbidity and, ultimately, mortality, as summarized in Figure 10.1.

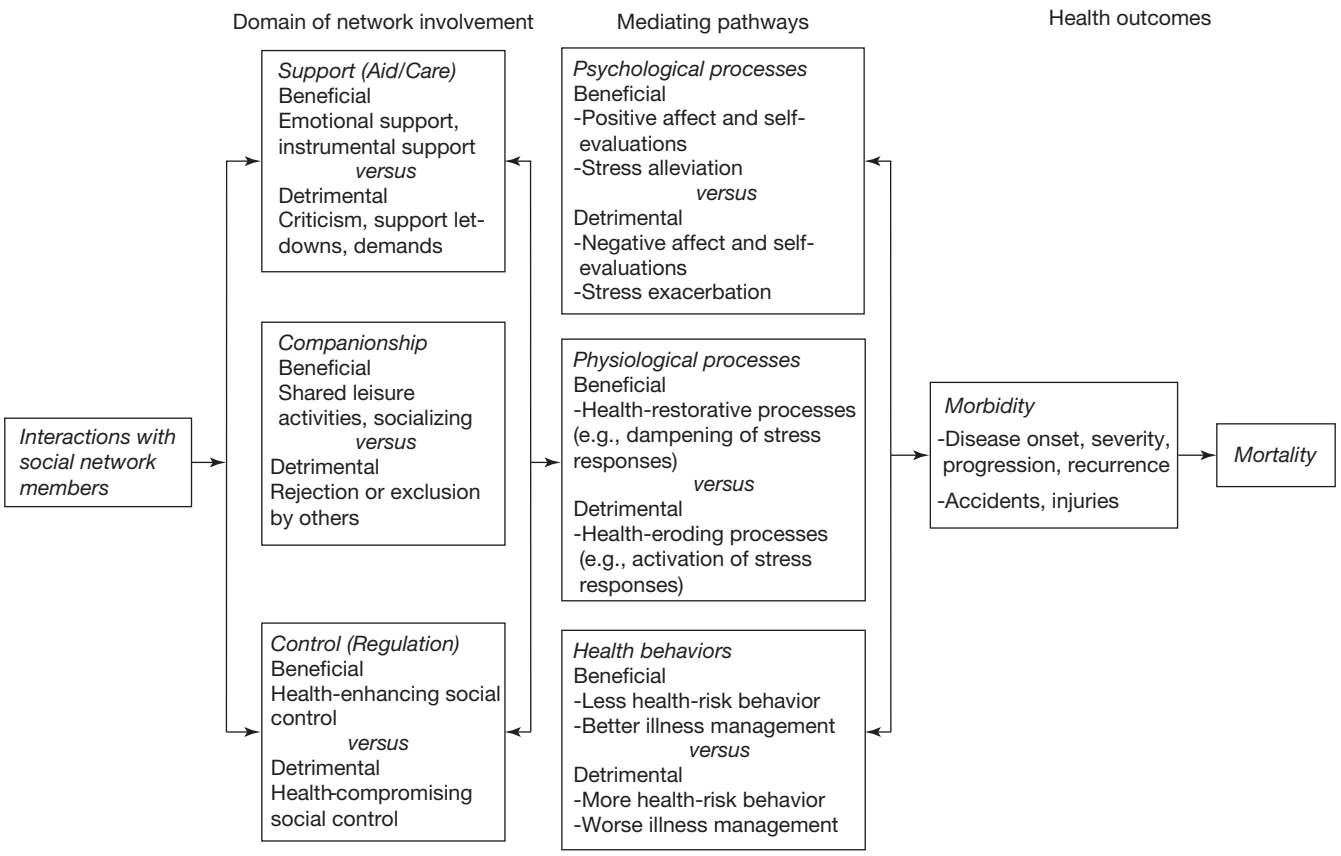

Figure 10.1 ■ Model linking beneficial versus detrimental aspects of three domains of social network involvement to health.

Our discussion concentrates, therefore, on key health-related *functions* that social network members perform in each other's lives. This emphasis leads us to focus on *actual exchanges* between social network members (cf. Fischer, 1982)—the things they do to aid each other, to create enjoyable shared activities, and to intervene to prevent risky behavior and, conversely, the things they do that can be insensitive, hurtful, or intrusive. The health-related functions of social relationships—as reflected in conceptually distinct classes of social interactions—can be distinguished from global qualities or perceptions of social relationships that may have implications for health and well-being in their own right (e.g., Lakey & Drew, 1997; Sarason & Sarason, 2009). Both the specific classes of social interactions that people experience with their social network members and their global perceptions of those interactions and relationships are important pieces of the broader puzzle of how social network involvement affects health. We focus on the interactional piece of this broader puzzler, but we recognize that both "pieces" are consequential for health, and also that they are related to each other because global perceptions of one's social relationships are shaped by past and current interactions with parents, partners, friends, and other important network members (Mikulincer & Shaver, 2009; Sarason & Sarason, 2009).

HEALTH-RELATED FUNCTIONS PERFORMED BY SOCIAL NETWORK MEMBERS

Delineating the key health-related functions performed by social network members provides a basic point of departure for efforts to understand the causal pathways by which social networks affect health (Cohen, 1988; Heller & Rook, 1997; Wills & Shinar, 2000). Distinguishing among the key functions performed by social network members is also important in providing a framework for conceptualizing and evaluating the active ingredients of interventions designed to help people whose social ties are deficient in some way (Eckenrode & Hamilton, 2000; Heller & Rook, 1997).

Researchers most often cite social support provided by social network members, and the stress-alleviating effects of social support, as the key social network function that matters most for health (House, 2001; Rook, 1987; Rook & Underwood, 2000). Considerable evidence has demonstrated that social support can help to buffer people from the adverse effects of life stress, and researchers have begun to identify the physiological processes that may underlie the stress-buffering effects of support (Cohen, 2004; Uchino, 2006, 2010; Uchino, Cacioppo, & Kiecolt-Glaser, 1996). Yet the provision of social support

is unlikely to be the only aspect of social network involvement that affects health and well-being (House, 2001; Rook & Underwood, 2000). Other potential benefits of social network involvement have begun to receive attention, including the enhancement of mood and feelings of self-worth associated with everyday companionship (Rook, 1987, 1995) and the reduction of health-compromising behavior associated with others' efforts to monitor and control (or regulate) risky behavior (Lewis & Rook, 1999; Umberson, 1987). Because social support has been discussed extensively elsewhere (e.g., Cohen, 2004; Uchino, 2006, 2010; Uchino et al., 1996), we discuss it only briefly below to provide a point of departure for comparison with other health-related functions of social networks that have received less attention to date.

SOCIAL SUPPORT

The scientific literature on social support emerged in large part out of an interest in understanding whether social support affords some protection from the adverse effects of life stress. Given this initial impetus to research on social support, it is not surprising that researchers have most often construed support in terms of various types of aid and care that social network members provide to family members and friends in times of need (e.g., Burleson & MacGeorge, 2002; Cohen, 2004; Thoits, 1985). Researchers have been interested in investigating, for example, the effectiveness of emotional support (expressions of empathy, concern, and positive regard), informational support (advice or information that facilitates problem solving), and instrumental support (tangible assistance; e.g., House, 1981) in specific situations but, importantly, these different forms of support are conceptualized as having the same broad objective—to help people cope with stressful life experiences. Consistent with this dominant view, Cohen (2004) defined social support as "a social network's provision of psychological and material resources *intended to benefit an individual's ability to cope with stress*" (p. 676).

From this perspective, social support is fundamentally directed toward the provision of care and aid in times of need. This focus on the help-providing function of social ties is understandable given an interest in factors that limit the health-damaging effects of life stress, but it has tended to discourage investigation of other functions of social ties that may have implications for health (Rook & Underwood, 2000). We discuss next the health-related effects of two such functions—companionship and social control—and their conceptual differentiation from social support.

Before we discuss these other social network functions, however, it is important to acknowledge that social support sometimes goes awry, having unintended negative effects (see Figure 10.1). Social network members can provide social support that is perfunctory, insensitive, or intrusive, increasing rather than decreasing recipients' psychological distress (Coyne, Wortman, & Lehman, 1988; Revenson, Schiaffino, Majerovitz, & Gibofsky, 1991). Support that is perceived to be insincere, inappropriate, or incongruent with recipients' needs may threaten their feelings of self-efficacy, autonomy, and overall well-being. Transactions involving the provision and receipt of instrumental support over an extended period of time, as in the context of chronic illness, appear to be particularly fraught with risks (e.g., Newsom, 1999; Reinhardt, Boerner, & Horowitz, 2006). Social network members also can fail to provide expected support in times of need, and such support let-downs can be intensely distressing (e.g., Brown & Harris, 1978). These examples illustrate that social relationships—and even transactions involving support—can be a source of stress as well as comfort and aid (Rook, 1998; Uchino, 2010). Support researchers and researchers studying other health-related functions of social relationships must grapple with these dualities in seeking to develop a full accounting of the health-related effects of social relationships, a theme to which we return later.

COMPANIONSHIP

People seek relationships with others not only for the support they can derive in times of need but also for the opportunities they provide for enjoyable interaction and camaraderie (Rook, 1987; Simmel, 1949). Wright (1989) noted that researchers ascribe so much importance to the emotional and instrumental support provided by social relationships that they often overlook "plain, unvarnished camaraderie—the joking, griping, teasing, story-swapping, interest-sharing, hobby-sharing, note-comparing, kind of interaction" that are key elements of many close relationships (p. 218). Although the need for companionship first emerges in childhood, in the form of a desire for adult interest and participation in the child's play (Sullivan, 1953), it continues throughout life as a desire to be involved with others in mutually interesting and enjoyable activities.

Conceptual Differences Between Social Support and Companionship

Social support and companionship differ conceptually in a number of respects. First, *personal motivations* for seeking companionship may differ from those underlying support, with companionship motivated by the desire to experience hedonic rewards (e.g., positive affect, stimulation) and support motivated by the desire to reduce emotional distress and to obtain assistance with personal problems (cf. Thoits, 1985).

Companionship and support also may differ in their *importance across different life contexts* (Rook, 1987). Companionship is likely to be important on an ongoing basis as part of the fabric of everyday life, whereas support provided by others is likely to assume singular importance

in times of significant life stress. Similarly, companionship and support may differ in their *importance for different dimensions of well-being* (Bolger & Eckenrode, 1991; Buunk & Verhoeven, 1991; Haines & Hurlbert, 1992; Rook, 1987). If social support is particularly important when an individual's equilibrium has been disrupted by a stressful life event, then it may contribute to well-being primarily by restoring equilibrium (by alleviating distress and helping the individual plan a course of action to deal with the stressor). In this sense, exchanges of support help to return the individual to a baseline (pre-stressor) level of functioning, but they may do relatively little to boost well-being beyond this baseline level. Shared recreation and other forms of companionship, in contrast, may help to elevate well-being beyond a customary baseline level. Weiss (1974) argued in this regard that friendships "offer a base for social events and happenings" and "in the absence of such ties life becomes dull, perhaps painfully so" (p. 23). Social support may be particularly effective, therefore, in reducing significant threats to health and well-being, whereas companionship may be particularly effective in boosting emotional well-being (Rook, 1987, 1995).

Receiving social support may have *potential costs* that are not experienced when people enjoy companionship with others. Receiving social support from others can make one feel indebted to or less competent than the support provider (Bolger & Amarel, 2007; Fisher, Goff, Nadler, & Chinsky, 1988; Newsom, 1999). Companionship does not entail the asymmetries that characterize a helper–help relationship and, therefore, may be less likely to elicit ambivalent reactions of gratitude and indebtedness. Simmel (1949) noted that companionship has an inherently egalitarian structure because it occurs between equals, thereby reducing the psychological discomfort associated with hierarchical relationships. Consistent with this idea, some evidence suggests that companionship may play a stronger role than social support in sustaining self-esteem among people experiencing a major life transition (Hirsch, 1980).

Potential Mechanisms Linking Companionship to Health

Several different mechanisms can be posited by which companionship may affect health (see Figure 10.1). First, shared leisure activities are responsive only "to the requirements of pleasure" (Larson, Mannell, & Zuzanek, 1986, p. 116), and companionship, accordingly, is a key context in which people experience *positive affect* in the course of their daily lives (Kleiber, Hutchinson, & Williams, 2002; Rook, 1987). Positive affect, in turn, has been found to have health-protective effects (Ostir, Ottenbacher, & Markides, 2004; Pressman & Cohen, 2005). In a recent review, Pressman and Cohen (2005) concluded that positive affect is associated with lower morbidity, fewer symptoms and less pain associated with health conditions, and (among older adults) greater longevity. Low positive affect and a dearth of pleasurable social activities have long been implicated, as well, in the onset and maintenance of some psychological disorders, such as depression (e.g., Lewinsohn, Biglan, & Zeiss, 1976; Rohde, Lewinsohn, Tilson, & Seeley, 1990). Companionship may contribute to physical and psychological health, therefore, partly through its role as a source of enjoyable activity and positive affect in daily life.

Positive affect contributes, moreover, to greater *resilience* and optimism, psychological resources that help people withstand life stress more effectively (Kleiber et al., 2002; Salovey, Rothman, Detweiler, & Steward, 2000; Tugade & Fredrickson, 2004). In a related vein, restorative activities, such as sleep, exercise, relaxation, and recreational activities, play an important role in helping to reduce the impact of life stress and, therefore, the health-related toll of life stress (Cacioppo & Bernstein, 2006; Smith & Baum, 2003). Companionship generates positive affect, which contributes to resilience, and it also helps people transcend their current concerns and problems (Kleiber et al., 2002). When people get together to socialize, it is often with the goal of leaving behind worries about work, family members, or other problems. Companionship may be an important *restorative activity*, one often woven into the fabric of daily life, that helps limit the health-damaging effects of stress.

Affirmation of self-worth may be another mechanism by which companionship affects health and well-being. The potential role of emotional support in sustaining recipients' feelings of self-worth has been widely discussed (Wills & Shinar, 2000), but less attention has been paid to companionship in this regard. Yet companionship may contribute meaningfully to the preservation of self-esteem. "When people choose each other as companions for their leisure time, a commodity that is usually limited and therefore precious, they signal behaviorally that they view each other with high regard. That is, they do not need to verbalize feelings of respect and appreciation; their actions convey these sentiments" (Rook, 1987, p. 1139). In fact, companionship has the potential to convey another person's regard more clearly than does social support (Iwasaki, 2001). Friends and family members who provide support in times of need may be seen as doing so either because they genuinely care about the recipient or because they feel obligated to provide help. Attributional ambiguity therefore may surround perceptions of their motivations for providing support, thereby diluting the positive impact of the support provided (Rook, 1987; Suls, 1982). Companionship, in contrast, is more likely to be viewed as emerging from genuine liking and mutual enjoyment of one another's company (Rook, 1987).

Detrimental Effects of Lacking Companionship

The potential mechanisms that link companionship to health can be thought about not only in terms of those who have companionship but also those who lack companionship. In many ways, the latter mechanisms can be seen as parallel to those just discussed (see Figure 10.1).

People who lack companionship would be likely to experience less positive affect and more negative affect, less likely to develop resilience and other psychological resources that would help them withstand life stress, less likely to have restorative experiences that help to dampen stress responses, and more likely to experience feelings of low self-worth (particularly if they feel rejected or excluded by others; Baumeister, DeWall, Ciarocco, & Twenge, 2005; Cacioppo & Hawkley, 2005). Although the categories of mechanisms that link the presence or absence of companionship to health may be substantively comparable, we do not think that the health effects themselves are necessarily comparable. Based on evidence of the distinctive potency of negative interpersonal experiences relative to positive interpersonal experiences (Newsom, Rook, Nishishiba, Sorkin, & Mahan, 2005; Rook, 1998), we anticipate that the harmful effects of lacking companionship may differ from, and exceed in magnitude, the beneficial effects of having companionship. This is an empirical question, however, and one that is directly analogous to questions raised recently by researchers as to whether the correlates of social isolation and social integration (House, 2001), or psychological well-being and psychological distress, are distinctive or mirror opposites of each other (Ryff et al., 2006).

Evidence of the Health-Related Effects of Companionship

Studies examining the health-related effects of companionship or comparing the effects of support and companionship are relatively sparse, but the research conducted to date supports several preliminary conclusions. First, support and companionship appear to be distinguishable empirically (Rook, 1987, 1994), even though they often co-occur in particular relationships. Second, support and companionship appear to have somewhat different correlates, with companionship related more reliably than support to emotional health, relationship satisfaction, and loneliness (Bolger & Eckenrode, 1991; Buunk & Verhoeven, 1991; Newsom et al., 2005; Rook, 1987). Third, in cross-sectional and longitudinal studies, companionship has been found to be more strongly linked than support to which social network members come to be regarded as friends (e.g., Fischer, 1981; Hays, 1985), and some research suggests that the search for new friends is motivated more by the desire to enjoy companionship than by the desire to have more social support (Jerome, 1981).

In addition, evidence from several studies suggests that companionship helps to buffer people—sometimes more effectively than social support—from the adverse effects of academic stressors (e.g., Bolger & Eckenrode, 1991; Iwasaki, 2001), work-related stressors (e.g., Buunk & Verhoeven, 1991; Iwasaki, Mannell, Smale, & Butcher, 2005), daily hassles (e.g., Iso-Ahola & Park, 1996; Rook, 1987), and chronic stressors that cannot be resolved through problem-solving efforts (e.g., Thompson, Futterman, Gallagher-Thompson, Rose, & Lovett, 1993). Companionship helps to provide an escape, even if temporary, from the stressors of the day, and it may trigger physiological processes that help to counter harmful stress responses. For example, the neuropeptide, oxytocin, which is released in response to positive social bonding (Carter, Williams, Witt, & Insel, 1992), has been implicated in buffering the adverse effects of the stress hormone, cortisol (e.g., Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003). When people face serious life disruptions, however, companionship may be insufficient to provide protection from the harmful effects of stress. In a study that distinguished major and minor life stress, companionship appeared to be more effective than social support in buffering people from minor life stress. Social support, in contrast, appeared to be more effective than companionship in buffering people from major life stress (Rook, 1987).

Clues also exist in the literature suggesting that companionship may be related to the risk of mortality as strongly, or more strongly, than is support, at least among the elderly. Older adults who have more friends or more frequent interaction with friends have been found in several studies to live longer, controlling for demographic characteristics, current and prior health status, and other factors that might account for the association (Giles, Glonek, Luszcz, & Andrews, 2005; Litwin, 2007; Maier & Klumb, 2005; Rasulo, Christensen, & Tomassini, 2005). In this work, involvement with family members was less reliably related to longevity. In seeking to interpret this pattern, Litwin (2007) speculated that friendship mobilizes specific processes that may serve to reduce mortality risk. We believe that the processes mobilized involve companionship. We base this speculation on evidence from other research that friends are particularly likely to function as sources of companionship in later life, whereas family members are particularly likely to function as sources of support (especially instrumental support; e.g., Agneessens, Waege, & Lievens, 2006; Rook & Ituarte, 1999). This leads us to believe that companionship may be at least partly responsible for the distinctive links between friendship involvement and mortality documented in this work.

The body of empirical evidence that has a bearing on how companionship affects health expands greatly if we invert the question to ask how the *lack* of companionship affects health. Reframing the question in this way leads us to consider research that has examined the health effects of loneliness and social exclusion. Loneliness has been linked to persistently elevated negative emotions (Hawkley, Preacher, & Cacioppo, 2007), more chronic stress (Hawkley & Cacioppo, 2007), greater cardiovascular activation (Cacioppo et al., 2002), reduced physical activity (Hawkley, Thisted, & Cacioppo, 2009), and impaired sleep (Cacioppo et al., 2002). These associations have been documented controlling for demographic characteristics, self-rated health, and various psychosocial factors (e.g., hostility, social support, perceived stress). Both loneliness

and the threat of social exclusion also have been found to impair self-regulation, leading to poor control over emotions and health behaviors (Baumeister, DeWall, Ciarocco, & Twenge, 2005; Hawkley et al., 2009). All of these processes increase the risk of disease onset and progression.

The health-damaging effects of loneliness accumulate over the life span (Hawkley & Cacioppo, 2007). Social rejection and isolation in childhood and adolescence have been linked to reduced exercise and other cardiovascular risk factors in adulthood (Caspi, Harrington, Moffitt, Milne, & Poulton, 2006). Although loneliness may reflect more than one underlying social deficit, a lack of companionship is a prominent feature in its conceptualization and assessment (Russell, Peplau, & Cutrona, 1980; Weiss, 1974), and it is plausible that a lack of companionship is implicated in some of the health-damaging effects documented in these studies (e.g., Sorkin, Rook, & Lu, 2002).

Future Directions for Research on the Health-Related Effect of Companionship

Considered together, these different lines of research suggest that companionship may play a more varied and consequential role in sustaining health and well-being than has been recognized to date. Companionship, like social support, is an important component of many close relationships. Analyses are needed that grant companionship a conceptual status on a par with that granted to social support in efforts to understand how social network involvement affects health. These two classes of social network involvement make complementary contributions to health and well-being that need to be understood more fully.

Because companionship has been examined infrequently in studies of the health effects of social network involvement, many questions remain about the nature of its contributions to health and well-being. We illustrate a few such questions here. One question concerns how different types of companionship (e.g., passive versus active forms of shared leisure; Kleiber et al., 2002) might be linked to health, analogous to the more widely studied question of how different types of social support (e.g., emotional, informational, instrumental support) are linked to health. Previous research provides clues that differentiating among types of companionship may be a useful direction for future research. For example, a daily diary study of older adults found that spending time with friends, as compared with family members, was associated with more positive mood and greater arousal. This difference appeared to be attributable to the fact that the older adults engaged in active forms of leisure with their friends (e.g., hobbies, sports, cultural activities) but passive forms of leisure (e.g., watching television) with their family members (Larson et al., 1986)

Another issue for future research concerns how much companionship is necessary to yield health-related benefits. Is the association between companionship and health linear, or does a threshold exist beyond which additional companionship contributes little to health and well-being? Support researchers have asked similar questions about the gradient of social support effects (Cohen, Gottlieb, & Underwood, 2000; House et al., 1988). Baumeister and Leary (1995) argued that humans have a universal need to form and maintain a minimum quantity of positive social relationships, beyond which additional relationships offer diminishing returns. What this minimum is, for different people at different points in the life span, remains unclear and warrants exploration in future studies.

In thinking about people who lack companions for shared activities—those who might suffer from abject feelings of loneliness—an important question concerns the extent to which they turn to nonsocial or parasocial alternatives to derive some of the stimulation and pleasure (Rook & Schuster, 1996) or the sense of connection (Epley, Akalis, Waytz, & Cacioppo, 2008) ordinarily derived from interaction with close network members. Evidence suggests that people who suffer from loneliness or lack close relationships do seek to forge substitute social ties and may turn to nonsocial activities (e.g., solitary hobbies) and parasocial alternatives (e.g., connections with pets), but it is not clear whether these substitute activities and connections afford physical or mental health benefits (Epley et al., 2008; Zettel & Rook, 2004). Expanding research on the health-related effects of companionship seems like a worthwhile goal, as does investigation of another important function of social networks—social control.

SOCIAL CONTROL

Social network members may influence each other's health not only by serving as sources of support and companionship, but also by serving as sources of control or regulation. Durkheim (1897/1951) provided early evidence that people who are embedded in a network of social ties are likely to be deterred from engaging in risky or self-injurious behavior.

Theorists have distinguished between two basic mechanisms of social control (e.g., Durkheim, 1897/1951; Hughes & Gove, 1981; Umberson, 1987). First, social network relationships often involve significant role obligations, such as marital or parental obligations, that are thought to exert a stabilizing and restraining influence on behavior. The parents of a young child, for example, may curtail their alcohol intake or limit other risky behavior so as not to jeopardize performance of their parental role responsibilities. This source of self-restraint, which arises from existence of role obligations to significant others, has been termed *indirect social control* (Umberson, 1987). Second, constraints on behavior also can result from social network members' explicit attempts to prompt others to engage in sound health behaviors or, conversely, to refrain from engaging in risky or unsound health behaviors (Hughes & Gove, 1981; Umberson, 1987). Such explicit attempts to regulate another person's behavior

have been termed *direct social control* (Umberson, 1987). These attempts may take the form of persuasive appeals, reminders, and contingent rewards as well as criticism, threatened sanctions, and coercion (Lewis & Butterfield, 2005; Tucker & Anders, 2001; Umberson, 1987).

Conceptual Differences Between Social Support and Social Control

Social control, therefore, fundamentally involves constraints on behavior, which sometimes entail interference and negative feedback from others. The core element of constraint highlights a basic difference between social support and social control. Social support theorists generally take the position that support is beneficial to the extent that is affirming (e.g., Kahn & Antonucci, 1980), whereas social control theorists argue that regulatory actions by others may be beneficial even when they are not affirming (Rook, 1995). For example, pressuring a family member to end his or her substance abuse is apt to be beneficial if it induces behavior change even if the action is decidedly unwelcome. In this vein, Hughes and Gove (1981) argued that others' regulatory actions may arouse psychological distress even though they lead to less risky behavior and more stable functioning: "Constraint may be the source of considerable frustration; at the same time it tends to reduce the probability of problematic or maladaptive behaviors" (p. 71). The idea that social control may foster improved health behavior even while it provokes psychological distress has come to be known as the dual effects hypothesis (Hughes & Gove, 1981; Lewis & Rook, 1999; Rook, Thuras, & Lewis, 1990). More recent formulations have extended the idea of dual effects to include other potentially negative outcomes of social control attempts. For example, social control attempts may communicate that an individual has poor self-control, which could erode feelings of self-efficacy (e.g., Franks et al., 2006; Rook, 1995). In addition, resentment, guilt, or embarrassment experienced in response to others' social control attempts could sow the seeds for relationship conflicts or withdrawal.

Recognizing that others' control attempts can be unwelcome illustrates another basic difference between social support and social control. Although people often seek social support from others, they are less likely to seek social control. Social control, by definition, involves efforts to induce a person to discontinue an established health-compromising behavior (one presumably maintained by rewards of some kind) or to initiate a health-enhancing behavior in which a person has shown little prior interest or history of sustained success. Thus, compared to providers and recipients of social support, sources and targets of social control are less likely to share the same behavioral goals. Social control transactions that occur in the context of chronic illness may take on a somewhat different meaning that could qualify this conclusion, however, as we discuss later.

Potential Mechanisms Linking Social Control to Health

This discussion highlights the notion that social control is linked to health through two primary, and largely opposing, processes (see Figure 10.1; Hughes & Gove, 1981; Lewis & Rook, 1999; Rook et al., 1990). On the one hand, social control may discourage health-compromising behaviors and encourage health-enhancing behaviors, thereby contributing to better health and, ultimately, a lower risk of mortality (Lewis & Rook, 1999; Umberson, 1987). On the other hand, to the extent that social control involves attempts by others to constrain behavior (as distinct from self-restraint of behavior), it may arouse psychological distress, erode feelings of self-efficacy, and kindle relationship tensions (Lewis & Rook, 1999; Tucker & Anders, 2001). Negative emotions increase the risk of morbidity and mortality through their effects on endocrine, immune, and cardiovascular systems. Specifically, negative emotions have been found to be associated with activation of the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic nervous system (SNS; e.g., Jorgensen, Johnson, Kolodziej, & Schreer, 1996). In addition, recurring strains and conflicts in close relationships expose people to the physiological sequelae of chronically activated HPA axis or SNS activity (e.g., elevation in blood pressure, heart rate) and may impair immune functioning (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; Kiecolt-Glaser et al., 2005). Chronically activated and dysregulated physiological systems, in turn, increase risks for a variety of pathologies (Baum & Posluszny, 1999). The psychological and relational costs of social control, therefore, may reduce or even cancel the hypothesized health benefits of social control, although the net effects of social control on health are not yet fully understood.

Evidence of the Health-Related Effects of Social Control

Most research examining the health-related effects of social control has focused on direct social control. The work conducted to date suggests several conclusions. First, social control appears to be distinguishable empirically from social support (Franks et al., 2006; Helgeson, Novak, Lepore, & Eton, 2004; Lewis, Butterfield, Darbes, & Johnston-Brooks, 2004), although members of close relationships (such as marital relationships) often engage in both health-related support and health-related control (Franks, Wendorf, Gonzalez, & Ketterer, 2004). The co-occurrence of support and control in many close relationships makes it challenging to identify their distinctive effects, in much the same way that social support researchers often have found it challenging to evaluate the distinctive effects of different kinds of social support (Wills & Shinar, 2000).

Second, mixed evidence has emerged in the literature regarding the effects of social control on health behaviors. Some studies have found social control attempts

by social network members to be related to less health-compromising behavior (such as smoking) and to more health-enhancing behavior (e.g., exercise, sleep, and good dietary practices; Rook et al., 1990; Thorpe, Lewis, & Sterba, 2008; Tucker, 2002; Tucker & Anders, 2001; Umberson, 1992; Westmaas, Wild, & Ferrence, 2002). Other studies, however, have found social control attempts by social network members to be related to worse, rather than better, health behavior (Lewis & Rook, 1999), including greater hiding of unsound health behavior (Lewis & Rook, 1999; Tucker & Anders, 2001) and pretended adoption of sound health behavior (Thorpe et al., 2008). How findings linking greater social control to worse health behavior should be interpreted remains a matter of ongoing discussion in the literature. Such findings may indicate that negative health behaviors elicit social control attempts or, alternatively, that social control attempts encourage poor health behaviors (e.g., by provoking behavioral reactance or undermining self-efficacy for health behavior; Franks et al., 2006; Lewis & Rook, 1999; Tucker & Anders, 2001).

Studies of social control that have assessed distress have yielded fairly consistent evidence that social control can be distressing. In an early study, Hughes and Gove (1981) found that people who lived with others (and who presumably were subject to monitoring and control attempts by others) reported lower rates of health-risk behavior but, at the same time, reported more psychological distress. Subsequent studies that have assessed actual social control attempts by social network members have found that the targets of such attempts tend to exhibit increased distress, such as feelings of anger, guilt, and resentment (e.g., Lewis & Rook, 1999; Tucker & Anders, 2001; Tucker, Orlando, Elliott, & Klein, 2006). In other studies, social control has been linked to distress only among particular groups, such as those with low relationship satisfaction (Tucker, 2002) or only when coercive (rather than persuasive) tactics of social control are used (Lewis & Butterfield, 2005; Tucker & Anders, 2001).

The evidence from this body of empirical work is leading to revised formulations of the dual effects hypothesis that emphasize affective reactions as mediators of the effects of social control attempts. Specifically, social control is predicted to have adverse effects on health behavior (undermining rather than fostering sound health behavior) to the extent that it elicits negative emotions, such as resentment or anger (Lewis & Butterfield, 2005; Lewis & Rook, 1999; Okun, Huff, August, & Rook, 2007; Tucker & Anders, 2001).

The circumstances in which social control is likely to elicit negative emotions have begun to be delineated, with a strong emphasis on the nature of the social control tactics used by social network members. Specifically, negative emotions are thought to emerge when social control attempts reflect the use of more coercive and critical strategies; in contrast, negative emotions are not expected, and positive emotions actually may occur, in response to the use of noncoercive social control strategies, such as reminders and persuasive appeals (Lewis & Butterfield, 2005; Lewis & Rook, 1999; Okun et al., 2007; Tucker & Anders, 2001). Evidence in support of these revised formulations has begun to emerge, although an empirical challenge confronting researchers is the fact that social network members frequently use multiple strategies of influence (Lewis & Butterfield, 2005).

Social Control in the Context of Chronic Illness

Much of the work discussed above has been conducted with general community samples rather than patient samples (Stephens et al., 2009). More recently, researchers have become interested in the effects of social control in the context of chronic illness, particularly illnesses that require long-term adherence to a regimen of daily health behaviors (e.g., prostate cancer, Helgeson et al., 2004; HIV, Fekete, Geaghan, & Druley, 2009; diabetes, Thorpe et al., 2008; cardiac rehabilitation, Franks et al., 2006; knee replacement surgery, Stephens et al., 2009). Close social network members, such as spouses, often seek to participate in a partner's chronic illness management (Revenson, 1994), and they are likely to share the overarching goal of facilitating the individual's adherence to prescribed health behaviors (Franks et al., 2006). Sharing a common overarching goal may cause the meaning and dynamics of social control attempts experienced by patients to differ from those experienced by relatively healthy individuals. Patients, for example, may be more likely to regard their spouses' or other family members' social control attempts as well intentioned and, perhaps, legitimized by the treatment-related mandate for behavior change. As a result, patients might be less likely to react negatively to such social control attempts. On the other hand, the demands of the illness and worries about lapses in treatment adherence may lead spouses or family members to engage in particularly intense social control attempts, possibly provoking negative reactions in patients.

The sparse evidence that exists regarding the effects of social control in the context of chronic illness does not provide a basis for predicting which of these alternatives is likely to be more common. Social control has been linked in some studies to negative emotions (Stephens et al., 2009; Thorpe et al., 2008) as well as feelings of appreciation (Rook & Ituarte, 1999) and to worse health behavior (Franks et al., 2006; Helgeson et al., 2004; Thorpe et al., 2008) as well as better treatment adherence and physical functioning (Stephens et al., 2009).

The inconsistent pattern of findings may reflect the influence of unmeasured variation in how spouses or members of other close dyads construe the disease management process. For example, if the day-to-day tasks of managing the disease are viewed as a collaborative rather than an independent endeavor, patients may react more favorably to social network members' involvement in their health (Berg et al., 2008), perhaps including their influence attempts.

The inconsistent findings also may reflect the largely singular focus in previous studies on social control. This focus is understandable given the emerging status of the literature on health-related social control, but it has tended to limit attention to other functions performed by network members that might interact with social control to affect health. More generally, gaps exist in our current understanding of the joint effects of different health-related functions performed by social network members (Rook & Underwood, 2000). Addressing these gaps is a priority for future research, and we illustrate this point below by considering plausible, but decidedly different, joint effects of social support and social control that warrant investigation.

Interactive Effects of Different Social Network Functions: An Illustration Involving Social Support and Social Control

Social network members' involvement in the illness management process often involves a mix of health-related social control and social support, rather than one form of involvement exclusively (Franks et al., 2006). Yet the potential health effects of experiencing both controlling and supportive interactions with network members have rarely been studied. Potential interactions between social support and social control have been discussed thus far in the literature primarily with reference to dilemmas that members of close relationships may face as they seek to balance their desire to influence a significant other's health behavior with the desire to preserve harmony in the relationship (Rook, 1995). For example, a spouse who is concerned about her husband's escalating alcohol use following a job layoff may alternate between providing emotional support to help him deal with the stress of unemployment and exerting social control to pressure him to curtail his drinking. Social control tactics that are sufficiently intense to induce the desired behavior change may do so at the expense of goodwill in the relationships. Dillard and Fitzpatrick (1985) referred to influence attempts that succeed in prompting behavioral compliance while simultaneously provoking resentment as a "pyrrhic victory." Social control tactics that involve considerable tact and sensitivity, in contrast, may preserve goodwill in the relationship but may fail to achieve the desired behavior change objective (Miller & Boster, 1988; Rook, 1995). These examples suggest that social support and social control might be viewed as incompatible functions, with social control dampening or canceling the effects of social support and vice versa.

Yet it is also possible that social control and social support could have compatible and mutually facilitative, rather than contradictory, effects. A prior history of supportive exchanges in a relationship with a social network member may make the network member's efforts to exercise control more tolerable and, perhaps, more effective (Rook & Underwood, 2000). For example, an elderly widower may be more responsive to his daughter's persistent efforts to get him to stop smoking when the daughter has a strong track record of providing support than when she lacks such a record (Rook, 1995). Social control attempts may not detract from relationship quality, therefore, when they occur in relationships that, at other times, have functioned as dependable sources of support (Rook & Underwood, 2000).

Future Directions for Research on the Health-Related Effects of Social Control

The preceding examples illustrate the need to investigate the interactive dynamics and effects of social control and social support. Such investigations may help to shed light on a question that remains to be understood: When do social control attempts have the intended benefit of contributing to improved health behavior without the unintended effect of provoking psychological distress and or relationship tensions? Clues from existing studies suggest that it may be useful to search for answers in the specific health context under consideration (e.g., Stephens et al., 2009; Thorpe et al., 2008), in the particular strategies of social control used by network members (Lewis & Rook, 1999), and in perceptions of the appropriate role for a close network member in a focal person's health (Berg et al., 2008).

Analyses are also needed that provide a full accounting of the net impact of social control on health, particularly if social control often has opposing effects on health behavior and psychological or relational health. Perhaps the distress aroused by heavy-handed social control attempts tends to be short lived, whereas the behavior change prompted by such attempts tends to be long lived. In such cases, the net effects on health over time might be positive. On the other hand, if heavy-handed social control attempts lead to chronic or recurring psychological distress or relationship conflicts, the net effects on health might be negative or neutral, even if behavior change occurs. The adverse health effects of stress and negative emotions on endocrine, immune, and cardiovascular systems are well documented (e.g., Jorgensen et al., 1996; Kiecolt-Glaser et al., 2002). In view of such evidence, it is important to evaluate the significance for health of the negative emotions and relationship stress that may be engendered by network members' social control attempts.

In a related vein, it may be important to consider the potential health consequences for the sources, as well as the recipients of social control, particularly if social control attempts often trigger stress and conflict in close relationships (August, Rook, Stephens, & Franks, 2008). Spouses may feel burdened, for example, by having to monitor and seek to prompt behavior change in partners who engage in unsound health behavior, and they may suffer when their partners react with resentment or hostility. Such burdens may be amplified in the context of chronic

illness, as spouses may experience ongoing obligations to be engaged in their partner's disease management—obligations that may be particularly stressful or burdensome if the partner exhibits poor treatment adherence and self-care (August et al., 2008). Research on caregiving suggests that providing extended support and care for seriously ill family members is associated with experiencing elevated levels of stress hormones, poor antibody production, and poor self-reported health (Vitaliano, Zhang, & Scanlan, 2003). Extrapolation from this research suggests that social network members who feel compelled to engage in sustained social control attempts over time may experience adverse effects themselves.

The dominant focus of the emerging literature on health-related behaviors has been on direct social control; yet it is possible that indirect and direct social control may work in concert to influence these behaviors. For example, when social network members perceive individuals with significant role obligations (e.g., spouses, parents) to be unable to self-regulate their health behavior, the network members may mobilize to exert direct social control and, at the same time, to shore up the individuals' understanding of their role obligations. Future research, therefore, could fruitfully explore links that may exist between indirect and direct social control.

Finally, our discussion of social control thus far has emphasized the hypothesized risk-deterring role of social control in social network relationships. Yet social network members clearly sometimes encourage undesirable, rather than desirable, health practices (Cohen, 1988; Rook et al., 1990). This is reflected, for example, in evidence indicating that adolescents sometimes recruit their peers to use illegal substances and to engage in other risk behavior (e.g., Jessor, Donovan, & Costa, 1994; Wills, McNamara, Vaccaro, & Hirky, 1996). Adults have been studied most often in the emerging literature on health-related social control, and in this work undermining forms of social control have been found to be rare (e.g., Rook et al., 1990). Still, an important task for social control researchers is to develop theoretical frameworks for predicting when social network members will or will not engage in undermining forms of social control and how recipients will respond to competing sources of influence, such as parents versus peers (e.g., Wills, Resko, Ainette, & Mendoza, 2004).

CONCLUSION

Social network members interact with each other in many ways that have consequences for their health and longevity, but exactly how and why these interactions affect health remains poorly understood (House, 2001). Researchers have tended to emphasize social support as pivotally important in their search for answers to these "how" and "why" questions. We share the view that social support warrants a prominent place in efforts to understand the health effects of social network involvement, but other classes of interactions matter too. Cohen et al. (2000) observed that some researchers posit social support as an overarching construct that subsumes "any process by which social relationships might promote health and well-being" (p. 4). We understand the appeal of such a higher order construct that is perceived to capture the essence of various constituent interpersonal processes considered beneficial to health. This perspective poses problems, however, as it blurs distinctions between processes that are fundamentally different in a number of respects, it cannot easily accommodate processes that are decidedly hurtful and harmful, and it encourages the unnecessarily limiting view that the effects of the constituent processes all operate through perceptions of the supportiveness of social network relationships and interactions.

Brisette, Cohen, and Seeman (2000) noted in this regard that social integration is often equated with access to social support resources, but they cautioned that "it is not clear that support has anything to do with the health effects of being socially integrated" (p. 69). We believe that social support does play an important role in explaining the health effects of being socially integrated, but we do not believe it is the whole story. Companionship and social control, like social support, are common elements of most close relationships. Together, social support, companionship, and social control represent conceptually and empirically distinct functions of social bonds that have relevance, in different contexts and through different mechanisms, to basic human needs for aid and care, for enjoyment and stimulation, and for constraints on risky behavior when self-restraints fail (Rook & Pietromonaco, 1987). Interactions between social network members in these three domains have the potential to be uplifting and helpful or disappointing and hurtful. We encourage researchers to investigate the separate and synergistic effects of social interactions in these three domains, with the hope that this will extend our understanding of how social networks affect health.

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11 Stress and the Workplace: 10 Years of Science, 1997–2007

Alankrita Pandey, James Campbell Quick, Ana Maria Rossi, Debra L. Nelson, and Wayne Martin

This chapter broadly addresses stress in the workplace, with emphasis on environmental and social factors in stress. Within this context, we focus on new science within the period of 1997–2007. However, it would be unreasonable to ignore established and valid research that predates 1997 for that reason alone. Therefore, we treat science and scientific practice that predates 1997 as a baseline that moves into the 10-year period of our focus. Thus, the chapter includes as a foundation work before 1997 and builds on top of that foundation from leading research in the 10 years of emphasis. The chapter is organized into five major sections that correspond to constructs in our work stress process model, which provides a context and guide for interventions (see Figure 11.1). The first three sections of the chapter track the stress process in the workplace, from the causes of stress, through the latest science on the psychophysiology of stress, to the outcomes of stress in the workplace. The last two sections of the chapter focus on preventive management actions for stress in the workplace. The first of these sections is titled "stress prevention" and the second is titled "managing stress." The past 10 years have brought a host of new developments in workplace stress research and scientific practice and also have confirmed many aspects of earlier knowledge in the field.

CAUSES OF STRESS

As we move through our review, as guided by the model, some definitions are in order (adapted from Quick, Quick, Nelson, & Hurrell, 1997). The term "stress" represents the over-arching umbrella; that is, it forms the domain in which we study an individual's experience of demands and consequences at work. Stressors (demands) are the physical or psychological stimuli that serve to trigger the stress response within the individual. As such, they are the causes of stress faced by workers. The outcomes, or consequences, that follow from the stress response, can be positive (eustress) or negative (distress or strain). In this first section of the chapter, we explore the causes of stress (stressors or demands) that appear frequently in studies of work stress over the past 10 years as articulated in Figure 11.2.

Before turning to specific stressors, it is important to recognize the dominant theoretical frameworks and their effect on the way we view work-related causes of stress. The theory of preventive stress management (Quick & Quick, 1984) construed articulated stressors as demands that were grouped into four categories: physical demands (from the physical work environment), role demands (stemming from expectations, both inside and outside the workplace), task demands (arising from the type of work performed), and interpersonal demands (associated with relationships at work). From this framework, a host of studies emerged that focused on specific demands in each category. Prevalent in the early research was a focus on role conflict and ambiguity, work/home issues, and research on job types (Quick, Quick, Nelson, & Hurrell, 1997).

The job demands/job control model posits that it is the level of demands in a job, in concert with the level of control, that lead to job strain. Specifically, jobs with high demands and low control (i.e., "high-strain" jobs) lead to distress (Karasek & Theorell, 1990). Considerable support exists for this model. Most recently, a longitudinal study of 812 employees in Finland indicated an association between high-strain jobs and the risk of cardiovascular mortality (Kivimaki et al., 2002). The early distinguishing factor in this model was the interaction of the demand level with the amount of control. Recent studies, however, have indicated that low job control in and

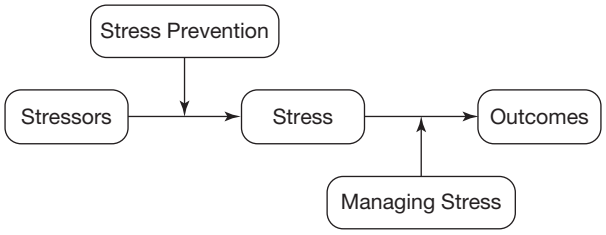

Figure 11.1 ■ The work stress process with interventions.

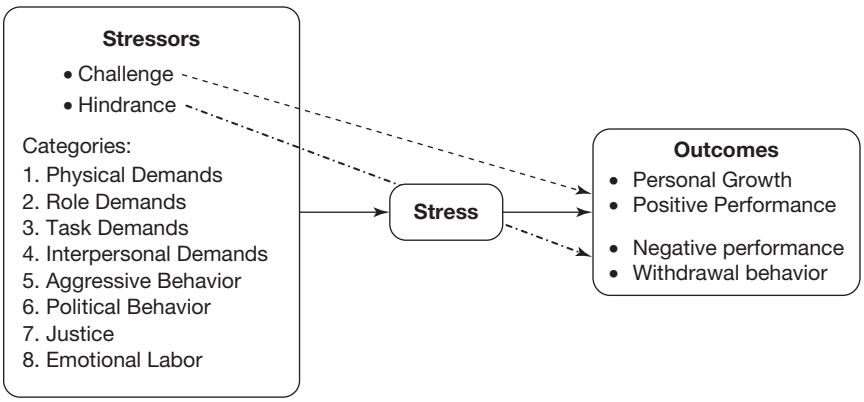

Figure 11.2 ■ Stressors and outcomes.

of itself is a critical risk factor for distress (Hemingway & Marmot, 1999).

The effort–reward imbalance model proposed by Siegrist (1996) posits that it is the mismatch of high effort expended at work with attendant low rewards that leads to distress and negative health outcomes. In this model, rewards include not only compensation, but also job security and broader career opportunities. Support for the model has been found across various occupations (van Vegchel, de Jonge, Bosma, & Schaufeli, 2005).

A two-dimensional stressor framework also emerged that considered stressors to be either challenges or hindrances. Challenge stressors are associated with personal growth and achievement, whereas hindrance stressors thwart task accomplishment and personal growth (Cavanaugh, Boswell, Roehlin, & Boudreau, 2000). Challenge stressors are positively associated with job performance, whereas hindrances are negatively related to performance (LePine, Podsakoff, & LePine, 2005). In addition, challenge stressors have been positively associated with job satisfaction and organizational commitment; hindrance stressors are negatively associated with satisfaction and commitment, but positively associated with withdrawal behavior and work strain (Podsakoff, LePine, & LePine, 2007).

In summary, the dominant theoretical frameworks have complementary views of stressors. Evidence indicates that low control, high overall demands, an imbalance of efforts and rewards, and stressors that are viewed as hindrances, all have detrimental consequences in the workplace for individuals and organizations. We now turn to a more specific look at the stressors that have dominated researchers' attention in the past decade.

STRESSORS AS CONTEMPORARY CONCERNS

In addition to growing bodies of research conducted within the broad stress frameworks, there are many studies that examine discrete stressors. Before 1997, we saw job type, gender, and work–home issues emerge as dominant themes. These stressors continue to garner research attention, but, in addition, our review indicates four other stressors that are joining their ranks: aggression at work (consisting of bullying, violence, and sexual harassment), politics in the workplace, justice issues, and emotion work/emotional labor.

BULLYING/VIOLENCE/SEXUAL HARASSMENT

Of considerable concern, especially in terms of national surveillance systems, is increased aggression in the workplace and its attendant distress and strain. In a 20-country study of psychosocial risk factors, workplace bullying, violence, and harassment emerged as some of the top risks in the workplace, and researchers called for the implementation of an international surveillance system to monitor these risks, among others (Dollard, Skinner, Tuckey, & Bailey, 2007). A large-scale study of 890 human service workers echoed these findings. Exposure to violence and threats emerged as one of the stressors for human service professionals. Exposure to violence at work was a strong predictor of absenteeism (Rugulies, et al., 2007).

Bullying involves negative, aggressive behavior that is a threat to a target's self-esteem or professional competence. With bullying, the victim is unable to defend himself/herself against the aggression. Typically, bullying persists over a considerable period of time. At work, bullied employees report significant psychological strain, especially mental fatigue (Agervolds & Mikkelson, 2004). Bystanders of bullying also report distress, and there is evidence that certain contextual influences may make bullying a more frequent stressor. Bullying is likely to occur in stressful work situations in which there is substantial interpersonal conflict along with destructive leadership styles. Bullying is more prevalent in work situations in which immediate supervisors avoid dealing with stressful situations (Hauge, Skogstad, & Einarsen, 2007).

Sexual harassment produces a host of negative outcomes for both individuals and organizations, and distress is one such outcome (Shaffer, Joplin, Bell, Lau, &

Oguz, 2000). Even relatively low intensity but frequent episodes of sexual harassment have significant negative effects for working women in terms of psychological and job-related outcomes (Schneider, Swan, & Fitzgerald, 1997). And sexual harassment need not be face-to-face. Female employees in call centers frequently experience sexual harassment over the telephone, which leads to higher strain and lower job satisfaction and job performance (Sczesny & Stahlberg, 2000). The prevalence of sexual harassment in the workplace, despite guidelines on sexual harassment published in 1980 by the Equal Employment Opportunity Commission, has led to calls for treating sexual harassment as a chronic workplace problem. Researchers argued that it should be treated in a manner similar to other chronic health problems in the workplace, complete with an identification of its precursors and the development of strategies for its prevention (Bell, Cycyota, & Quick, 2002).

POLITICS/POLITICAL BEHAVIOR

Another stressor receiving increased research attention is that of organizational politics. What is interesting about this particular stressor is that, depending on how it is defined, its effect is not necessarily negative. When politics is defined as actions by individuals in their own self-interests without regard to the well-being of others, there is evidence of a positive relationship with job strain (Harris & Kacmar, 2005). In addition, job strain is a possible mediator of a positive relationship between politics and subsequent aggressive behavior in organizations (Vigoda, 2002).

However, when political behavior is defined simply as the use of influence, a different pattern of relationships emerges. For individuals with a negative reputation, political behavior has been related to increased emotional exhaustion and lower job performance ratings, but for those with a positive reputation, it was associated with decreased emotional exhaustion (Hochwarter, Ferris, Zinko, Arnell, & James, 2007). There is also evidence that political skill, which is the ability to influence others and act in ways that enhance personal and/or organizational goals, can have a neutralizing effect on distress. Greater political skill was found to reduce the negative effects of role conflict on several strain indicators, including anxiety, somatic symptoms, and physiological distress (Perrewe, Zellers, Ferris, Rossi, Kacmar, & Ralston, 2004).

JUSTICE AND FAIRNESS IN THE WORKPLACE

Perceptions of unfairness in the workplace constitute another source of stress that is the focus of research attention. Three specific forms of justice have been investigated, including procedural justice (fairness of organizational processes), distributive justice (fairness of outcomes received by individuals), and interactional justice (fairness of interactions with others in the organizations, most often supervisors). In general, favorable evaluations of organizational justice have been related to lower job strain (Elovainio, Helkama, & Kivimaki, 2001).

Recent studies have focused on justice climate and on ways to increase justice at work. Group-level perceptions of justice climate (distributive and procedural justice), as well as individual-level perceptions, were significantly related to lower levels of anxiety and depression (Spell & Arnold, 2007). Among nurses who experienced a pay cut, insomnia was reduced when the nurses' supervisors had been trained in interactional justice (Greenburg, 2006). This study showed that interactionally fair treatment by supervisors exerted a buffering effect on strain resulting from being underpaid.

EMOTION WORK

There is a growing body of stress research focusing on emotion work and/or emotional labor. Employees, particularly those in customer service, are expected to manage their emotions in accordance with display rules. Pressures to act in ways that are often inconsistent with the experience of one's emotions are characteristic of emotional labor. When the experience of conflict between emotions and behavior becomes chronic, there are negative effects on psychological and physical health (Schaubroeck & Jones, 2000).

Two forms of acting have been identified that help employees behave in accordance with the organization's display rules. Surface acting is modifying one's facial expressions, whereas deep acting is modifying one's inner feelings. Research has indicated that surface acting is related to greater job stress (Grandey, 2003). High emotional demands and emotional labor have been identified as key psychosocial risk factors in the workplace and as such they are important targets for organizational risk management.

THE STRESS RESPONSE: RECENT DEVELOPMENTS IN PSYCHOPHYSIOLOGY AND WORK STRESS

In the past decade, the field of psychophysiology has made some clear moves from the laboratory into the workplace, intervening to prevent and manage stress. And, because of modern capacities to monitor biological signals, psychophysiological interventions can be crafted that elegantly address problems in situ.

In the following text, we highlight three diverse examples that illustrate that psychophysiological interventions can be employed in the workplace to reduce the effects of stress: the prevention of musculoskeletal repetitive strain injuries (RSIs) with surface electromyography (SEMG) biofeedback, promising developments in the use of physiological monitoring of sleepiness for professional

drivers to prevent accidents, and interventions to reduce the sequelae of workplace stress using heart rate variability feedback.

RSIs are the bane of a workforce that increasingly interacts with technology, and can create both pain and functional limitations that impair work. RSIs may stem from both physical and psychosocial stressors (Peper et al., 2003), as well as from the effect of stress-related hyperventilation on muscle behavior of the shoulders and neck (Schleifer et al., 2002). Peper et al. (2003) devised an innovative strategy to address RSI using SEMG biofeedback and respiration training at workstations. Subjects' muscle tension levels and respiration rates were monitored at baseline and then while using a keyboard and mouse. The subjects were provided information about their muscle tension while performing the task. Finally, they were trained using active SEMG feedback to engage only the muscle tension necessary to the task, to incorporate "microbreaks" into their workflow, and to employ diaphragmatic breathing as they performed computer-based work. This intervention resulted in subjective reports of diminished arousal and tiredness, as well as lower, more functional levels of muscle tension while working.

Driver fatigue and sleepiness constitute grave dangers to the driver and to others. If interventions can be found that sense sleepiness, then accidents due to drowsiness may be averted and lives saved. Papadelis et al. (2007) physiologically monitored fatigued drivers operating vehicles (a professional driver was in the front passenger seat and had full controls to operate the car if needed). The results pinpointed precursors to dangerous levels of sleepiness observed in both the electroencephalogram and the electrooculargram signals. This type of monitoring may eventually be designed into vehicles, so that drivers can receive real-time feedback on their degree of alertness.

Heart rate variability biofeedback (Gevirtz & Lehrer, 2003) can be used to reduce stress and its effects on both mind and body. Barrios-Choplin, McCraty, & Cryer. (1997) provided a stress management training program to workers that involved heart rate variability monitoring and feedback. Results included improvements in several job performance variables, as well as a reduction in blood pressure readings for hypertensives. McCraty et al. (2003) examined a stress reduction program with similar use of heart rate variability feedback, and found a decrease in stress indicators, notably including significant reductions in blood pressure. Finally, B. Hinojosa (personal communication, 27 March, 2008) gave teachers a brief training experience in heart rate variability feedback. Teachers then engaged in home practice using a paced breathing relaxation recording designed to optimize breathing and heart rhythm. The teachers reported significant improvements in their capacity to manage stress, as well as in their ability to share their newfound skills with their families and students.

These examples of innovative use of SEMG biofeedback, neurophysiological monitoring, and heart rate variability feedback show the bright potential of psychophysiology to enhance the management of stress.

OUTCOMES OF THE STRESS PROCESS

We now focus on the outcomes of the stress process as noted in Figure 11.2 and expanded in Figure 11.3. Time magazine in 1983 called stress the "Epidemic of the Eighties" (Time Magazine, June 6, 1983), but now, two decades later, we know that stress is here to stay, not just a fad or passing health concern. Adult Americans report high levels of stress and distress. Even as far back as 1996, *Prevention* magazine found that about 75% feel that they experience stress one day a week and one out of three experience it more than two times a week. This is an increase over the 55% reported in 1983. Stress manifests in various severe psychological and physiological forms of distress when it is not well managed and channeled. The 1996 studies showed that 75–90% of visits to the physician are stress-related. The severity of these adverse

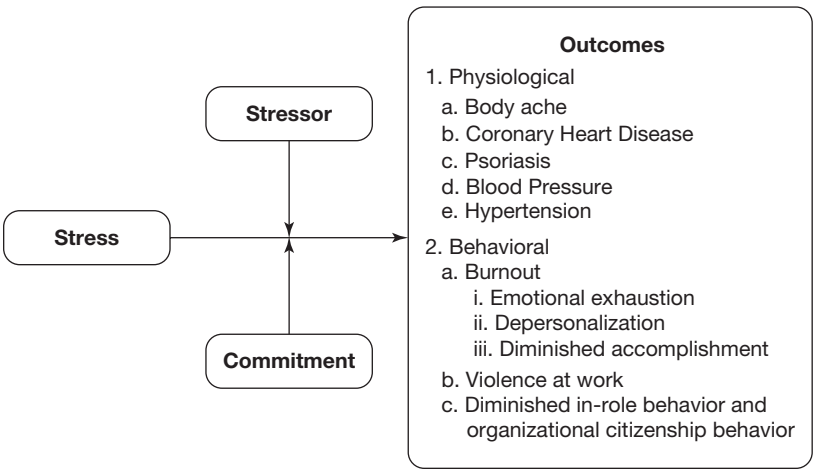

Figure 11.3 ■ Outcomes of the stress process.

outcomes of the stress process has led the American Institute of Stress to identify stress "America's number one health problem" and to place job stress very high on the list of major national concerns.

PHYSIOLOGICAL REACTIONS AS OUTCOMES

Reactions to stress are immediate and involuntary. As discussed extensively elsewhere in this volume, the stress response includes useful reactions to immediate physical threats that effectively promoted survival in early humans. These are initiated by activity of the sympathetic adrenomedullary system and the hypothalamic pituitary adrenocortical axis. Among the specific reactions that are part of the physiological stress response are elevations in heart rate and blood pressure, and increased flow of blood to large skeletal muscles and to the brain, adjustments that support adaptive physical (e.g., "fight or flight") and mental activities (e.g., decision-making). There are also elevations in blood sugar levels, produced by the breakdown of glycogen, fat, and protein stores, which adds to the amount of fuel that is available for effortful mental and physical responses. Other changes provoked by stress include faster clotting, which minimizes blood loss from lacerations, and alterations in blood flow that shunt blood away from organs that are not essential to successful defense against immediate physical threats (e.g., digestive and reproductive systems). As adaptive as these responses may be when elicited by acute, physical emergencies, they do little to facilitate survival when provoked by many contemporary stressors, which often involve psychological threats and require cognitive and behavioral solutions that do not entail vigorous, "fight or flight" action. The repeated activation of biological stress mechanisms by psychological challenges and threats is thought to exert an insidious, pervasive, and persistent effect on the body, resulting in "Diseases of Civilization"—hypertension, strokes, heart attacks, diabetes, neck aches, low-back pains, and several skin problems (American Institute of Stress Website).

TYPES OF OUTCOMES

Cordes and Dougherty (1993) suggested four major groups of stress consequences: physical and emotional, interpersonal, attitudinal, and behavioral, which, in turn, may be classified into two broader groups of constructs: (1) physiological and (2) behavioral (Selye, 1983). We first discuss behavioral outcomes and then physiological ones.

Behavioral Outcomes of Stress

Among the behavioral effects of stress, one of the more severe outcomes is burnout. Maslach (1982) argues that burnout has three components: emotional exhaustion, depersonalization (felt distance from others), and diminished personal accomplishment. According to a review by Lee and Ashforth (1996), the outcomes of emotional exhaustion and depersonalization are strongly linked to increased turnover intentions and lowered organizational commitment, and only weakly associated with control coping. Maudgalya, Wallace, Daraiseh and Salem (2006) reviewed prior literature on burnout among IT professionals finding that exposure variables such as role ambiguity, role conflict, and job tasks led to higher job burnout. They concluded that managers of IT employees must be aware of these exposure variables and take steps to protect employees for company and employee well-being.

Other behavioral outcomes include acting nervously and impulsively, and showing lower tolerance toward others, in some cases leading to increased aggression (Vigoda, 2002). One of the more severe outcomes of stress in the workplace is violence that erupts when men and women feel pushed to the breaking point and no longer able to tolerate stress. Acting out with violence is one way to draw attention to their plight. Violence in the workplace takes different forms at different levels. At the lowest level it involves swearing and mild sexual aggression, escalating to threats to the organization or to coworkers, and on to suicide attempts, physical altercations, and damage to life and property (Johnson & Indivik, 1994). Stressful work environments also lead to bullying as a study in Norway recently demonstrated (Huage, Skogstad, & Einarsen, 2007). Bullying also increases in the absence of proper supervisor intervention.

Stress has also been found to have a negative effect on in-role behavior, organizational citizenship behavior (OCB), and customer satisfaction (Tarris, 2006). Many organizations and their members benefit from OCBs, which take the form of discretionary activity that improves the social and psychological context in which the technical core of the organization operates (Allen & Rush, 1998; Van Scotter, Motowidlo, & Cross, 2000). Stress can significantly reduce OCBs, leading to decreased long-term benefits for employees (Chang, Johnson, & Yang, 2007).

The effects of stress on performance differ depending upon the level of affective organizational commitment, or the worker's emotional attachment to the organization. Commitment can moderate the relationship between felt stress and job performance, so that stress is positively associated with performance when commitment is relatively high, and negatively associated with performance when commitment is relatively low (Hunter & Thatcher, 2007).

Physiological Outcomes

That the effect of work stress on heart health is negative is well known. Indeed, the news seems to become more depressing as more studies are carried out. A cohort study of 812 people who were free from cardiovascular disease showed that after an average period of 25.6 years of high job strain, high demands, and high work pace, there was a 2.2 increased risk of cardiovascular

mortality, while people with an effort–reward imbalance (low salary, lack of social approval, few career opportunities) had a 2.4 increased risk (Kivimäki et al., 2002). Also, job strain, in the form of high psychological demands combined with low decision latitude, increases the risk of a first coronary heart disease event (Aboa-Eboulé et al., 2007). Vital exhaustion, inability to relax, and sleep disturbances also appear to reflect demands such as overtime work, shift work, hectic work, and job strain, leading to elevations in risk factors for cardiovascular diseases. In particular, elevated blood pressure is seen as one of the underlying mechanisms through which work-related stress leads to cardiovascular diseases. Overtime work appears to operate as a stressor because it increases the demands on an employee attempting to maintain performance levels in the face of increasing fatigue (Rau, 2006).

Initial attacks and subsequent manifestations of severe skin afflictions, such as psoriasis, often appear to be due to stress. Ingram (1954) considered emotional stress to be the most potent precipitating factor in psoriasis. In a large postal survey of psoriasis patients conducted in the United States, the incidence of stress was found to be 40% (Seville, 1977). Other studies by Seville (1978, 1989) yielded similar findings. In yet another study, more than 60% of a sample of psoriasis patients believed that stress was a principal factor in the cause of their psoriasis (Griffiths & Richards, 2001).

The physical effect of stress exposures can accumulate over time. Stress is often quite literally a "pain in the neck" and/or in the lower back and shoulders, as a study on 413 New Zealand dentists found (Palliser, Firth, Feyer, & Paulin, 2005). The annual prevalence of pain both in the lower back or neck was 63%, with 49% experiencing pain the shoulders as well. Dentists scoring high on work-related stressors were more likely to have greater musculoskeletal discomfort.

Allostatic load (AL) is an index that enables the cumulative effect on the body of chronic stress to be assessed, and is derived from a set of relevant biological measures. Sun, Wang, Zhang, and Li (2007) conducted a 13-parameter AL study of 1,219 employees in China to assess the relationship between AL and strain. They found that participants with high job strain exhibited significantly higher AL than did those with lower job strain. In addition, their multiple regression results supported the relationship of decision latitude and job demands with AL, with AL positive related to job demands and negatively to decision latitude. This study suggested that work-related psychological stress may affect multiple-system physiological function and may reflect more than one risk factor.

Antecedent-Dependent Outcomes

The different outcomes of stress vary, depending on how it is caused. For instance self-employed people are more likely to have significantly higher levels of work stress in some studies, although details on the derivation of the stress measure were not provided (Lewin-Epstein & Yuchtman-Yaar, 1991; Parslow et al., 2004). Jamal (1997) also found that the self-employed reported more job stress. But there were no differences in mental health between these self-employed and other people. Self-employed subjects had significantly more psychosomatic health problems, which are physical disorders in which both emotions and thought patterns are believed to play a central role, and usually develop when a person's disease-fighting ability is weakened due to stress (University of Michigan Health System website). Sexual harassment is also a cause of stress that leads to specific outcomes such as depression and posttraumatic stress disorder. One study found unwanted sexual attention or sexual coercion to be stressors that women said constituted harassment, despite the retrospective nature of the event(s), which were an average of 11 years in the past (Schneider, Swan, & Fitzgerald, 1997; Dansky & Kilpatrick, 1997).

STRESS PREVENTION: PRIMARY PREVENTIVE STRESS MANAGEMENT

The first three sections of the chapter examined new research related to the stress process in organizations and the workplace. New causes, new applications of psychophysiology, and new stress outcomes are refining our knowledge of this important issue. What about the interventions that organizational leaders and health professionals have available for preventing and/or managing stress? What continues to work well and what does new research say? We begin by examining the theory of preventive stress management and the actions available within its framework. Gavin, Nelson, Quick, and Quick (2008) concluded that public health prevention, specifically primary, secondary, and tertiary prevention, has proved itself to be effective over the past 25 years. One major case study and intervention program within a large industrial organization over a 6-year period (Klunder, 2008) saved lives, prevented workplace violence, and averted $33 million in costs related to workplace grievances that did not materialize. Effectiveness was additionally and more broadly demonstrated in workplace intervention programs implemented in a wide range of occupations (Levi, 2000).

Because the preferred point of intervention in public health and preventive medicine is always primary prevention (Levi, 2000), we focus first on primary preventive stress management as presented in Figure 11.4. We explore the established practices of situational and environmental change as well as cognitive/psychological intervention. Although there is very limited new science on primary prevention during the past decade, we do examine important advances in cultural differences and selection, optimization, and compensation (SOC) behaviors that help inoculate the individual against distress.

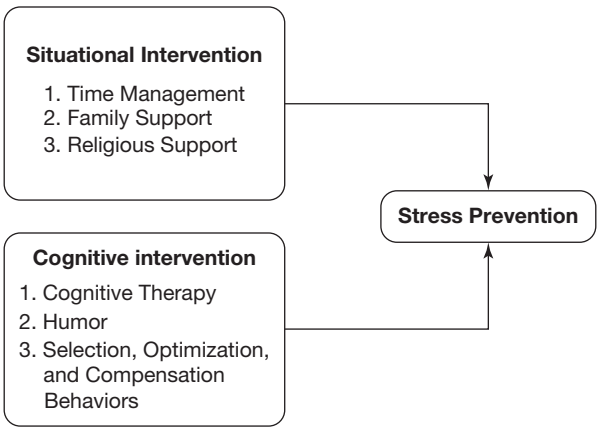

Figure 11.4 ■ Stress prevention.

We then examine secondary prevention interventions designed to manage stress. We take tertiary prevention, commonly known as therapy or therapeutic intervention, as beyond the scope of this chapter.

SITUATIONAL INTERVENTION: CHANGING THE ENVIRONMENT

Each individual has a different way of dealing with stress according to his/her personal experience and learning history. Situational approaches to managing stress are used by individuals and families because control over environmental influences can reduce the stress level of many of the people involved. The situational approach to stress management in the workplace includes the development of time management techniques, training in family relationship skills, and religious affiliation.

TIME MANAGEMENT

Time management strategies can be highly beneficial, maximizing personal energy and reducing stress. Each individual has a different level of personal energy in each phase of his/her life. This personal energy can be used to facilitate the individual's daily activities or to reduce emotional stresses caused by environmental influences. Performance peaks and the generally most productive times must be identified to maximize the use of the personal energy. It is important to specify realistic and measurable goals, avoid perfectionism, and allow flexibility for unexpected events. The individual's ability to manage his/her time in an effective way has positive effects on work-related stress (Macan, 1994). Time management can, in itself, reduce stress levels to the extent that it enables individuals to feel more confident and in control of their responsibilities.

FAMILY SUPPORT

The family can be either a stressor or a coping resource (Bhagat, 1983). Saleh et al. (2007) found that the families of orthopedic surgeons were a significant and positive source of support for those in the profession holding leadership positions, primarily in academic settings. However, family conflict also has been associated with psychological distress and physical complaints (Frone, Russell, & Barnes, 1996). Through interaction within the family, individuals acquire problem-solving techniques that can either reduce or increase their stress level. Three important ways for families to deal with stress are: reframing, mobilization, and passive assessment. Reframing is when the family redefines the stressful event in such a way as to make it more manageable. Mobilization refers to the search for and/or acceptance of help from others to solve a problem. Passive assessment is the ability of the family to accept problematic or conflicting issues, minimize negativity, accept differences, and understand and share problems with one another, as well as to give and receive support for all family members. Communication between family members is extremely important for increasing empathy and encouraging all family members to express themselves (Shaffer, 1983).

RELIGIOUS SUPPORT

The solidarity networks organized by churches, temples, and other religious centers are a source of support that can relieve professional and family stress. The environment of any given place of worship brings together a group of individuals who share beliefs and values. Their frequently similar point of view helps these individuals to relate better among themselves and to develop more empathy for one another. The sense of fellowship that results from religious involvement can reduce stress, create inner peace (Levin, 1984), and enhance positive emotional expression at work (Ashkanasy, Hartel, & Zerbe, 2000).

COGNITIVE INTERVENTION: CHANGING THE WAY WE THINK

This approach focuses on identifying and restructuring negative thinking. It is based on the idea that attitudes and thoughts underlie an individual's mood instead of or in addition to external events. Cognitive approaches include the use of professional counseling and the use of humor at work.

PROFESSIONAL COUNSELING AND COGNITIVE THERAPY

Cognitive therapy is based in part on the principle that thoughts affect people emotionally and physiologically,

and can trigger anxiety and depressive disorders. The therapy focuses on teaching individuals to recognize and reframe negative, dysfunctional thinking. It is used in conjunction with behavioral techniques. Many studies have indicated the positive effect of cognitive therapy in improving mood and regulating stress (Ellis & Harper, 1975; Seligman, 1991).

HUMOR AT WORK

Vaillant (1977) identified humor as one of the mature adaptive mechanisms in his 35-year update of the Grant Study results of adult life adjustment. He identified humor as the ability to express one's thoughts and feelings without discomfort to oneself or others. In a major literature review of humor and work, Duncan, Smeltzer, and Leap (1990) surveyed theories and research and then described a specific application illustrating the importance of humor at work. Laughing as one expression of humor has been shown to have a positive effect on the body and on health (Robinson, 1991). Laughing stimulates the brain to block the production of immunity suppressors such as cortisol, and may accelerate the production of beta-endorphin.

NEW PREVENTIVE INTERVENTIONS: ATTENDING TO CULTURE AND CHANGING BEHAVIORS

Situational and cognitive interventions have been well established and continue to appear effective in the appropriate context. What is new in workplace stress prevention is attention to cultural differences and cultural context as well as the introduction of new behaviors aimed at restructuring the work and the family environment. Attention is always focused on the setting in which the stress process occurs, with the aims of managing the sources of stress and/or demands.

CULTURE AND STRESS

In the past decade the increasingly international presence of stress research has brought considerable attention to the effect of culture. A particularly interesting study by Schaubroeck, Lam, and Jia (2000) demonstrated the effects of culture in a U.S.–Hong Kong comparative study. These researchers examined collective efficacy and self-efficacy in the job stress process for bank tellers. Within the U.S. culture, job self-efficacy was an instrumental moderator in the linkages of job demands with psychological health symptoms and turnover intentions, such that for those tellers high in job self-efficacy, high levels of job control reduced job stress. However, for U.S. tellers low in job self-efficacy, high job control exacerbated, and low job control reduced, levels of job stress. By contrast, collective efficacy, in contrast to job self-efficacy, showed the same interaction pattern for the Hong Kong tellers. Thus, high control was helpful for those with high collective efficacy in high-demand jobs, whereas low job control was helpful for those with low collective efficacy in high-demands jobs. Cultural differences may play an important role in the stress process and must be factored into preventive stress management strategies.

SELECTION, OPTIMIZATION, AND COMPENSATION BEHAVIORS

With regard to job and family demands, inter-role conflicts, in which role pressures from work and family are found to be mutually incompatible, often arise (Greenhaus & Beutell, 1985). This conflict takes two directions. Work-to-family conflict occurs when experiences at work interfere with family life. Family-to-work conflict occurs when experiences in the family interfere with work life. These can be prevented using SOC behaviors, which are defined based on the operation and coordination of three components: selection of goals or behavior components; optimization of the means to reach these goals; and compensation, or the use of substitutive means to maintain functioning when previous means are lost or blocked (Freund & Baltes, 1998). The SOC model spells out four self-management strategies for pursuing and maintaining personally relevant goals: (a) elective selection (developing and committing to a hierarchy of personal goals), (b) optimization (engaging in goal-directed actions and means), (c) loss-based selection (changes in the goal or the goal system in response to loss), and (d) compensation (acquisition and use of means in response to loss). What are the effects of behavioral strategies aimed at reducing the amount of demands or stressors experienced both on the job and at home? Baltes and Heydens-Gahir (2003) found that the use of SOC behaviors in the work and family domains was positively related to lower amounts of job and family demands or stressors. These lower amounts of stress in both domains led to lower levels of work-in-family (WIF) conflict and family-in-work (FIW) conflict, and this held when controlling for hours worked, gender, job involvement, family involvement, social support, and supervisor support.

MANAGING STRESS: SECONDARY PREVENTIVE STRESS MANAGEMENT

Stress reduction may be accomplished through a set of secondary prevention stress management approaches. Secondary prevention is aimed at altering the individual's or the organization's response to necessary and/or inevitable demands and stressors that cannot be eliminated or removed. Established secondary prevention practices that are well grounded, and have new supportive research in the past 10 years, include relaxation in its many and varied forms, life style approaches that involve physical

exercise and diet, and techniques based on new research on the role of the supervisor in the workplace. Figure 11.5 sets forth the framework for the review in this section.

RELAXATION: REVERSING THE STRESS RESPONSE

To treat stress effectively, a multifaceted approach is required. Although there are many techniques that may temporarily manage the causes or symptoms of stress, no single approach presents an efficient solution. The choice of relaxation techniques to cope with stress should be determined by (1) the specific needs of individuals, and (2) the techniques that best suit those needs.

ABDOMINAL BREATHING

Abdominal breathing allows the individual to fill his/her lungs with oxygen, releasing carbon dioxide, and to downregulate the sympathetic nervous system. Intense emotions, such as anxiety and anger, change the breathing rhythm, which becomes shallow and fast. An effective breathing pattern is fundamental to most forms of relaxation (Fried & Grimaldi, 1993). Other advantages associated with this type of breathing include energy conservation and greater ability to cope with stress and control emotions (Freeman, 2001d). The individual also learns how to better concentrate on what is happening in the here and now (Hendricks, 1995).

PROGRESSIVE MUSCULAR RELAXATION

Progressive muscular relaxation involves the voluntary control of the body's skeletal muscles. The voluntary contraction and relaxation of various muscles allows individuals to identify the difference between tension and relaxation, thus enabling them to learn to promote muscle relaxation (Jacobson, 1964). Muscular tension is a behavioral response that activates neuromuscular circuits (McGuigan, 1997). The use of progressive muscle relaxation has been shown to help reduce stress level and to alleviate chronic pain in various medical conditions (Freeman, 2001d).

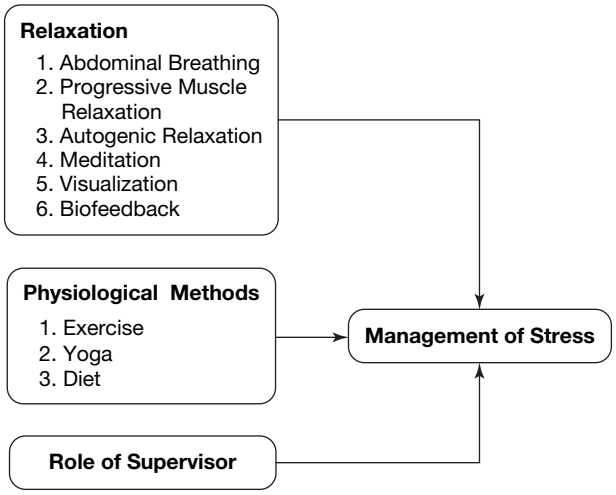

Figure 11.5 ■ Managing stress.

AUTOGENETIC RELAXATION

Autogenetic relaxation is a form of self-hypnosis that can serve as a relaxation technique for controlling responses to a specific stressor (Jencks, 1973). It makes use of the individual's mental control over physiological processes. It consists of creating a passive psychological posture while the individual mentally repeats a series of hypnotic self-messages that can cause physiological changes. The focus is on the body sensations experienced while the individual repeats the self-messages.

MEDITATION

Meditation is a state of consciousness characterized by inward attention and deep relaxation (Murata, Takahashi, Hamada, Omori, Kosaka, & Yoshida, 2004). The practice of meditation is one of the most widely recognized stress management tools and is most often used in stress management programs in the workplace (Murphy, 1996). It consists of focusing the attention on a mantra (string of words) or passive stimulus to "empty the mind" of thoughts while a state of homeostasis is experienced. Meditation can put the body in a profound state of relaxation called hypometabolism. Oxygen consumption, metabolic level, and activation of the sympathetic nervous system are all decreased, as is brain activity. One of the most popular meditation interventions used in the work setting is mindfulness meditation. It involves the production of a state of nonevaluative awareness of the ongoing situation (Shapiro, Astin, Bishop, & Cordova, 2005). For full benefits and to lead to positive behavioral changes, regular practice is required (Freeman, 2001c).

VISUALIZATION

Visualization is a thought with a sensory focus. The word visualize has been used interchangeably with mental imagery, active imagination, and daydreaming. Some of these practices imply the use of spontaneous techniques; others are oriented or induced. All involve the ability individuals have to create an image using their five senses. Visualization can occur even without the presence of a specific stimulus. It can be felt as a sensation or perception and influence mechanisms at the emotional, cognitive, and sensory levels. The relaxation state inhibits mental activity, enabling individuals to focus intensely on the experience.

The final outcome is to reduce sympathetic nervous system arousal. Its practice has been effective in the treatment of various illnesses (Freeman, 2001d; Lazarus, 1984).

BIOFEEDBACK

Biofeedback is the immediate return, through electronic sensory devices, of information about physiological processes (heart rate, blood pressure, muscle tension, brain activity, peripheral temperature, electrodermal activity). It enables individuals to regulate their reactions to stress voluntarily by showing when physiological processes are altered. Lehrer, Carr, Sargunaraj, and Woolfolk (1994) reviewed the different methods of biofeedback that can be used independently or in conjunction with other methods of relaxation. It is an appropriate tool for the control of reactivity to a specific source of stress (Schwartz, 1995). When individuals learn how to relax and control these physiological processes, the mind is trained to manage the body, thus regulating physical and emotional states (Brown, 1978).

PHYSIOLOGICAL AND PHYSICAL EXERCISE: STRENGTHENING THE PERSON

With the growing demands and pressures at work over the past decade throughout the industrial corridor of Europe–U.S.–Japan and Asia, it is important that professionals take care of their life style, prioritizing physical activity and the quality of their diet.

EXERCISE

One of the best ways to reduce stress is through physical activity such as aerobic exercise. Studies have consistently indicated the numerous emotional and physical benefits of regular exercise activity (2003). Physical activity has been found to have a positive effect on multiple outcomes (Freeman & Lawlis, 2001). It affects brain chemistry, enhances self-esteem and self-confidence, and decreases stress (Blumenthal, Jiang, Babyak, Krantz, Frid, Coleman, Waugh, Hanson, Appelbaum, O'Connor, & Morris, 1997). Aerobic exercise contributes significantly to both physical and mental well-being. Other benefits of systematic physical exercise are increases in motivation and self-discipline.

YOGA

Yoga works with breathing, muscle stretching, concentration, and balance. It differs from other physical exercises in that it places a strong emphasis on both mental and physical fitness. It can reduce stress and relieve muscular tension and pain (Gura, 2002) and improve oxygen consumption and respiration (Telles, Reddy, Nagendra, 2000). Yoga postures have been associated with decreased sympathetic nervous system activity (Vempati & Telles, 2002). The goal of yoga is to make people aware of their body, mind, and physical and mental endurance. The exercises stimulate arterial blood flow everywhere in the body. This process induces the release of tensions, enabling individuals to acquire mental discipline and explore their mental potential.

DIET

A healthy diet balances vitamins, proteins, minerals, fiber, carbohydrates, and fats, as well as overall caloric intake. This provides energy to cells and the raw material for growth, in addition to keeping all organs in order and reconstructing tissues. The diet should include food low in fat, salt, refined sugar, and caffeine. Ideally, meals should be smaller and more frequent. Stress can cause an increased appetite for sweets (Elliott, 1995) and it can affect gastric secretions that are indispensable to good digestion. For this reason one should be relaxed while eating, something that can be difficult under conditions of high work stress.

ADVANCES IN THE ROLE OF THE SUPERVISOR

Command and control leaders and managers are supervisors who can generate stress (Sutton, 2007). The problem with certain supervisors is quite clear and the emotional havoc they wreak in workplace can be enormous. Sutton (2007) therefore argues for building civilized workplaces in which individuals are able to work in healthy emotional relationship, or "resonantly," to use Boyatzis's terminology (Boyatzis & McKee, 2005). There is good new research that advances the role of the supervisor as an active, positive force in managing the stress of the workplace. Harris and Kacmar (2005) show the buffering role of supervisors in the perceptions of the politics and strain relationship. That is, while politics can have a negative effect in the workplace, their research with 1,255 respondents in two different organizations found that the supervisor can have a positive buffering effect for subordinates; thus, as we noted earlier, organizational politics need not turn out badly.

POLITICAL AND INTERPERSONAL SKILLS

The political skills of supervisors, their personal and interpersonal skills, and their leadership styles can be powerful and important agents in the workplace for managing the stress process in a healthy, positive way. Perrewé et al. (2004) report evidence that is very important in this regard, suggesting that supervisors who develop positive political skills are able to ameliorate workplace stress before it becomes destructive and distressing. In a similar

vein, Quick, Macik-Frey, and Cooper (2007) suggest that a key ingredient in authentic, resonant leadership development is the process of psychological testing and feedback with regard to emotional competence. The development of emotional competence requires acquisition of the twin skills of intrapersonal intelligence and interpersonal intelligence. Interpersonal skills first require self-awareness, which is an essential foundation to self-management. Both self-awareness and self-management are intrapersonal skills. Emotional self-control is a force multiplier in a leader's job performance and helps relationship building.

SOCIAL SUPPORT ON THE JOB

Social support by supervisors and colleagues in the workplace continues as a perennial positive agent for managing stress, warding off depressive symptoms and other ill psychological outcomes of the stress process. Dormann and Zapf (1999) found this to be the case in a three-wave longitudinal study around Dresden in the former East Germany with a random sample of 543 citizens. Support from supervisors need not be unreasoned and does not obviate either skeptical or critical exchanges. Strong and supportive supervision must be embedded within it the capacity to deliver feedback that can lead to course corrections on the part of subordinates (Nelson & Quick, 2009).

CONCLUSION

The period of 1997–2007 has seen some significant advances in stress science, many of these focused on the causes of stress in the workplace. Work environments in the industrial nations are in many ways less civil than in the past, even if they are physically safer and more secure than they once were. Hence, the nature of the stress is becoming more psychological in nature, though workplace violence is an exception to this rule. We have seen new advances in knowledge of the outcomes of the stress process as well, though much of our previous knowledge continues to be confirmed and elaborated upon. The solid foundation for stress prevention and managing stress that emerged in the late twentieth century has been validated and refined. These skills and interventions are in current practice in many workplace settings. However, there are new advances in both primary prevention and in the secondary preventive stress management skills that help to avert and/or to manage the inevitable, and in some cases necessary, modern workplace stressors.

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12 The Challenge of Stress in Modern Organizations

Ashley Weinberg and Cary Cooper

Organizations are human creations. As such they are subject to the same complex mix of processes that govern our lives, including creation and evolution, politics and conflict, communication and relationships. Whether one envisions organizations as sandcastles on the beach, weathering in the tide and wind, or as more permanent structures constructed to withstand the climatic conditions of business and public sector environments, many will agree that the challenges facing organizations are greater now than ever before. Some will point to the implications of the 1929 Wall Street Crash, and others further back to the Industrial Revolution of the eighteenth century, to pinpoint the periods of momentous change for organizations. However, as a creative species, we have learned to identify and exploit opportunities for development and growth in such times. We know that adaptation is vital for survival and although limited in our ability to change our biology and brain structure, humans have found within the workplace expression for a number of the processes we recognize in nature. The key difference is that we believe we can exert some level of control over this aspect of our lives and play a useful role in society through work, whereas our contribution to the overall survival of the species is less easily defined.

One could argue that good work helps progress in the grand scale of things, as do productive family lives and positive citizenship behaviors. Commensurately organizations seem to have the capacity to generate structures, consistency, rules, and outputs that clearly define human activity. This may create the alluring impression that it is possible to exert some measure of control, which generates a set of expectations for our working lives. However this also presents a dilemma: Should we accept these expectations as realistic or not? After all, successful blockbuster movies are those that challenge our personal versions of reality, and current events in organizational life are increasingly mirroring this trend. The collapse of organizations around the world through financial insecurity and ethical impropriety, the impending climatic change linked to pollution by organizations, and the need to adapt to expanding populations and migrations, feature in the organizational storylines that increasingly affect our lives. Furthermore, these are amplified by global technological advances and mean that change is more instant than evolutionary. In other words, disappointment is only a mouse-click away, or for those keen to evolve, opportunity is just around the corner.

Stress in organizations is not, therefore, a surprising phenomenon. Its sources are manifold, its processes complex, yet its outcomes well-recognized and well-known. The effect of strain on individuals and organizations is both intriguing and illustrative of the variation in our lives. Along with such symptoms, this chapter aims to highlight the current challenges faced by organizations, including the demanding effect of change, people–work, and modern working practices. Furthermore, in the light of previous research and in the spirit of human survival, ways of combating such challenges are considered.

Selye's early definition of stress in a human context encompassed the positive as well as negative effects. However in the settings of work organizations, while there also exists the potential for seeing both sides of the coin, the tendency in research has been to emphasize the negative outcomes. For the sake of consistency with the remainder of this volume, and in the spirit of examining challenge as a potential source for gain in organizations, the focus of this chapter will remain on where things have gone wrong, leading to an examination of how things can progress positively. Perhaps a useful starting point is an audit of the known stress experienced by individuals and the organizations for which they work, but before embarking on that, it is important to note that in this context, we are focusing on strain as an outcome of any stress process. In that sense, strain represents the consequences of stress and provides the initial focus for this chapter. Later on we shall move to look at the stressors, or in other words, the causes of stress in organizations.

INDIVIDUAL SYMPTOMS OF PSYCHOLOGICAL STRAIN IN THE WORKPLACE

The individual symptoms of strain are manifold and can be found in cognitive, physiological, and behavioral outcomes, whether the individual is a member of the working population or not. However the range of expression

of such symptoms within organizations can take on a different significance as these become linked to individual and team performance issues, organizational failures, and possibly financial and legal consequences. The example of hospital doctors performing clinical tasks with significantly less confidence while reporting higher levels of distress (Williams, Dale, Glucksman, & Wellesley, 1997) is a useful one to help focus the mind. Similarly, one might imagine how difficulty in making decisions or general worries about future performance might affect job holders with responsibility for air traffic control or a nuclear power plant. Furthermore, psychosomatic symptoms of strain can include headaches, muscle trembling (such as a twitching eye), excessive perspiration, lack of appetite, indigestion, sickness, shortness of breath, and even a decrease in sexual interest (Cooper, Sloan, & Williams, 1988). All of these are consistent with over-activation of the body's "stress response" and, while often short-lived, it is the chronic presence of physical symptoms that can lead to long-term health difficulties. Most strikingly, a Europe-wide study of more than 10,000 pregnant women working 40 or more hours per week found that 40% of those in jobs with a high mental workload, such as busy administrative and clerical roles, gave birth prematurely (Di Renzo, 1998).

The most serious health outcome as a symptom of anything, including strain, is death. Death from overwork, or "karoshi" as it is known in Japan, is evidence of a cultural emphasis on the significance of work organizations in the lives of employees, placing considerable pressure on workers to adhere to expectations that may in turn result in serious health consequences. The death of a junior doctor in the United Kingdom after working more than 120 hours without sleep demonstrates that overwork is a potential danger wherever it occurs. Netterstrom and Juel (1988) studied 2,465 Danish bus drivers over a 7-year period and found that workload—as assessed by measuring the intensity of traffic on certain routes—was the factor most strongly associated with heart disease.

Changes in individual behavior can also indicate that the employee is experiencing strain in some way. Most obviously, attendance at work is likely to be noticed, as is lack of presence. However a phenomenon recognized since the decline in job security in many sectors is that of "presenteeism," where the employee experiences pressure to be seen as the person who works hardest by arriving earliest and leaving latest. Unfortunately for such individuals, this is not a guarantee of higher productivity, and national statistics seem to bear this out, comparing those employees in the United Kingdom who work a longer week on average than counterparts in France and Germany. The issue of decreased work performance has been scrutinized in a major United States study of 4,115 employed people, which projected that for more than 130 million working days per year, employees' performance was impaired by psychological and emotional strain (Kessler & Frank, 1997).

An increased rate of errors in employees' work is consistent with poorer levels of concentration, while symptoms of tiredness and cognitive overload have been blamed by some investigations for fatal mistakes on the U.K. railways. Additionally, feeling the pressure of a set of demands has been linked to mistakes while carrying out everyday tasks (Reason, 1988), and so it is not unreasonable to assume that errors are made in most jobs, but some are more likely to stand out than others. It is how the organization deals with these mistakes that can either compound or exacerbate the problems for the staff concerned—an appropriate organizational culture that promotes safety is not simply a clear example of good practice, but also a portent of organizational well-being (e.g., Zohar, 1980).

In addition to the availability and quality of work of employees under strain, their emotions may also be transformed along with a reduced tolerance of challenging situations. This can impair an individual's ability to manage interactions, and the individual may fail to communicate with others clearly, or at all, or may rise quickly to irritability. Such behavioral symptoms are particularly noticeable in organizations reliant upon the trading of feelings for success. Given the increasing switch from manufacturing to service industries, the investment of emotional labor by a host of organizations, ranging from call centers to public sector health and social care, may be drawing upon already strained employee resources. The negative consequences can range from low morale among staff to greater dissatisfaction among customers as employees feel unable to put on the face the organization would have them wear. A link between psychological strain and incongruent emotions felt while doing a job has already been established (Brotheridge & Lee, 2003). Burnout has become a familiar problem among occupational groups working with the public, comprising the negative mix of emotional exhaustion, depersonalization of clients, and a lack of experienced personal accomplishment (Maslach & Jackson, 1986). The effect on organizational functioning is likely to be evident in many ways, as will be seen later in this chapter.

ORGANIZATIONAL SYMPTOMS OF STRAIN

As has been discussed, burnout and its symptoms are evident not only in the individual, but also in barometers of organizational well-being. This is because the symptoms, if they are not addressed, can develop into a climate of sub-optimal functioning, in which it is accepted by co-workers that "this is how the job makes us feel." Low morale is often evident in the lack of discretionary activities in which employees engage, that is, those behaviors that are carried out by workers, but are not enforced by employers. These include voluntary overtime, attendance at training courses, and prosocial

activity, the latter ranging from simply being friendly to colleagues to making suggestions as to how to improve the workplace (Warr, 1999). For the receivers of the product or service, low morale can manifest itself in poorer quality, miscommunication and, ultimately, customer dissatisfaction. Along with complaints, poorer productivity, greater staff turnover, elevated absenteeism rates, and industrial unrest are additional potential symptoms of organizational strain. Furthermore there is evidence to suggest that the incidence of unacceptable behaviors, such as bullying, is greater in sectors under pressure, such as higher education (Kinman & Jones, 2004).

"Stress-related disorders" ranks second to musculoskeletal difficulties as the leading cause of absenteeism from work. In the early 1990s, the U.K. Department of Social Security (1993) reported that 80 million working days were lost each year due to illness related to psychological and emotional strain. Now, overall sickness absence accounts for 66 million working days at a cost of £3.4 billion in the U.K. public sector alone (Confederation of British Industry [CBI]/AXA, 2006). Absenteeism rates have been found to vary between industries, with the average figures in the public services (8.5 days per year) higher than that for the private sector (6 days per year (CBI/AXA, 2006). Similarly, the toll of psychological strain related to work has also been calculated in the United States to cause up to 54% of all absenteeism (Elkin & Rosch, 1990).

Additionally, staff turnover is a high profile indicator of poor organizational health, although dependent on a range of factors, including "sickness culture" (Martocchio, 1994). An average correlation of 0.37 between emotional exhaustion and intention to leave one's job indicates the strength of the relationship between emotional strain and costs to workplace organizations (Lee & Ashforth, 1996).

PREVALENCE OF PSYCHOLOGICAL STRAIN IN ORGANIZATIONS

Psychological health problems comprise the largest group of health difficulties in the United Kingdom, as "in any one week, 18% of women and 11% of men have significant psychiatric symptoms" (Royal College of Psychiatrists, 1995). These figures have changed little in recent years, although, notably, the proportion receiving treatment has actually doubled (Office of Population Census and Surveys, 2002). The prevalence of psychological strain is highest among the unemployed, at 23%, compared to 10% of those working full-time and 14% of those working part-time (OPCS, 1995). Lower socioeconomic status is linked to greater risk of problems; however, it is usually higher socioeconomic groups that attract the attention of research studies. Among these there is a troubled picture for public sector workers, particularly in professional roles. While 20.5% of the general population report high levels of symptoms of strain (Taylor, Brice, Buck, & Prentice-Lane, 2004), the figures are comparably higher among employees in teaching, health, and social work.

Fifty percent of academic and academic-related staff in U.K. higher education institutions report poor psychological health, which is among the highest of any occupational group (Kinman & Jones, 2004). However, the elevated levels of strain that occur in comparable groups, such as 43% of university employees in Australia (Winefield et al., 2003) and 57.2% civil servants in local government in Japan (Nadaoka, Kashiwakura, Oija, Morioka, & Totsuka, 1997), show that this is a global rather than national pattern. These elevated levels of strain may well relate to changing expectations and increasing demands on employees in this sector. Following reforms to the U.K. National Health Service in the early 1990s, Cooper and Sutherland (1992) found high symptom levels among general practitioners taking responsibility for fund-holding budgets. Weinberg and Cooper (2003) also found that political party candidates showed raised levels of strain several months after their successful election as members of Parliament, suggesting a long-term negative effect of the job on individual well-being.

The abstract map of employee well-being may be subdivided in a number of ways. Therefore, within the occupational groups studied to date, it is possible to highlight further trends that suggest the vulnerability of certain sections of the workforce, although this is not to argue that others do not deserve scrutiny. Wall et al.'s (1997) survey of more than 11,000 National Health Service staff indicated gender differences in its findings, with women managers (41%) and women doctors (36%) registering higher proportions experiencing poor psychological health. However, within medical specialties, 48% of general practitioners (Caplan, 1994) and 46% of child psychiatrists (Littlewood, Case, Gater, & Lindsey, 2003) reported particularly high levels of strain. Comparisons between urban-based and more suburban hospitals have also produced different prevalence rates among healthcare workers, for example, 40% (Weinberg & Creed, 2000) versus 26.8% (Wall et al., 1997), and outside of medicine, the levels of strain between teams of social workers exposed to different organizational cultures also vary (Thompson, Stradling, Murphy, & O'Neill, 1996).

Consideration of occupational suicide rates should not be regarded as straightforward given the complexity of contributory factors. However, these rates are higher among doctors than in the general population (Lindeman, Laura, Hakko, Lonnqvist, 1996), and access to the means of committing suicide has been found to contribute to the raised number of incidences among farmers (Howton, Fagg, Simkin, Harriss, & Malmberg, 1998). Clusters of suicides have also been recorded within localities and even specific organizations, but establishing a link between such expressions of extreme distress and a particular workplace is fraught with political as well as methodological difficulties; consider, for example, the media scrutiny of the Paris Renault Center

following the deaths of three employees by suicide (*The Guardian*, 2007).

ORGANIZATIONAL STRESSORS

Having provided an overview of the symptoms of strain in organizations, this section highlights some of the major challenges facing the workforce and explores how these are linked to employee experiences of strain. While this list has the potential to be as long as the number of organizations that exist, there are common themes, characterized by a struggle for control at the interface between the organization and the individual employee, which may be distilled into the following: the psychological contract, the process of organizational change, the nature of modern working, and the role of emotions at work.

THE PSYCHOLOGICAL CONTRACT

The psychological contract represents the unwritten set of mutual expectations held by organizations and their employees, which can play a major role in determining attitudes and behavior in the workplace. The psychological contract as a concept has attracted much discussion in recent years and not a little disagreement, particularly in relation to how much it is a written or unwritten phenomenon. However, there appears to be consistency regarding the importance of fairness and trust (Guest, Conway, Briner, & Dickman., 1996) and the "dynamics of mutuality" (Rousseau, 2003, p. 229) within the relationship between employees and employer. Indeed, where organizational support is perceived to be low it is likely that the psychological contract assumes even greater significance (Coyle-Shapiro & Conway, 2005), and it is highly relevant in times of change. One stress outcome is the violation of the psychological contract, which in turn affects a range of workplace behaviors (Turnley & Feldman, 2000). Violations are recognized where the mutual set of obligations fails to be met by one party (in current research contexts this is usually on the part of the organization), resulting in differences between what the employee expects and actually receives (Coyle-Shapiro & Conway, 2005).

The study of violations of the psychological contract is a growing area for research. From an objective standpoint, this work focuses on how the mutual expectations between employer and employee have become unmatched. Sometimes this can happen as a result of "interpretations of patterns of past exchange . . . as well as through various factors that each party may take for granted" (Robinson & Rousseau, 1994, p. 246). However, violations often come about as the result of broken promises, which can carry with them far more emotion than a simple mismatch in expectations. A diary study of managers' daily experiences revealed that 69% of the sample of 45 reported violations during one 10-day period, with an average of one broken promise per week (Conway, Briner, & Wylie, 1999). The negative effect of breaches in the psychological contract has also been documented, with both emotional exhaustion and job dissatisfaction recorded as outcomes in financial sector workers (Gakovic & Tetrick, 2003). In a sample of more than 800 managers involved in organizational change scenarios, links were found between psychological contract breaches and subsequent job performance (e.g., dodging duties, wasting time), but violations were more strongly related to employees looking for another job and displaying less organizational citizenship (e.g., less volunteering for extra duties, or defending of the image of the organization) (Turnley & Feldman, 2000).

A relevant example is provided by changes in U.K. public sector organizations over the past 25 years, particularly in health and social care, higher education, and legislative government, as heads of industry and policy makers "set in motion a revolution in the nature of the employment relationship the like of which they never imagined. For they have shattered the old psychological contract and failed to negotiate a new one" (Herriot & Pemberton, 1995, p. 58). Before this major shift, mutual expectations saw employees prepared to commit to the goals of public service, displaying conformity and loyalty, while trusting the employer to value their efforts and well-being (Herriot & Pemberton, 1995). In return, public organizations were able to offer job security, a career path, and the necessary training to cement this transaction. Changes fuelled by globalization, technological innovation, and government ideology dismantled such assumptions and created increasing reliance on economic considerations. The new psychological contract shared by employees and their agencies reflects this change. In particular, the emphasis on "managing" the functions offered by the public sector, including health, social care, and education, has been perceived by many as a shift away from ensuring professional standards of service delivery. This is not to say that this "new managerialism" is necessarily motivated by a less customer-focused approach, but that it has produced an increased preoccupation with efficiency and accountability. From the employee's standpoint, success at work tends to mean longer working hours and greater pressure to deliver paper-based targets, along with the ability to withstand change and uncertainty. In return, public sector organizations offer a job that is, on average, less well-paid than private sector roles, and that is increasingly subject to performance-related criteria. U.K. research findings have revealed very high levels of psychological strain among the affected occupational groups (Taylor et al., 2004), greater sick leave than in private sector jobs (CBI/AXA, 2006), as well as increased staff turnover from occupations such as nursing (Scott, 2002) and social work (Huxley et al., 2005), resulting in skill shortages. However, alongside these outcomes, policy makers tend to highlight the

financial benefits and enhanced efficiencies in organizational functioning, as well as claiming greater choice for the service user.

Some would argue that this has encouraged a return to the scientific management principles referred to as Taylorism, named after Frederick Winslow Taylor, an early industrial efficiency expert. In other words, those characteristics salient in many private sector environments, including the production line, have found a new welcome in the changing priorities of service delivery in public sector organizations. This is not to say that Taylorism has deserted the private sector, rather it has been seeded in new fields and taken root in the service rather than manufacturing areas. Hence there is copious research into call centers, where the scripting of interactions for employees has served to take control away from the individual (e.g., Zapf, Isic, Bechtoldt, & Blau, 2003; Holman, 2002).

This type of change to the psychological contract can be seen as a major one, but of course this depends on how essential individuals view it to be to their relationships with their jobs. To employees facing what are perceived as unacceptable violations of their psychological contract, Herriot and Pemberton (1995) offer three possible courses of action: "Get safe, get out or get even!" Any or all of these have clear implications for organizational behavior and well-being.

MANAGING ORGANIZATIONAL CHANGE

Change is often ironically referred to as the constant feature of work, and while there can be little doubt that the effect of the psychological contract has been clear in particular jobs, this is not simply due to change itself, but rather to the way in which that change is managed (Giga & Cooper, 2003). Indeed, the mishandling of such situations has even drawn a directive from the European Parliament to oblige European employers to provide advance notice of any major organizational change (Giga & Cooper, 2003).

Whatever the political reality, change is always likely to send reverberations through an organization. It affects employees in a number of ways, both through the change process and its outcome. Findings have illustrated the positive effect on workers' well-being when they are given some measure of control over their work environment during a period of uncertainty (Bordia, Hobman, Jones, Gallois, & Callan., 2004) and, similarly, change need not be negative where careful management of the process is exercised (Firns, Travaglione, & O'Neill, 2006). A large study of 8,504 Swedish employees revealed clear benefits for the well-being of employees who had been involved in change processes rather than being on the receiving end of them, with those who participated experiencing half the rates of absenteeism and depression of the nonparticipants (Karasek & Theorell, 1990). In terms of the outcomes of organizational change for employees who survive the process, these are not always negative. With regard to the highly prevalent use of downsizing, Vahtera, Kivimaki, and Pentti (1997) found increased incidence of musculoskeletal disorders among staff who remained with the organization, whereas Travaglione and Cross (2006) found that some employee behaviors were not significantly affected by "survivor syndrome" and could be helped through effective management. One major area of culture change demanding this type of organizational action is higher education, which has consistently registered some of the highest and fastest rising levels of strain both among academic staff in Australia (Gillespie, Walsh, Winefield, & Stough, 2001), and in the United Kingdom, where almost half of a sample of 1,100 university staff have seriously considered leaving and 69% reported their job as "stressful" (Kinman & Jones, 2004).

Macchiavelli famously highlighted the difficulties associated with bringing about change, linked as they are to the fears and desires of those whom it affects. Without assessing emotions, all change risks failure, and the significance of emotional intelligence among employees likely to lead such processes should not be underestimated (Scott-Ladd & Chan, 2004). The number of change agents often adopting the guise of consultants has increased since the 1980s boom, and the importance of employing those who are well-equipped to deal with complex and unpredictable situations (Spence-Laschinger et al., 2004) serves to re-emphasize issues of process management. Given the prevalence of change in the working world, managers' roles inside and out of the organization are ever more demanding, and the quality and quantity of management support are key issues. Understandably, employees have a certain level of control over their working environment and therefore turn to their line manager to take overall responsibility. This may not always be a fair expectation by the employee but, remembering that control is important for individual well-being, it means that the stakes on the actions of the line manager are often high. This is the case for their staff as well as for themselves. The availability of support from a line manager has been shown to be a major predictor of employees' psychological health (Weinberg & Creed, 2000), and the gathering pace of management coaching suggests that organizations and managers alike are recognizing the pressure to be ever more flexible to demands.

Globalization has further highlighted cross-cultural differences in working practices and it is interesting to note national variation in the coping strategies utilized in the workplace. For example, Bulgarian managers are more likely to employ both control coping (objective and planning strategies) and support coping (seeking help and using nonwork resources) than are managers from the United Kingdom, United States, and India (Bernin et al., 2003). Cultural differences in leadership style are also highly relevant to change scenarios, with Middle Eastern countries prioritizing process needs, such as

diplomacy, over performance outcomes, as in western and southern Europe (Abdalla & Al-Homoud, 2001).

THE NATURE OF MODERN WORKING

The nature of work has changed dramatically with the spread of the information superhighway and the transfer of emphasis from manufacturing to service provision. Accompanying this, as has been mentioned, are the Taylorist principles of job specialization, often meaning a lack of autonomy as well as deskilling for the individual worker. This is particularly evident in modern day call centers where—just as on the production line—the work is divided into component parts and operatives are required to follow prescribed actions, with little variety or control over their work tasks (Zapf et al., 2003).

However there is no doubt that new technology such as email has made the distribution of documents easy and the process of written communication much speedier. The ubiquitous laptop and desktop computers have been a tremendous aid to the modern work environment; however, there are indications of a long-term negative effect on employees who are seated for prolonged periods at computer terminals, ranging from musculoskeletal difficulties (Aaras, Horgen, & Ro, 2000) to psychological strain (Ekberg et al., 1995). This may be related to the finding that where computers have been introduced to an office environment, clerical employees have reported increased workloads (Liff, 1990). Once again, new technology has molded expectations and tended to take control away from individual employees. Meanwhile, advanced manufacturing technology used in the mass production of anything from cars to newspapers is seen as producing speedier and more flexible working (Chmiel, 1998), with the added value for the organization of saving labor and guaranteeing standardized products and quality. However new technology driven by management concerns can result in failure where the role of the employees has not been adequately consulted or considered. Not uncommonly, technology is welcomed with hostility, not because of the newness, but rather due to the workers' perceptions of the underlying motives of the management in introducing the change (Arnold et al., 1998).

Without an obvious outlet for frustrations with new technology, the emotions experienced by workers can result in anything from sending "flame mail" to accessing the Internet for nonwork–related tasks. However, electronic performance monitoring (EPM) has made it possible for managers to see what is on the employee's computer screen. In the United Kingdom, employees have already been fired from their job for sending inappropriate emails, and public sector organizations have announced steps to stamp out illicit use of the Internet at work. Like so many initiatives, EPM can be justified on organizational grounds as a means of providing useful feedback to employees on their performance (Stanton, 2000), but the implications for employees are decreased privacy and increased workloads (Carayon, 1994).

Greater workloads can easily translate into raised working hours as employees remain in work longer to meet the organization's expectations. This can have effects on workers' health as well as home life. Since the proposal of a 10-hour working day at the Manchester Quarter Sessions in 1784 (Federation of European Employers, 2005a), the United Kingdom has established a reputation for having the longest average working week in Europe. However, the adoption of a more Americanized approach to working times by newer European Union members, such as Poland, means that the average U.K. working week of 44.8 hours is now only 1.1 hours higher than the EU average (Federation of European Employers, 2005b). While 22% of U.K. employees are working more than 45 hours per week, this is lower than the United States and Japan (Chartered Institute of Personnel and Development, 2006). In the United States between 1976 and 1993, men and women increased their average annual working hours by 233 and 100 hours, respectively (Bureau of Labor Statistics, 1997), with 76.6% of employees working more than 40 hours per week, compared to more than 87% of the working populations of Czech Republic, Hungary, and Slovakia who report these hours (International Labour Organization, 2007). The link between overwork and ultimate outcomes for individual health such as premature death (Michie & Cockcroft, 1996) and coronary heart disease (Russek & Zohman, 1958) illustrates the sinister effect of long working hours. Furthermore "presenteeism," where staff stays longer at work so as to be seen to be doing a good job and of value to the organization, may help to create an impression of a "committed" employee. Given the drop in perceptions of job security across Europe (ISR, 1995), such presenteeism is perhaps not surprising.

The longest working week in the world occurs in Pacific Rim economies (International Labour Organization, 2007), where Singaporean and South Korean employees spend 46 hours in the workplace each week (*The Standard*, 2005). However, pressure from both unions and government has seen the institution of a 5-day week in South Korea as well as moves in Japan to ensure that its employees take their full holiday entitlement to balance the routine of long hours of overtime. The frequency of "karoshi" (death from overwork) has led to a series of legal cases fought by widows accusing their husbands' former employers of corporate killing. Overwhelmed by the pressures of an increasingly competitive society, there is a rise in self-inflicted deaths among city dwelling 20- to 35-year olds in China, where suicide is the fifth most common cause of death (*The Guardian*, 2005a). On a brighter note, the leisure and retail industries have begun to burgeon in some of the information technology–dominated cities of southern India, and similar outcomes are anticipated in Malaysia, where the Saturday morning shift worked by its one million civil servants has been revoked (*The Standard*, 2005).

Long working hours also create pressure at the home–work interface, with recognized negative effects for employees and their organizations (Brough & O'Driscoll, 2005). Seventy-one percent of U.K. managers recognize that home is at least as important as work, but they continue to put in long hours, despite also believing that these are having an adverse effect on relationships with their partner (72%) and/or children (77%) (Worrall & Cooper, 2001). Strain-based conflict is brought on by the spillover of negative emotions from work to family and home (WFC) or vice versa (FWC), bringing with it a range of outcomes for either the work or home domain. Difficulties at home could see the employee underperforming at work, making errors and failing to meet expectations (FWC) (Frone, 2003), while WFC has been shown to contribute to burnout for nurses and engineers (Bacharach, Bamberger, & Conley, 1991) and to poor psychological health for politicians (Weinberg & Cooper, 2003). In the longer term, this can mean increased rates of depression, greater alcohol consumption (Noor, 2002), and more coronary heart disease (Haynes et al., 1984). However, research into stress in organizations paints a more complete picture where both work and nonwork factors are assessed. Phelan et al. (1991) interviewed 1,870 employees of Westinghaus Electrical Corporation during a period of organizational change and found the key predictors for depression (which affected 27.2% of the participating employees) were: personal or family history of depression, lack of intrinsic job rewards (e.g., the valuing of individual's contribution at work), conflicting work roles, negative work events, past psychiatric history in the employee's spouse, strain in the marital relationship, and a reduced sense of personal control. In a similar study on the objectively assessed experiences of U.K. National Health Service staff, employees diagnosed with anxiety and depressive disorders were compared with same-sex and age-matched colleagues working in the same job role and were found to have a significantly greater number of objectively stressful situations both inside and outside of work (Weinberg & Creed, 2000). Lack of management support was the single greatest work-based predictor of minor psychiatric disorder (Weinberg & Creed, 2000).

EMOTIONS IN THE WORKPLACE

As human creations involving human components, organizations are subject to the effect of emotions. Organizational psychology research is increasingly recognizing the significance of emotions, whereas at one time these were considered of secondary importance (Ashkanasy et al., 2002; Fineman, 2000). Hence, Affective Events Theory (Weiss & Cropanzano, 1996) recognizes the effect of work events on employee emotions and highlights the role of cognitive appraisal in shaping such reactions. However while concepts encompassing emotions are a growing feature of the literature, these have yet to be fully integrated into existing approaches to research and intervention. Workplace relationships and communication naturally come under the spotlight of this area and, since the beginning of the millennium, the positive concept of emotional intelligence and the negative effect of bullying have rapidly moved to research's center stage. In relation to organizational strain, the latter is examined after scrutiny of emotional labor, which characterizes the interface between client and employee.

The significance of emotions at work may not be immediately apparent from the plethora of widely employed call answer systems we encounter in the business world. Human communication costs organizations money and, as an integral part of this, so does human emotion. The often perceived more economical choice is to provide a series of recorded, emotionless options, although it is hard to estimate how many potential customers are actually dissuaded from doing business by this impersonal approach. Consequently, personal or one-to-one service has become a major selling point, and the dilemma facing many large customer service organizations is whether to invest in delivering human contact and emotion through their representatives, or to avoid this wherever possible. Each carries a cost to the organization, and the result has been a compromise: the introduction of scripted interactions for their employees. This is the essence of emotional labor, where the "management of feeling to create a publicly observable facial and bodily display" (Hochschild, 1983, p. 7) leads the employee to "create an impression that is part of a job" (Smither, 1998, p. 43). It is part of almost any job that involves working with other people, where the employee is obliged to consider not only the task at hand, but also the manner in which it is accomplished, and has relevance to an estimated two-thirds of workplace interactions (Mann, 1997).

The manner in which the employee's emotional display is conveyed can depend on his/her ability to "act" or "fake" apparent emotion (verbally or nonverbally), or at a deeper level "by directly exhorting feeling . . . or by making use of a trained imagination" (Hochschild, 1983, p. 38), such that the workers really feel the emotion that they perceive the situation demands. The outcome of convincing others that the employee is experiencing the appropriate emotion is clearly significant to the organization, for example, appearing concerned about a complaint or smiling to reassure a client. However, where the priorities of the organization do not match those of the individual, emotional dissonance is likely to be experienced by the employee. This is where the employee is required to "express organisationally desired emotions not genuinely felt" (Morris & Feldman, 1996, p. 986). Call centers (Taylor, 1998) represent an extreme example of this type of interaction, reminiscent of early twentieth century management styles, where employee–client conversations are scripted and often monitored, thus removing individual freedom from the worker to respond as he or she actually feels. Indeed, this has been shown to diminish job performance (Goldberg & Grandey, 2007).

Given the widespread prevalence of emotion work across a range of occupations, it is hard to define certain job roles as requiring significantly more emotional labor than others (Brotheridge & Grandey, 2002). However, it is recognized that surface acting and the faking of emotions inherent in so much emotional labor are significantly correlated with emotional exhaustion and depersonalization (Brotheridge & Grandey, 2002), which in turn characterize burnout. This suggests that emotional effort that is incongruent with felt emotions can in turn promote psychological strain (Brotheridge & Lee, 2003; Zapf & Holz, 2006), as has been demonstrated in growing numbers of occupations ranging from holiday agents (Guerrier & Adib, 2003) to legal representatives (Harris, 2002).

Emotional labor may be seen as a legitimate and integral component of certain jobs, however, the misuse and abuse of emotion provides a sobering contrast. Bullying in organizations appears to be widespread and occurs where "one or several individuals persistently over a period of time perceive themselves to be on the receiving end of negative actions from one or several persons, in a situation where the target of bullying has difficulty in defending him or herself against these actions" (Hoel & Cooper, 2000). Referred to as bullying in the United Kingdom and Ireland, it is known as "mobbing" in Germany and Scandinavia and "workplace harassment" in the United States and Canada. Although only relatively recently highlighted in workplace research, its prevalence indicates the existence of a widespread problem. A national U.K. survey of more than 5,288 employees found that 10.5% were currently bullied (Hoel, Cooper, & Faragher, 2001) and that 49.4% of British employees had experienced or witnessed bullying at work in the previous 5 years (Hoel, Faragher, & Cooper, 2004). The most frequently occurring problems were for those employed in the prison, postal, and teaching occupations (Hoel et al., 2001), although it seems to be widespread regardless of organizational culture (Hauge, Skogstad, & Einarsen, 2007). Bullying affects men and women employees equally, although women perpetrators tend to be coworkers and the males are likely to be either coworkers or supervisors (Vartia & Hyyti, 2002). The effect is on both the physical and emotional well-being of the victims (Einarsen & Mikkelsen, 2003) and has also been found among those witnessing bullying (Hoel et al., 2004). Findings in the United States shockingly record that 97% of Asian, Hispanic, and African American employees had experienced some form of bullying in the previous 5 years (Fox & Stallworth, 2005).

While bullying represents an extreme yet unfortunately commonplace expression of emotion, discrimination is no less undermining a manner of oppression. Like bullying, the motivation for discrimination varies and, similarly, its targets can be drawn from anywhere in the workplace. What might be justified as a "personality clash" may actually represent discrimination against an individual, while the phrase the "glass ceiling" describes the invisible layer within an organization that prevents people from a whole group gaining access or promotion to the higher echelons of management (Davidson & Cooper, 1992). However defined, it is a source of much emotion at work, and those on the receiving end of discrimination may find that it is due to prejudice toward their gender, ethnicity, religion, sexuality, age, or disability. In its most stark form, discrimination exists as a pay differential that sees members of demographic groups receive systematically less than their counterparts. For example, this is particularly pronounced between genders in the United Kingdom, where male pay averages around 19% higher than for women (Arulampalam, Booth, & Bryan, 2005–2006). This gap is greater in the private sector, where woman are paid on average 45% less than their male colleagues (*The Guardian*, 2005b), and is accentuated at the higher end of the pay scales. This contrasts with an average gender pay differential of 12% in Denmark and 23% in Finland, whereas in Austria the gap is widest at the lowest end of the wages spectrum—an example of the "sticky floor" phenomenon, in which employees find it hard to move away from the bottom of the pay scale (Arulampalam et al., 2005–2006). For members of ethnic minority groups, studies have shown increased rates of dismissal (Wilson, 2005), and discrimination however expressed has been highlighted as a predictor of psychological illness in both the United States (Darity, 2003) and the United Kingdom (Bhui et al., 2005).

A RESONANCE MODEL OF ORGANIZATIONAL STRESS

Having highlighted key stressors for organizations and their employees, it is useful to consider the mechanism linking these and symptoms of strain, before addressing the issue of interventions. The model presented here is configured along the same principles of the frequency of sound waves and vibrations, which can resonate with objects and cause them to vibrate. Normally this does not cause a problem for the objects concerned, but where the vibration is of a sufficient frequency to cause extreme resonance this may lead to damage and ultimately collapse. Relevant examples include the opera singer whose singing shatters the wine glass and the collapsing of bridges caused by earthquakes, such as the San Francisco–Oakland Bay disaster of 1989. Taking human tolerance for stress as a comparison, where one or more factors significant for the employee resonate to such an extent that exceeds the limits of the individual to cope, then the outcome can prove injurious to their psychological and/or physical health. Given the variety in the frequency and potential resonance of one or a combination of factors for an individual in the world of work, the model is not prioritizing the features shown, but rather dividing them for

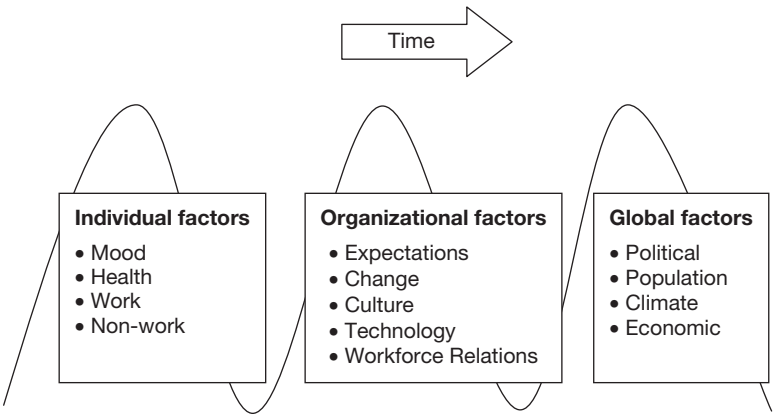

Figure 12.1 ■ *Resonance model of organizational stress*: As employees and organizations experience varying levels of pressure from different domains of their existence, there is considerable potential for synchrony between stressors. Consequently individual and organizational capacities to cope are challenged and where these are exceeded, collapse is likely, in the same way the resonating frequency of sound and shockwaves can lead to the shattering of physical structures.

the sake of ease of interpretation into individual, organizational, and global factors (Figure 12.1). Any combination may produce positive or negative outcomes for the working population, as described in the early part of this chapter.

TACKLING ORGANIZATIONAL STRESS

The law in many countries stipulates minimum standards of health and safety in the workplace as well as codifying the responsibilities of the employer to the worker. Yet, given the broad brush approach of organizations to any stressor and the need for individuals to safeguard their health, the optimal action is to ensure that organizations and their employees facilitate well-being at work. The final part of this chapter highlights the range of strategies that can be used to this end. The approaches fall into three broad categories (Schmidt, 1994), but these should not be viewed as exclusive of each other, as a combination of strategies may yield the best outcomes. Furthermore these interventions can be at the level of the individual and/or the organization (Giga, Cooper, & Faragher, 2003):

- Primary interventions focus on the prevention of problems at the organizational level, for example, job redesign and restructuring relationships between departments.
- Secondary interventions aim to manage the symptoms of strain and target the individual/organization interface, for example, stress management programs such as fitness training, relaxation techniques, and time management.
- Tertiary interventions are designed to aid the individual or organization that may need more specialized help to deal with the strain, for example, employee assistance programs offering counseling or referral for medical help through an occupational health department.

PREVENTING STRAIN IN THE WORKPLACE—PRIMARY LEVEL INTERVENTIONS

Primary level or organizational interventions that prevent strain among the workforce seem at first sight a highly attractive option to those who wish to improve the well-being of all employees. However, the reality of trying to introduce and evaluate such initiatives means that they tend to be the least favored of the three approaches highlighted (Giga, Faragher, & Cooper, 2003). "Organizational stress is different from coping with individual stress. Organizations are not simply mechanistic, they are subject to important psychological processes that influence the ways people manage their work relations" (Health Education Authority, 1997). In part, this explains why interventions at the level of the organization are reported relatively rarely. Therefore, despite the wide range of potential initiatives, progress in preventing strain at work has been described thus far as "disappointing" and therefore "a significant barrier to . . . reducing work-related stress" (Kompier, Cooper, & Geurts, 2000, p. 375). Organizational politics plays its part in hindering reforms to working practices, with senior level management tending to attribute difficulties to employee-related factors (Giga, Cooper, et al., 2003). Nevertheless, a wide variety of options exist (Elkin & Rosch, 1990; Giga, Cooper, et al., 2003).

The initial placing of the employee in the organization is a key point at which to ensure individual well-being by appointing appropriately and thus preventing the problems of poor performance, low morale, and increased turnover. U.K. employment law encourages the organization to take employees as they find them, but proactive induction processes including job previews help to ensure a good match of mutual expectations and to reduce workers' uncertainty (Schweiger & DeNisi, 1991). Following on from this, effective appraisal systems (kept separate from pay considerations) and staff development programs prepare employees for their future either within or outside the organization

(Sutherland, 2005). Furthermore, both role ambiguity and role conflict can have damaging effects on employees' well-being, whereas the use of realistic goal setting has led to decreased absenteeism in the insurance industry (Quick, 1979).

From earlier discussion of the psychological contract it is clear that the design of work is integral to job control and, where this has been augmented, improved job satisfaction and productivity has been recorded in settings as diverse as machine tool operation (Jackson & Wall, 1991) and retail outlets (Miller, 1994). Given that any change can lead employees to question their organization's view of them, even where the intended effect is positive, effective communication systems contribute to improved organizational functioning (Adkins, Quick, & Moe, 2000). Indeed, team work in itself is beneficial for psychological health (Borrill et al., 1998). For example, active promotion of healthy working through regular employee meetings, as part of a long-term organizational commitment, can boost employee well-being and diminish sickness absence (Aust & Ducki, 2004). As new innovations in computer-filled offices produce new challenges to employee well-being, initiatives tackling "technostress" are ever more welcome (Arnetz, 1996). The role of organizational leadership in facilitating employees' ownership of interventions (Nytro, Saksvik, Mikkelsin, Bohle, & Quinlan, 2000) underlines the importance of participative change, as highlighted earlier. However, this presumes that managers possess the appropriate skill set to achieve such a goal. The growth in coaching may well address this key issue. In a U.K. study of National Health Service managers, an "upward feedback" intervention found improved employees' ratings of their managers following training on 10 behavioral dimensions (e.g., creating a team environment, providing feedback, communication), as well as improved psychological health, with statistically significant decreases in symptoms of depression and anxiety among both managers and their staff (Borrill et al., 1998). A similar study in a university setting during a period of organizational change has found improvements in well-being among managers participating in a management coaching program at the same time as increased psychological strain was found among managers in a control group (Weinberg, 2008).

There are also methodological reasons why organizational interventions per se are tricky to evaluate. These include the rarity of studies utilizing random allocation, although support for alternative approaches such as the case study (e.g., Kompier et al., 2000) and retrospective comparisons (Randall, Griffiths, & Cox, 2005) is gaining. Such approaches are likely to be welcomed by researchers, especially as one comprehensive review of the published literature from 1970 to 1996 identified only four studies that met the authors' research criteria (van der Klink, Blonk, Schene, & van Dijk, 2001). Kompier et al. (2000) have contributed to broadening the literature in this area by attempting to gather data on an organizational intervention from each of 14 European Union member countries at that time. Eleven nations submitted data and nine of these were included in the final analysis, with interventions ranging from policy changes to training and even wholesale redesign of work. Three studies (from The Netherlands, Belgium, Sweden) reported significant decreases in absenteeism and, with the addition of the Danish data, four projects indicated financial benefits (Kompier et al., 2000). Seven interventions demonstrated positive self-reported effects, such as fewer health complaints. Only the Dutch intervention featured a valid control group, with the others relying on appropriate evaluation measures, but overall the authors accepted that "it is at least plausible that the positive outcomes can largely be attributed to the intervention programmes" (Kompier et al., 2000, p. 385).

It also makes sense to assess the perceptions and coping strategies adopted by employees as these are likely to have an effect on the effectiveness of organizational change (van der Klink et al., 2001). Therefore, when looking to reform jobs with low levels of control, organizational interventions that increase autonomy are recommended and should be accompanied by cognitive-behavioral measures that modify how the individuals view the work (van der Klink et al., 2001). Additionally, a more comprehensive stress prevention and management package that has the support of top-level management, and that fully involves the relevant parties, seems to represent the ideal, provided this is directed at both the person and the work environment (Giga, Cooper, & Faragher, 2003). A participative approach that engages workers in its design, implementation, and evaluation is more likely to yield positive results (Elo, Leppanen, & Sillanpaa, 1998) and, where possible, the effect of factors at the home–work interface should also be taken into account (Weinberg & Creed, 2000). Where both the change and the manner of its introduction are important (Kompier et al., 2000), one major difficulty is accurately evaluating the effect of an organizational intervention such that individual variables affecting psychological and emotional health are identified.

STRESS MANAGEMENT AT WORK—SECONDARY LEVEL INTERVENTIONS

By far the most popular approach to tackling psychological and emotional strain in the workplace has been via "stress management": in other words, the identification of symptoms of strain and the introduction of methods to help individual workers deal with them. The potential drawback of this approach is the idea that the onus for improving well-being rests with the individual rather than with the organization. This is undoubtedly easier for the organization and is generally less likely to

cause political fall-out, but runs the risk of conveying an unhelpful message about the workplace.

Since the 1980s, the stress management industry has boomed, promoting awareness and recognition of psychological and emotional strain, as well as teaching employees' skills designed to reduce physiological and psychological arousal levels (Murphy, 1996). Examples include exercise programs (e.g., on-site gymnasium), relaxation workshops, cognitive coping strategies (e.g., time management), and biofeedback (Cooper & Cartwright, 1994). These approaches may be sponsored by the organization and are designed to enhance the coping strategies of the individual in the context of the workplace. One-third of stress management interventions involve either relaxation or cognitive-behavioral therapy and these are the most popular forms to be found (Giga, Cooper, & Faragher, 2003). A large-scale review of 17 relaxation and 18 cognitive-behavioral therapy studies found that, overall, the latter were more effective in reducing symptoms of strain (van der Klink et al., 2001). Additionally, multimodal interventions employing more than one strain management technique showed success in reducing symptoms (van der Klink et al., 2001). However, in evaluating the range of secondary level interventions, there are reservations over the tendency to offer this opportunity in white-collar jobs and in a generalized rather than situation-specific manner, with further concerns over failure to maintain stress management skills over time (Murphy, 1996).

Workplace health programs have achieved popularity in organizations, particularly in North America, where they provide "vigorous cardiovascular exercise, activities which promote muscle tone and flexibility, life style counselling and fun and fellowship" (Dishman, 1988). Such programs claim to cut illness costs, improve productivity, and maintain good health, but evaluation is less than systematic (Schreurs, Winnubst, & Cooper, 1996). Where this has occurred, benefits have been found for both the physical and mental health of the employee, as well as the functioning of the organization (Voit, 2001). Members of a U.K. corporate health and fitness club were found to be significantly more positive in their mood and emotional state than both nonmembers and those on the scheme's waiting list in terms of levels of energy, elation, clear-headedness, and confidence (Daley & Parfitt, 1996). An evaluation of the employee fitness program at the ING bank in The Netherlands demonstrated a significant decrease in absenteeism for both regular and irregular participants, and indications of an overall improvement in scores on a general measure of tension, agitation, and anxiety, compared to nonparticipating employees (Kerr & Vos, 1993). A study of automobile manufacturing plants in Michigan, US, went further and established the cost-effectiveness and clear benefits for well-being of employee health and fitness schemes that provide a range of exercise options as well as follow-up counseling (Erfurt, Foote, & Heirich, 1992).

TREATING THE WALKING WOUNDED—TERTIARY LEVEL INTERVENTIONS

The concept of Employee Assistance Programs (EAPs), featuring counseling as the main component, has gained popularity over a number of decades along with the realization that it is important for workers to have opportunities to discuss confidentially their emotions and psychological well-being with a third party independent of their organization's management. The EAP has been defined as a "mechanism for making counseling and other forms of assistance available to a designated workforce on a systematic and uniform basis and to recognized standards" (Reddy, 1993). Employee counseling was introduced at the Western Electric Company in the 1920s and 1930s, where the Hawthorne Studies led the organization to the conclusion that they "should manage workers" irrational emotions by paying more attention to their feelings and concerns" (Lee & Gray, 1994, p. 218). Interviews with 20,000 employees as part of the company's research into productivity highlighted the link between the opportunity to express emotions about work and improved functioning as well as a decrease in tension (Arthur, 2000).

Use of EAPs has burgeoned in recent years and in the U.K. more than 1.75 million employees across 775 organizations have access to such a service, which represents a growth of 40% since 1994 (Arthur, 2000). Four-fifths of large and more than one third of medium-sized United States employers utilize EAPs (Lee & Gray, 1994), where the emphasis is less on self-referral than in the United Kingdom (Cuthell, 2004). The first EAP to support doctors—an occupational group often reluctant to seek help because of entrenched self-perceptions of their helping role – was established in 1987 in Canada and this example was followed by the British Medical Association in 1996, with a 24-hour stress hotline that received 6,000 calls during its first 2 years of operation, including from doctors, medical students, and family members (*The Lancet*, 1998).

A successful and well-used EAP is characterized by commitment from the highest organizational level, involvement of relevant stakeholders, clear policies and procedures, protection of employee confidentiality, proper publicity of the services offered, and provision for follow-up of the service users (Arthur, 2000). As the need for EAP provision has been recognized and increasingly implemented, research has begun to turn to evaluating their effectiveness and assessing the well-being of those individuals making use of them. At one point, U.K. employers were spending £6 million annually on EAPs, yet only one-third of these schemes were objectively evaluated and only half of these used comparison group data (Highley & Cooper, 1993). Given the role of EAPs not only in providing care but also in sending a message from the organization about how it treats its employees, the prospect of evaluation can cause unease. With this in mind,

the limited evidence has been mixed, with the Australian civil service EAP breaking even (Blaze-Temple & Howat, 1997) and the U.S. state of Ohio's EAP failing to lead to reductions in staff absence and turnover (McClellan, 1989). However, the decrease from 84.5% to 27.6% in a study of U.K. NHS employees reporting high levels of distress following counseling is an indication of the direct benefit for individuals (Borrill et al., 1998), which in turn facilitates better organizational functioning. Similarly, a study of the U.K. Post Office EAP revealed statistically significant reductions in symptoms of depression among 60% of service-users and of anxiety among 62% of service users (Cooper & Sadri, 1991). Among this "improving" group of employees, there was a 22% drop in the number of days' sick leave. Most promisingly from an evaluation perspective, the EAP supplied to 30% of the Fortune 100 companies produced significant improvements in attendance, work performance, and relationships, as well as levels of psychological strain (Masi & Jacobson, 2003).

The need for EAPs is underscored by findings in which 42.3% of respondents to a survey of users scored either the maximum score or one short of the maximum score of 12 on the General Health Questionnaire, and that approximately two-thirds of participants would have stayed away from work in the absence of counseling provision (Arthur, 2002). Careful handling of distressed employees is a clear priority, especially as revisiting old feelings can be counterproductive by interfering with the mental processing of highly stressful or traumatic events (Sijbrandji, Olff, Reitsma, Carlier, & Gersons, 2006). Notwithstanding such considerations, the combination of organizationally and individually tailored solutions is most likely to yield the best outcomes for employees and employers alike.

CONCLUSION

"If the ethical arguments are not always clear and organizational success is seen as one-sided in favour of the employer, then legal reasons usually focus the minds of employers and employees alike" (Weinberg & Cooper, 2007, p. 47). Whatever one's perspective, the effect of organizational stress on employees as well as on corporate functioning is indeed costly. This chapter has highlighted the range of symptoms of strain in the workplace at both individual and organizational levels and identified the key challenges at the interface between workers and their employers. These stressors included the psychological contract (using the U.K. public sector as an example), change management, modern working conditions (including working hours, new technology, and the home–work interface), and the role of emotions at work (emotional labor and negative relationships including bullying and discrimination). Causes of stress have been highlighted in a new Resonance Model of Organizational Stress which emphasizes the variation over time in our experience of the world of work, provided by individual, organizational, and global factors, any combination of which may lead to positive or negative consequences through resonance of factors crucial to employees. With the positive in mind, three approaches to tackling organizational stress have been considered, comprising preventative, stress management and treatment strategies, and considerable scope remains for research in any combination of these promising avenues. In a world of work characterized by change, some of it dramatic and some incremental, the key to survival is to ensure harmony between those factors that promote well-being. We have varying degrees of control over these and the challenge awaiting organizations, employees, and researchers is how best to identify and manage the resonance of stressors that could spell disaster for the fragile balance of our working lives.

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13 Racism as a Psychosocial Stressor

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Eliminating racial/ethnic disparities in health is a national priority, articulated by Congress in the goals for Healthy People 2010 (People, 2008). Racism or ethnic discrimination has been identified as a chronic psychosocial stressor contributing to many of these health disparities. But how does racism affect health? The aim of this chapter is to identify the mechanisms through which acute episodes of ethnicity-related maltreatment lead to the type of chronic stress responses that can contribute to the development and maintenance of stress-related physical disorders.

Expanding on the work of Swim and Stangor (1998), we examine questions about the relationship of racism to health from the target's perspective, that is, from the perspective of the individuals at whom prejudice and discrimination have been directed. We begin by reviewing definitions of racism and delineating the different types of ethnicity-related maltreatment to which individuals may be exposed. Next, we identify the paths through which these different types of exposure produce psychological changes that can initiate and maintain a chronic stress response.

It is important to note that although we are discussing the experience from the target's perspective, we do not intend to communicate the idea that perceptions of racism are "all in the target's mind." Instead, we hope to illustrate the ways in which psychological responses to ethnicity-related maltreatment have pervasive effects that can be identified, understood, and potentially prevented or ameliorated. In this way, our approach is consistent with the stress-coping paradigm that guides the examination of the mechanisms through which other psychosocial stressors (e.g., job strain, interpersonal conflict) affect health.

DEFINITIONS

There are a number of proposed definitions of racism and ethnic discrimination. One widely used definition was presented by Rodney Clark and colleagues in a paper published in 1999 in *American Psychologist*. Racism was defined as "the beliefs, attitudes, institutional arrangements, and acts that tend to denigrate individuals or groups because of phenotypic characteristics or ethnic group affiliation" (Clark, Anderson, Clark, & Williams, 1999b, p. 805). Contrada has used the more general term, ethnic discrimination, and defined it as unfair treatment received because of one's ethnicity, where "ethnicity" refers to various groupings of individuals based on race or culture of origin (Contrada et al., 2000, 2001). In line with these definitions, we view racism or ethnic discrimination as a form of social ostracism in which phenotypic or cultural characteristics are used to render individuals outcasts, making them targets of social exclusion, unfair treatment, and threat and harassment (Brondolo, Brady, Pencille, Beatty, & Contrada, 2009).[1]

Racism can occur on multiple levels: cultural, institutional, and interpersonal (Harrell, 2000). Cultural racism can occur when the methods used to communicate cultural values (e.g., film, television, advertisements) convey information about the social status or characteristics of different ethnic/racial groups. In some cases, the communication of negative information about the demeaned status of certain groups is made explicit. But in many cases, the communication of status-related messages occurs implicitly. For example, studies indicate that the media more often display the faces of Blacks accused of crimes than the faces of Whites accused of crimes (Dixon, 2008). This practice reinforces negative stereotypes of Blacks. Movies and TV programs that portray African Americans or Latinos primarily in the role of the criminal, but not in the role of hero, contribute to the notion that people of color are not "in the mainstream" and should be viewed as deviant. Similarly, individuals may infer that their ethnic/racial group is low in status if members of their group do not hold positions of power (e.g., in government or business) and are not depicted in positions of power even in media representations of

[1] There is little consensus on the best terms to use to distinguish among groups based on phenotypic or cultural characteristics, and both scientific and political factors influence the debate. Some groups (i.e., Blacks) have been considered "racial" groups despite the lack of biological evidence for distinct races; whereas others (i.e., Latinos) are considered ethnic groups, but have also had their ethnicity referred to as a "race." In this paper, we have chosen to use the terms "race" and "ethnicity" and "racism" and "ethnic discrimination" interchangeably.

reality (e.g., advertisement, TV programs). When advertisements employ only European American models to communicate a product's beauty and desirability, individuals with different phenotypes (e.g., darker skin) may perceive themselves, and be perceived by others, as "less beautiful" (Imarogbe, 2004).

Although there are differences of opinion concerning the definition of institutional racism, it generally involves specific policies and/or practices of institutions (e.g., government, business, schools, churches) that consistently result in unequal treatment for particular groups (Better, 2002; Griffith, Childs, Eng, & Jeffries, 2007; Lea, 2000; Macpherson, 1999). Institutional racism may occur at different levels within an institution, ranging from the attitudes and actions of personnel to the policies and practices of upper administrative structures. Using this definition of institutional racism, examples include cases in which local government jurisdictions establish requirements for voting that, in effect, restrict the rights of individuals to vote based on their ethnicity or race. Institutional racism can also include lending practices that result in a lower rate of approved home mortgages for Black Americans, contributing to racial segregation in housing (see Henkel, Dovidio, & Gaertner, 2006).

Individual-level or interpersonal racism has been defined as "directly perceived discriminatory interactions between individuals whether in their institutional roles or as public and private individuals" (Krieger, 1999, p. 301). Operationally, perceived interpersonal racism refers to the target individual's self-reports of exposure to racist interactions. Interpersonal racism may have psychological and physiological effects when experienced vicariously, rather than directly, as when individuals become aware of racism directed at their family, friends, or others sharing phenotypic or cultural characteristics (Krieger, 1999).

Interpersonal racism may encompass different types of experiences ranging from social exclusion, workplace discrimination, and stigmatization to physical threat, harassment, and aggression (Brondolo, Thompson et al., 2005; Contrada et al., 2001). Social exclusion includes various different acts in which, for example, individuals are prevented from participating in social interactions, rejected by others, or ignored by service personnel. Stigmatization can include both verbal and nonverbal behavior directed at the targeted individual and communicating a message that he or she has a demeaned status (e.g., a look of disgust or a verbal expression of the belief that the target is lazy or stupid). Workplace discrimination can include acts ranging from those that signal lowered expectations to a refusal to promote or hire an individual of a particular race or ethnicity. Threat and harassment can include potential or actual damage to oneself, family, or property. These experiences of maltreatment are considered aspects of interpersonal racism if the targeted individual believes that the maltreatment was motivated entirely or even partially by racial or ethnic bias.

Interpersonal racism is often, but not always, a function of contact between majority and minority group members. In our studies of convenience samples of community members and students, we asked individuals to indicate which group was most likely to treat them in a discriminatory fashion. Substantial proportions of all groups we have studied indicate that "Whites" are most likely to target them for discrimination. Across studies, 53–61% of Blacks, 51–54% of Latino(a)s, 28% of Chinese, 47% of Filipinos, 42% of Asian Indians, and 49% of Koreans reported that they were most likely to be targeted for discrimination by White individuals. However, participants also reported being targeted by other minority groups, with, for example, 49% of Chinese, 40% of Koreans, 27% of Asian Indians, 28% of Filipinos, and 22–24% of Latino(a)s reporting that they were most likely to be targeted by Blacks. Smaller percentages of individuals reported being targeted by Latino(a)s and Asians.[2]

In addition, our studies demonstrated the presence of intragroup racism. Some participants from all groups reported that they were most likely to be targeted by individuals of the same ethnicity. Intragroup racism was reported by 20–28% of Blacks, 8–15% of Latino(a)s, 7% of Chinese, and 9% of Asian Indian participants. In future studies, it will be important to understand the factors eliciting intragroup racism.

There is considerable evidence that aspects of racism, such as the degree of intentionality and explicitness, have changed over time as norms supporting acceptance of egalitarian attitudes have become more widespread (Katz & Hass, 1988; McConahay, 1986; McConahay, Hardee, & Batts, 1981; Saucier, Miller, & Doucet, 2005). Specifically, there has been a decrease in overt racism, including cases in which the racial bias of the actor would be evident to any observer (e.g., when explicit racial terms are used in an interaction) and the evidence of maltreatment clear (e.g., arguing or physical threat). Instead, more discriminatory acts are perceived as covert. In these cases, the racial bias motivating the act and the degree to which it is discriminatory or damaging are perceived by the targeted individuals, but may not be clearly discernable to others (Taylor & Grundy, 1996). Often, the maltreatment itself is subtle (e.g., a glance, physical withdrawal, or tone of voice), with signs of conflict not readily apparent to a casual observer. For example, African Americans are aware that some individuals hold highly negative and prejudicial beliefs about African Americans, including the belief that they

[2] We have conducted 13 studies on more than 3,000 participants. The participants were drawn from convenience samples of community-dwelling adults at local medical centers, primary care practices, and other community sites as well as from our university community. The data on inter- and intragroup racism come from two studies on Blacks and Latinos including over 1,000 participants, and the data on Asian subgroups come from a sample of 531 individuals.

are unclean or dangerous. Consequently, if someone rises and walks away when an African American individual enters the room, the African American person may reasonably suspect that the individual is acting in a discriminatory manner. This is particularly likely to happen if the individual is known or suspected to hold prejudicial beliefs. However, without conscious awareness of these stereotypes, others who observe the interaction may not be aware that the behavior (i.e., walking away) may elicit concerns among African Americans that racial bias may have been a factor motivating the behavior.

In our qualitative research, we asked participants (college students and community members) to provide stories of experiences of interpersonal racism.[3] Many respondents gave examples in which they reported feeling socially excluded because others refused close contact, and they believed it was because of their race or ethnicity (e.g., "I was on a crowded subway and a White lady chose to stand instead of sitting next to me."). Examples of workplace discrimination included experiences in which individuals were assigned lower level jobs requiring cleaning or physical labor because of their race (e.g., "I had to clean all the sinks while the White girls got to walk around.") Examples of stigmatization included episodes in which targeted individuals felt unfairly characterized as less worthy or valuable because of their race (e.g., "He feels that I am not good enough for her even if I treat her good; he puts in her head that all Latinos are bad and unfaithful"). Examples of race-related physical threat and harassment include episodes in which there was either overt or implied threat of aggressive behavior (e.g., "An officer said to me, 'Get your Black butt back here or I'll take you away.'").

Race-based maltreatment can occur even when the "perpetrator" is not consciously aware of the motivations for his or her behavior. Cultural attitudes toward ethnic groups and the individual's prior experience can shape implicit attitudes (i.e., attitudes outside our conscious awareness) and subsequently influence our interpersonal interactions (Dovidio, 2001; Dovidio, Kawakami, Johnson, Johnson, & Howard, 1997; Dovidio et al., 2008). There is some suggestion that these biases contribute to racial disparities in the quality of health care (Smedley, Stith, & Nelson, 2003). Although the notion of implicit bias expressed in interracial exchanges can be difficult to accept, we commonly acknowledge this idea when considering other kinds of social interactions. For example, in hindsight, we understand that we may have behaved badly (e.g., yelled at a spouse or a child because we were anxious or angry) without having fully understood our concerns and motivations at the time.

[3] We changed minor details of the settings or wording of the examples to protect the respondents' confidentiality.

INTERPERSONAL EFFECTS OF CULTURAL AND INSTITUTIONAL RACISM: INTERACTIONS ACROSS LEVELS OF ANALYSIS

Events that occur within a cultural or institutional framework also have interpersonal consequences occurring on an individual level. Our focus on interpersonal racism is consistent with the methods of other investigators who have examined the interpersonal effects of other major social stressors (Ruiz, Hamann, Coyne, & Compare, 2006; Smith, Gallo, & Ruiz, 2003). For example, recent studies of the effects of socioeconomic status (SES) on interpersonal relations and daily moods and experiences have yielded insights into the mechanisms through which poverty may affect individual health (Gallo, Smith, & Cox, 2006). These mediators (e.g., daily mood, negative social exchanges) may offer meaningful targets for intervention.

To apply this approach to the study of racism, we can consider the potential individual or interpersonal effect of cultural or institutional racism. For example, when the media communicate messages that associate negative characteristics with a particular ethnic or racial group, they may sanction maltreatment toward members of that group and thereby promote discriminatory behavior in members of other groups. More specifically, media depictions of Blacks as violent criminals may potentiate anti-Black violence, especially in ambiguous circumstances.

In addition to effects on members of other groups, those in the targeted group may internalize these stereotypes (i.e., self-stereotyping) or develop chronic concerns about conforming to those stereotypes (i.e., stereotype threat) (Contrada et al., 2000; Steele, 1997). This internalization may occur even when targeted individuals are not aware of exposure. A wealth of research has demonstrated the effects of stereotype threat on cognitive, performance, and affective responses, and a growing body of research suggests that this self-stereotyping may influence health-related behaviors and outcomes (Sinclair, Huntsinger, Skorinko, & Hardin, 2005; Steele, 1997). These issues are discussed in more detail in a later section of this chapter.

Institutional racism is often manifested in interpersonal interactions. For example, when a real estate broker steers individuals to particular neighborhoods or denies that certain properties are available, the events can be seen as institutional racism (i.e., emerging from policies set by the brokerage company, the community, or local government), but the contact occurs in the context of a transaction between a customer and a real estate broker. In this particular example, the exchange between broker and customer may be overtly cordial. However, if the net result is that the targeted individual is socially excluded or blocked from living in a desirable area because of his or her race or ethnicity, the interaction could be considered a form of ethnicity-related interpersonal maltreatment. This is the case, even if the broker is not aware or does not acknowledge that he/she is making these business decisions based in part on the race of the customer.

Together, cultural, institutional, and interpersonal racism can have particularly deleterious interpersonal consequences when they result in residential segregation. Williams and Collins (2001) present evidence that African Americans are more likely than other groups to live in substantially segregated neighborhoods, and that this segregation can have independent effects on health and well-being. In contrast to low-income Whites (who tend to live in more socioeconomically diverse neighborhoods), low-income Blacks and Latinos are more likely to live in impoverished neighborhoods, with substantially fewer social, health-related, and educational resources and opportunities. The importance of intergroup racism notwithstanding, intragroup racism in the context of residential segregation may be particularly detrimental for the development of close social support networks and community-based resources and opportunities.

In summary, racism can be expressed through cultural communication, institutional polices, and/or interpersonal behavior. The effect, if not always the conscious intent of the perpetrator of racism, is to transmit the message that members of the targeted group can and should be excluded and/or rejected and do not deserve the same social or economic opportunities, or the same protections against dangerous or unfair treatment, as others. All forms of racism can have individual-level effects, influencing the way others think and feel about and behave toward members of the targeted group, and the way the targets think and feel about themselves and others, even when the race-related bias is not conscious or explicit.

Each episode of ethnicity-related maltreatment presents multiple challenges over the short and long term. Targets must address the interpersonal exchange through conflict management, negotiation for a blocked opportunity, or social avoidance. In addition, the target must contend with emotional consequences, including painful feelings of anger, nervousness, sadness, and hopelessness, and the physiological correlates of these emotional experiences. Once exposed to ethnicity-related maltreatment, either directly or vicariously, targets must consider the possibility that they will face ethnicity-related maltreatment again in the future and must prepare for that possibility.

PROCESSES OF TRANSITION FROM ACUTE EPISODES OF ETHNICITY-RELATED MALTREATMENT TO CHRONIC STRESS

Examining racism from the target's perspective makes it clear that ethnicity-based maltreatment is potentially a significant public health problem. In this view, an episode of ethnicity-based maltreatment serves as a precipitating event, initiating a series of acute and more enduring changes in cognition, affect, behavior, and physiological activity within the individual. In turn, these changes increase the risk for future stress exposure, intensify the physiological response to these stressors, impair the ability to recover from stressor exposure, and ultimately contribute to long-term pathophysiological changes. The immediate and subsequent effects of exposure are modified—often intensified—by the presence of other environmental stressors (e.g., poverty, crime) and the inadequacy of psychosocial resources (e.g., social support, educational opportunities), conditions that themselves may also be direct or indirect consequences of racism. Potential deleterious effects may be avoided or reduced by coping behaviors, but the relative lack of clearly effective coping strategies limits the available choices.

In this section we describe and review literature addressing potential processes through which acute exposure to ethnicity-related maltreatment can result in a sustained stress response and negative health outcomes. The major components of these processes are depicted in Figure 13.1. Each component is addressed separately, but it is important to note that they are likely to interact with each other, often in complex ways involving feedforward and feedback pathways.

MODEL OVERVIEW

Acute episodes of ethnicity-related maltreatment, experienced either directly or vicariously, may occur sufficiently frequently to serve as a persistent source of stress (Brondolo, Kelly et al., 2005; Klonoff & Landrine, 1999; Peters, 2004). But the frequent occurrence of these exposures is only one factor that contributes to their long-lasting effect. Because they can affect the target person's ability to acquire self-knowledge, situations involving racism have long-term implications for the development of those cognitive and behavioral activities that are aimed at optimizing relationships between the self and the social environment, and in turn influence the development of self-concept, self-regulation, and social identity (Inzlicht, McKay, & Aronson, 2006; Oyserman, Fryberg, & Yoder, 2007; Oyserman et al., 2003). These effects are partly a function of blocked opportunities to participate in activities that allow the target to develop and to learn about his or her own competencies (Cutrona, Wallace, & Wesner, 2006; Williams & Mohammed, 2009). These opportunities are thwarted both because racism restricts access to many vocational, educational, and recreational experiences, and because ethnicity-related maltreatment evokes self-protective mechanisms that can inhibit the target's willingness to participate (Burkley & Blanton, 2008; Sinclair et al., 2005; Steele, 1997). The target's ability to benefit from available opportunities also may be restricted because the target may be concerned that the performance feedback he or she receives will be influenced by racial bias. Self-knowledge may also be restricted because of the limitations in self-awareness

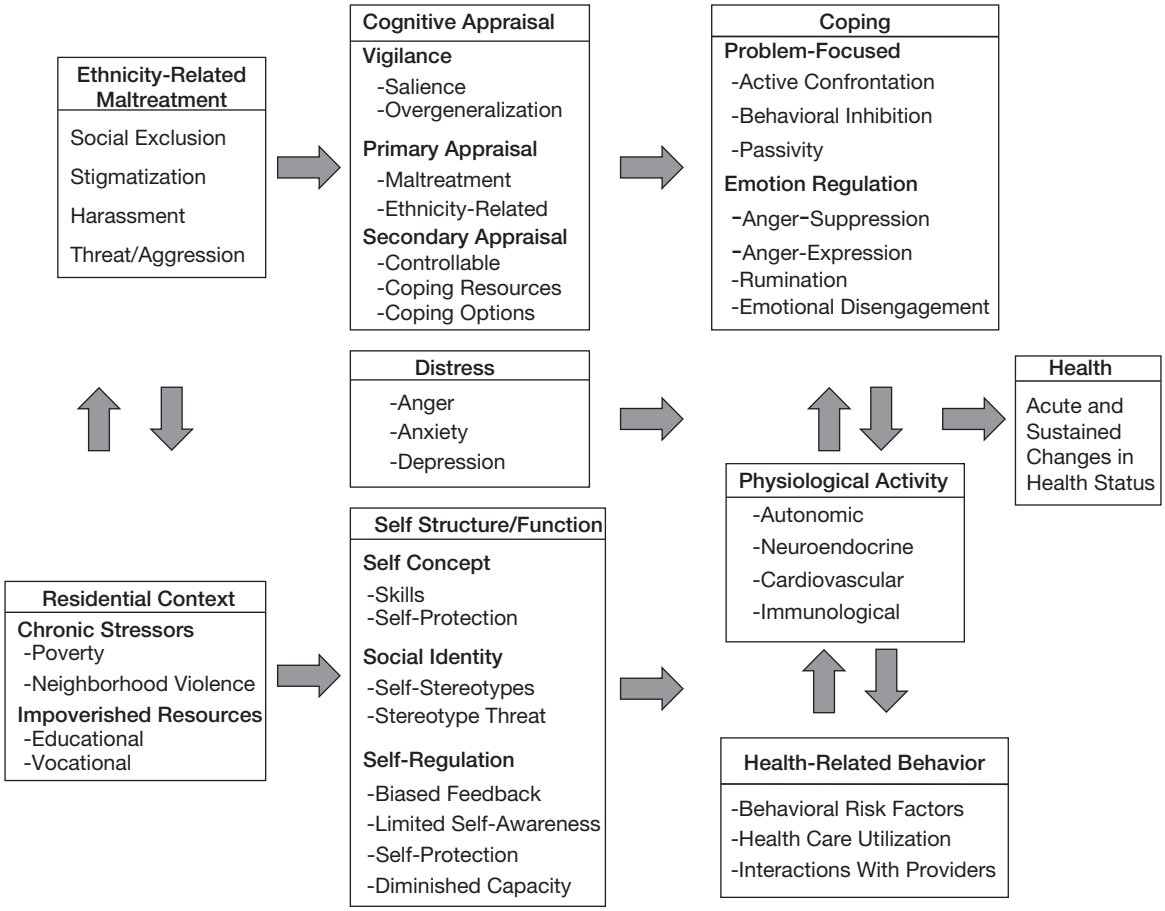

Figure 13.1 ■ Potential pathways leading from acute ethnicity-related maltreatment to health status.

that can develop in response to social exclusion (Hoyt, Aguilar, Kaiser, Blascovich, & Lee, 2007; Inzlicht et al., 2006).

Prior, repeated exposures to racism also affect cognitive appraisal processes through which new episodes of maltreatment are construed and evaluated. This increases the likelihood that they will be perceived as ethnicity-related and as threatening (Clark, Anderson, Clark, & Williams, 1999a; Outlaw, 1993). As a result, neutral interpersonal exchanges may be perceived as threatening instances of ethnic discrimination (Broudy et al., 2007; Brondolo, Brady et al., 2008). Even a single racist episode can promote vigilance and the use of cognitive-interpretative resources directed at detecting further episodes. Consequently, a broader range of experiences may be capable of serving as potential stressors, and routine, day-to-day experiences may elicit increasing distress, generating more frequent and/or more intense negative moods (Brondolo, Thompson et al., 2005).

Efforts at emotion regulation may be unsuccessful, in part, because there are so few effective strategies available for managing race-related maltreatment (Brondolo et al., 2009). Resolution of episodes of ethnicity-related maltreatment can be difficult, leading to impulsive anger expression or suppression, making rumination more likely, and rendering anticipation of new events more problematic. Consequently, targeted individuals are more likely to feel helpless and to perceive the situation as hopeless, prolonging negative mood states, and promoting social disengagement (Nyborg & Curry, 2003). In and of themselves, these disturbing negative mood states can further exacerbate difficulties in self-awareness and self-regulation (Compton et al., 2008).

Both acute appraisals of race-related threat and more sustained changes in mood may account for the effects of racism on physiological functioning. Acute episodes of ethnicity-related maltreatment are associated with increases in the reactivity of the autonomic nervous system (ANS) and alterations in neuroendocrine function (Brondolo, Rieppi, Kelly, & Gerin, 2003; Clark et al., 1999a; Harrell, Hall, & Taliaferro, 2003). A history of frequent exposure may create more sustained

activation (Brondolo, Libby et al., 2008; Steffen, McNeilly, Anderson, & Sherwood, 2003). The psychosocial sequelae of racism, including sustained experiences of perceived stress, depression, and other negative mood states, may contribute to changes in the brain and chronic alteration of peripheral physiological processes (Belmaker & Agam, 2008).

These different paths are likely to interact with each other and to sustain the effects of any single exposure. Their effect is augmented by the types of environmental stressors that often co-occur with high levels of racism, including poverty, neighborhood crime, and unstable family environments (Gallo & Matthews, 2003). The total, cumulative effects of these different pathways are likely to contribute to racial disparities in health through a number of specific disease mechanisms.

Racism-related impairments in self-regulation accompanied by negative mood states are likely to increase the risk for behaviors including smoking and alcohol use (Landrine & Klonoff, 2000) and to impair adherence to positive health practices (Borrell et al., 2007; Gee, Delva, & Takeuchi, 2007). Changes in autonomic and neuroendocrine function may remodel the brain, circulatory system, and immune function, as well as other physiological systems, and thereby contribute to the development of stress-related disorders. Subsequently, illness-related stressors (e.g., pain, disability, financial constraints) may prolong and exacerbate the stress effects of racism. Changes in the appraisals of social interactions as well as sustained negative mood states can reduce the likelihood and impair the effectiveness of health care utilization. Most importantly, these changes can drain available coping resources, making recovery from stress increasingly difficult and taxing (Gallo & Matthews, 2003). In the next sections we describe our own and other investigators' research to provide support for components of this model.

REPETITIVE EXPOSURE

For some groups, common forms of direct or vicarious ethnic discrimination, including ethnicity-related social rejection or exclusion, occur sufficiently frequently to be considered a persistent source of stress (Brondolo, Kelly et al., 2005; Peters, 2004; Contrada et al., 2001; Feagin, 1991; Klonoff & Landrine, 1999; Swim, Aikin, Hall, & Hunter, 1995). Research has indicated that members of many minority groups in the United States face continuing prejudice and discrimination in their daily lives (Al-Issa & Tousignant, 1997; Essed, 1990; Feagin & Sikes, 1994; Landrine & Klonoff, 1996). For instance, across four studies of convenience samples of Blacks with varying demographic characteristics, 80–100% of participants reported some experience of racism in their lifetimes (Klonoff & Landrine, 1999; Krieger & Sidney, 1996; Landrine & Klonoff, 1996; Peters, 2004). One study that used random-digit dial telephone surveying to contact 495 community-dwelling Black adults (≥18 years old) found that 60% reported at least one experience of racial discrimination within the past 3 years (Broman, Mavaddat, & Hsu, 2000). There are fewer studies of the epidemiology of exposure to ethnic discrimination for Asians and other groups, but recent evidence from samples we have studied suggests that more than 96% of Asian Americans, including those of Chinese, Indian, Pakistani, Filipino, Korean, and Bangladeshi descent, have also experienced discrimination over the course of their lifetimes (Atencio, Ullah, Kwok, & Brondolo, 2006).

Exposure to racism is likely to be recent or ongoing at any one point in time. A study of 153 Black adults approached on a university campus found that nearly all respondents—98%—reported at least one racist event within the past year (Landrine & Klonoff, 1996). Another study (Brondolo, Kelly et al., 2005) investigated episodes of racism during the past week among 449 Black and Latino adults. In this convenience sample, 74% of the participants reported at least one racial incident in the past week, and 55% reported three or more incidents. Thus, racial and ethnic minority individuals are not only likely to experience racism in their lifetimes, but may also have repeated exposure on a monthly or even weekly basis.

We have found that social exclusion is the most common type of ethnicity-related maltreatment that is reported (Brondolo, Kelly et al., 2005). Specifically, individuals were more likely to report having been socially excluded because of their race or ethnicity than they were to report being discriminated against at work, stigmatized, or threatened. We have found these effects in every ethnic and group we have studied, including individuals identifying as South Asian Indian, Chinese, Black, and Latino(a).

The frequency with which targeted individuals report episodes of race-based maltreatment may seem surprising. However, when examined from the target's perspective, the degree to which race-based social exclusion can pervade ordinary interactions becomes clearer. Specifically, the notion of relative valuation can clarify the ways in which perceptions of race-based exclusion and maltreatment can be elicited by a broad range of social interactions (Leary, 2005). Leary suggests that perceptions of social exclusion should be construed as being continuous rather than categorical in nature. Individuals experience social exclusion not only when they are rejected outright, but also when they perceive their value in another person's eyes to be less than desired, that is, when their "relative valuation" is low compared to their needs. Thus, an individual may feel excluded or rejected when he or she detects cues that suggest that a new friend is less enthusiastic about the relationship than the individual wishes.

Minority group members may perceive their relative valuation to be lower than desired when they experience themselves as less included than majority individuals. Perceived devaluation may occur even in the context of

actual inclusion (Leary, 2005). For example, a targeted minority individual may be accepted into a group or role (e.g., hired for a job), but may perceive subtle social cues (e.g., infrequent eye contact or unwelcoming vocal tone) that convey a level of respect or belonging that is less than complete or less than equitable in comparison to the way majority coworkers are perceived to be treated.

The gap between majority and minority individuals in the perception of ethnicity-based maltreatment is widened by differences in the focus of attention. In the example of perceived discrimination in the workplace, the actor (i.e., the majority group coworker) is attending to the fact that the minority target *has been included* (i.e., hired), and therefore concludes that no ethnicity-based maltreatment has occurred. In contrast, the target is attending to the *degree* of inclusion and to the gap between the level of inclusion experienced and the degree of inclusion desired or offered to nonminority members. Therefore, by contrast with the majority group coworker, the targeted individual may conclude that some form of discrimination has occurred.

Neglect can also serve as a form of social exclusion. For example, there is evidence that people are less willing to help members of minority groups, including most notably Black Americans. A recent meta-analysis reported by Saucier (2005) indicates that when White individuals believe that others will take responsibility, they are less likely to provide tangible assistance or other forms of aid to Blacks than Whites. The failure to help can be perceived as a form of racism by those targeted for neglect, even when no direct harassment is in evidence. Henkel, Dovidio, and Gaertner (2006) discuss one of the more widely known examples of this phenomenon—the experience of African American residents of New Orleans after Hurricane Katrina. Regardless of the conscious intent of the actors and despite denials from those responsible for providing assistance to the residents of New Orleans, many individuals viewed the failure to rapidly address the needs of the victims as evidence of racism, believing that greater help would have been offered had the residents been White (Henkel et al., 2006).

Disparities in social inclusion are more likely to be viewed in terms of racial bias if the targeted individual suspects that the rejection can be attributed, even in part, to prejudice concerning phenotypic or cultural characteristics. Judgments about the degree of prejudice in others are made quickly and reasonably accurately by targeted individuals. Studies have shown that on the basis of even extremely brief observations of nonverbal behavior, targeted individuals make accurate judgments about the degree to which others have prejudiced attitudes (Richeson & Shelton, 2005).

Since social distancing or rejection can encompass a range of experiences, from partial inclusion to outright rejection, a broader range of interpersonal interchanges may become potential racial stressors (Broudy et al., 2007; Richeson & Shelton, 2005). Consequently, even when the maltreatment involves neglect versus outright harassment, routine episodes of even low-level or vicariously experienced ethnicity-based maltreatment (including social exclusion) contribute to the sense that racism is a pervasive and unchangeable force in social life. As we discuss next, the degree of exposure to this potent stressor is likely to produce more pervasive changes in psychological and psychophysiological functioning.

PERCEPTION AND REGULATION OF SELF

Elliott and Eisdorfer (1982) discuss the notion that stressors constitute a challenge to the way individuals think about themselves. A substantial body of research supports this idea, and documents the ways in which racism, as a psychosocial stressor, affects the development of self-related knowledge structures, including self-concept and ethnic/racial identity, and thereby influences self-awareness. These changes can alter both affective and behavioral self-regulation, and are likely to have a long-term effect on health-promoting behavior and health status.

Acquisition of Self-Knowledge and Development of Self-Concept

Over time we develop a self-digest, a body of knowledge about our own abilities, attitudes, and interests (Higgins, 1996). The knowledge included in our self-digest is shaped by our direct experiences and through social learning. As we observe others (both similar to and different from ourselves) and absorb messages from the larger cultural milieu, we acquire a complex picture of our likely strengths and weakness, preferences, and aversions. Our self-concept is refined through self-awareness, guided by our observations of our own behavior and contemplation of our experiences, feelings, and performance.

However, racism, and in particular residential segregation, affects opportunities to engage in the types of activities that offer an opportunity to learn new skills and expand one's repertoire of ideas and competencies. In addition, targeted individuals will restrict their own participation in activities if they believe they cannot perform (i.e., self-stereotype), are afraid they will confirm others' negative stereotypes about their group (i.e., stereotype threat), or view the activities as irrelevant because they have little or no identification with their ethnicity. Moreover, targeted individuals often miss out on the benefits of participating in activities when racial bias affects the performance feedback they receive. Targeted individuals may be less able to use their own observations to develop an assessment of competencies, since racism, like other forms of social ostracism, affects the ability to tolerate self-awareness. Cumulatively these changes in knowledge structures and affective and motivational processes influence the ability to regulate one's own affect and behavior.

Limited Opportunities to Learn About the Self

The Effects of Social/Environmental Context

For targeted individuals, both institutional racism, especially in the form of residential segregation, and interpersonal racism, can affect access to certain educational, recreational, vocational, and interpersonal experiences (Williams, 1999; Williams & Mohammed, in press; Williams, Neighbors, & Jackson, 2003). For example, neighborhoods with fewer recreational resources and impoverished schools provide fewer opportunities to engage in academic, after-school, and community-oriented activities that will provide the experiences that can increase self-knowledge. High levels of community violence and lower levels of supportive social resources will limit the ability to engage in those activities that are available (Cutrona, Wallace, & Wesner, 2006). The possibility of encountering interpersonal racism in a new setting may serve as a barrier that limits the targeted individual's willingness to risk participation in the activities available outside his or her community (Pinel, 1999). However, the benefits of participating in new activities in a situation in which the individual is racially/ethnically isolated may be diminished, since there is some evidence of impaired performance when the individual is the lone member of a stigmatized group (Sekaquaptewa & Thompson, 2002). As a consequence, targeted individuals have fewer opportunities to learn new skills or to incorporate new ideas or approaches to problems. These restrictions in experience limit the target's ability to learn about his or her own capabilities, preferences, and access to resources.

Opportunities Lost

The Costs of Self-Stereotyping and Internalized Racism

Self-stereotyping and internalized racism may lead targeted individuals to restrict their own participation in activities seen as potentially dangerous, irrelevant, or distracting. Self-stereoptyping involves incorporating negative stereotypes into one's own identity. Targets may avoid tasks they believe they cannot perform well because they are a member of a group stigmatized for poor performance in this area (Sinclair et al., 2005). Internalized racism, a related concept, has been defined as "the acceptance, by marginalized racial populations, of the negative societal beliefs and stereotypes about themselves" (Williams & Williams-Morris, 2000, p. 255). For example, individuals may come to believe themselves to be less intelligent, by virtue of their group membership, if they belong to a group stereotyped as of inferior intelligence. These beliefs can restrict a targeted individual's motivation to initiate activities they believe are outside their competence. This reluctance may create a vicious cycle in which existing group stereotypes restrict an individual's willingness to engage in certain activities, further limiting their ability to develop new self-knowledge that may contradict the stereotype.

Stereotype threat, and a related concept, stigma sensitivity, are outgrowths of self-stereotyping, and are experienced when individuals are concerned that their performance in a particular arena will confirm the potentially biased and over-generalized beliefs that others hold about their group (Speight, 2007; Steele, 1997). For example, informing African Americans that they will be given a test that measures intelligence can activate concerns about validating others' stereotypes and causing further harm to other African Americans. A substantial literature suggests that stereotype threat can influence behavior, potentiating both overt and subtle withdrawal from engagement in activities that evoke these concerns (e.g., Burkley & Blanton, 2008; Steele, 1997).

In some cases, embracing the negative characteristic of one's own group can protect against threats to self-esteem when encountering failure (e.g., I can't do X, because my people can't do X, not because I am incompetent as an individual; Berkley & Blanton, 2008). However, over time, individuals may be unwilling to engage in activities that will challenge these stereotypes. They may be concerned that they will expose themselves or their group members to potential harm if their performance, in fact, confirms the stereotype (Cohen & Garcia, 2005; Inzlicht et al., 2006; Major & O'Brien, 2005; Spears, Doosje, & Ellemers, 1997).

Targets may also avoid participation in activities that do not accord with their ethnic/racial identity. Identities are underlying schemas that help individuals make sense of and respond to their experiences in the world and reflect engagement with particular roles (Oyserman, Fryberg, & Yoder, 2007). Quintana (2007) reviews prospective evidence suggesting that experiences of discrimination serve to shift internal schemas about the self, increasing the investment in and attention paid to racial or ethnic aspects of identity. Adhering to those behaviors that are associated with one's own group and rejecting behaviors associated with other groups can be seen as a strategy for promoting in-group identification and esteem (Fordham & Ogbu, 1986; Oyserman, Fryberg et al., 2007).

In some cases this can limit the motivation to participate in activities that do not conform to the individual's ethnic/racial identity. For example, Oyserman (1998) reports that some urban African Americans view efforts to control weight and to exercise as characteristics that are associated with middle class and White individuals. The more participants viewed these behaviors as inconsistent with their racial/ethnic identity, the less likely they were to engage in healthy eating habits.

Targets may also limit participation in goal-oriented activities in an attempt to manage the threats posed by ethnicity-related maltreatment. Oyserman et al. (2003) have demonstrated that acute exposure to ethnicity-related threat influences the target's attentional focus, rendering the individual more likely to focus on preventing harm rather than on promoting their own ability to achieve personal or professional goals. Over time, repeated exposure to ethnicity-related threats can shift attention to race-related issues and the responsibilities

that are associated with being a member of a particular racial group, rather than toward the development of competencies associated with other types of roles (e.g., as a student, professional, citizen, etc.).

Feedback Quality

Even when opportunity is available, racial or ethnic bias can affect the ability of the target to maximize his or her ability to learn from the experience. When there are cultural stereotypes about a particular ability (e.g., academic competence in Latinos), the quality of information a targeted individual receives about his or her own competence is compromised. In situations of overt bias (e.g., when someone indicates that they do not expect the targeted person to do well because they belong to a particular group—"Latinos can't do math"), even if the feedback is appropriately discounted, the target loses the opportunity to gain information necessary to enrich her knowledge about her own competence. In situations of attributional ambiguity, in which the targeted individual does not know if the individual providing performance feedback harbors racial bias toward the target's group, the target may decide that the feedback may not be reliable and should be at least partly discounted (Hoyt, Aguilar, Kaiser, Blascovich, & Lee, 2007).

Consequently, performance feedback may not be perceived to be valuable except in those rare instances in which it is relatively certain to be bias-free. This creates a feedback vacuum in which motivation to succeed may be diminished. Much research in industrial psychology suggests that motivation and performance are optimized when individuals have clear and achievable but ambitious goals, accompanied by high level of accurate performance feedback (Locke & Latham, 2002).

Self-Awareness

The difficulties presented by the lack of accurate feedback can be compounded when race-based ostracism makes individuals less willing to tolerate self-focused attention. Baumeister, DeWall, Ciarocco, & Twenge (2005) have demonstrated that when individuals are exposed to an experimental manipulation designed to make them feel excluded, or even to anticipate being excluded, they are less willing to tolerate self-awareness (i.e., to look in a mirror). Baumeister argues that individuals choose to restrict their attention, directing it away from the self, so that they do not encounter any further potentially painful reminders of their state of exclusion.

A series of studies on group-based ostracism conducted by Inzlicht et al. (2006) suggested that race-based ostracism may trigger the same attentional changes. When individuals experience an episode of race-based ostracism, they may, consciously or unconsciously, turn their attention away from the self. Frequent episodes of exclusion (e.g., being ignored in a restaurant) may lead to a habitual shift in attention away from the self (Inzlicht et al., 2006). As a consequence, targeted individuals may lose opportunities to learn to self-regulate by learning from their own mistakes. Over time individuals may avoid engaging in activities that may expose them to the pain of exclusion or harsh judgment.

In summary, racism can affect the growth of knowledge structures that underlie the development of individual self-concept, shape the development of ethnic or racial group identity, and influence self-regulation. Together, these effects can place considerable psychological demands on the target. The targeted individual must exert substantial effort to develop effective mechanisms for gaining accurate self-knowledge. He or she must exert more than the usual effort to engage in activities and generate extra motivation to create opportunities or to make use of opportunities despite potential psychic costs (James, 1994). Despite the pain associated with race-based ostracism, the targeted individual must learn to tolerate and benefit from self-awareness. Further, the targeted individual must develop strategies for critically evaluating messages about group characteristics, determining which information reflects prejudice and which reflects appropriate feedback. This requires sorting through emotionally laden and often conflicting information to identify group characteristics that support healthy functioning and can be integrated with individual identity (Oyserman, Fryberg et al., 2007). These cognitive and affective demands can add to the overall burden of stress faced by the individual and, if the demands are not met successfully, they can prolong stress exposure.

THREAT APPRAISAL AND COPING PROCESSES

Initial efforts to understand the ways in which racism affects health have examined racism within the context of the stress and coping theories of Lazarus and Folkman (Clark et al., 1999a; Harrell, 2000; Lazarus & Folkman, 1984; Outlaw, 1993). These writers have suggested that, as exposure to prejudice and discrimination can be unpredictable, threatening, and uncontrollable, the targets of racism are likely to perceive these events as stressful. They further suggest that the nature of racism is sufficiently toxic that it is likely to produce enduring changes in appraisals of threat and harm (Clark et al., 1999a; Outlaw, 1993). For some groups (e.g., American Blacks and Native Americans), race-related ostracism has been accompanied by violence and threats of extermination. Therefore, even relatively mild forms of interpersonal racism occurring in the absence of physical abuse may be perceived as threatening and harmful, because they may evoke concerns about mortality (Landau et al., 2004). In the following sections, we describe the ways in which ethnicity-based maltreatment affects primary and secondary appraisal processes, increasing the salience of events, and influencing the degree to which they are perceived as threatening and coping resources are perceived as inadequate. These

effects may generalize to the appraisals of other events, including routine interactions. Over the long term, these changes in appraisal are likely to lead to sustained negative mood, contributing to acute and sustained changes in ANS activity and dysregulation of the hypothalamic–pituitary–adrenal system (HPA).

Salience and Vigilance

Exposure to racial discrimination may affect both attentional and appraisal processes, making race-related events more salient and personally relevant (Mendoza-Denton, Downey, Davis, Purdie, & Pietrzak, 2002; Oyserman, Uskul, Yoder, Nesse, & Williams, 2007). Using various different paradigms, investigators have demonstrated that individual difference characteristics presumed to be a function of exposure to racism, including race-related rejection sensitivity and stigma consciousness, increase the salience of future episodes of ethnicity-related maltreatment and the expectation that one will be mistreated in the future (Mendoza-Denton et al., 2002; Pinel, 1999).

As we discussed in an earlier section, discrimination appears to influence the development of ethnic and racial identity (Quintana, 2007). Although there is a fairly substantial literature suggesting that certain aspects of racial identity, including racial or ethnic pride, are associated with greater well-being (Brondolo, 2009), there is also evidence that racial centrality or those aspects of racial socialization that foster an awareness of discrimination can make individuals more likely to perceive episodes of discrimination (Hall & Carter, 2006; Neblett, Shelton, & Sellers, 2004).

Altered Threat Perception

In addition to making race-related events more salient, past exposure to discrimination may make people more likely to appraise new situations as potentially threatening and harmful (Carter, 2006). We tested this hypothesis in a sample of community residents largely drawn from low-income communities (Brondolo, Thompson et al., 2005). To measure past episodes of perceived racism, we asked individuals to complete the Perceived Ethnic Discrimination Questionnaire-Community Version (PEDQ-CV; Brondolo, Kelly et al., 2005). The PEDQ-CV is a self-report instrument used to assess experiences of interpersonal racism. A 34-item scale assesses exposure over the lifetime, and contains subscales measuring race-related social exclusion, workplace discrimination, stigmatization, and threat and harassment. A 10-item past-week discrimination scale assesses the frequency of exposure over the past week to 10 different common types of race-based maltreatment.

Participants completed a measure of their appraisals of "episodes in which you are treated badly because of your race or ethnicity." This scale included affect items employed by Folkman and Lazarus (1988) to estimate appraisals of threat and harm. Participants who had higher levels of lifetime racism were much more likely to report that they perceived new events as threatening and harmful. These effects were independent of trait hostility and trait negative mood, suggesting that the effect of past exposure on reactions to new exposures and appraisals of the ability to manage these events are not simply a function of personality traits or affective dispositions.

The effects of racism on the appraisal process may generalize, influencing the degree to which routine events, including ongoing social interactions, are experienced as stressful. Other environmental stressors, such as low SES, have been shown to be associated with changes in perceptions of social interactions. For example, low SES is associated with the tendency to perceive events as threatening or dangerous (Chen & Matthews, 2001) or to reduce the positive affect associated with these exchanges (Gallo & Matthews, 2003). Those low in SES or with high levels of exposure to other background stressors may be more likely to perceive ambiguous interactions as harmful and capable of engendering negative feelings (Chen & Matthews, 2001; Gallo & Matthews, 2003; Gump & Matthews, 1999).

Recently, we have demonstrated that racism also influences the perceptions of day-to-day interactions (Broudy et al., 2007). Specifically, we have reported that past exposure influences the view of ongoing social interactions, even those that do not necessarily involve race. In one study we asked a multiethnic community sample of adults to complete diaries every 30 minutes to report on their moods and their day-to-day social interactions. Individuals who had higher levels of exposure to racism over the course of their lifetimes reported feeling more harassed, unfairly treated, or ignored during their routine social interactions. These effects were significant and substantial even after controlling for a set of personality characteristics including defensiveness (social desirability), hostility, cynicism, and anxiety, as well as comprehensive measures of SES. Similar associations of everyday maltreatment and diary ratings of social interactions have been reported by Taylor et al. (2004). Consequently, a broader class of events may now be perceived as stressful and trigger changes in affective and psychophysiological response.

Coping

The effects of appraising racism as a threat are compounded by the relative lack of effective coping options. Racism is a difficult topic to address, and there has been very little systematic research on strategies for coping with racism (Brondolo, Brady, et al., 2009). As Lazarus and Folkman (1984) have argued, the experience of stress is a function in part of appraisals of threat, but also of coping capability and resources. When individuals do not perceive themselves as capable of coping, race-based maltreatment will seem more threatening and will be

more persistently stressful. In the absence of viable problem-focused options, there will be a tendency to rely on emotion-focused coping.

Why is it so hard to cope? To a large degree racism is an uncontrollable stressor. The target generally cannot change the phenotypic characteristics that elicit the discriminatory behavior, nor can he or she prevent others from harboring prejudices (Kawakami, Phills, Steele, & Dovidio, 2007; Smith-McLallen, Johnson, Dovidio, & Pearson, 2006). Often the target cannot prevent discriminatory behavior, especially when it is subtle (Crockett, Grier, & Williams, 2003).

These perceptions of uncontrollability are exacerbated by limited options for actively coping with racism. Individuals are likely to feel restricted by a fear of retaliation, humiliation, and further social exclusion, as well as by concerns about their ability to control their own emotional responses to maltreatment. Until the relatively recent advent of legislation concerning race-based discrimination, there were very few options for recourse when targeted individuals faced racial discrimination at work. In the wider social realm outside the workplace, there are no formal guidelines for the management of discriminatory interactions.

Eradicating racism and developing strategies for managing racism as it occurs will require collaborative efforts on the parts of both majority and minority members. However, it has proved difficult to develop an effective dialogue. Lepore and Revenson (2007) propose that social constraints limit the effectiveness of certain social support interventions, including efforts to discuss serious issues. Talking about race-related maltreatment may entail discussions that are anxiety provoking for both the seekers and givers of support. For members of stigmatized groups, discussions of racism may evoke recollections that feel uncontrollable and are stressful. For members of a majority out-group, stereotype threat may be evoked if individuals become concerned about appearing cruel, uncaring, or insensitive when discussing race-related conflict (Richeson & Shelton, 2007). Anxiety on the part of both the in-group and out-group members may inhibit effective communication about race-related incidents. As Badr and Taylor (2006) indicate, when individuals receive messages that tend to minimize or deny aspects of their experience, attempts to communicate may be ineffective and associated with increased rather than decreased distress.

In other cases, talking about racism can perpetuate or heighten perceptions of threat. As Utsey, Ponterotto, Reynolds, & Cancelli (2000) points out, social comparisons may increase distress when individuals discuss discrimination with other members of their group. The experience of sharing episodes of ethnicity-related maltreatment may arouse greater anger as other individuals recount their own experiences. If the situations appear hopeless or if individuals in the discussion have had negative experiences managing race-related interactions themselves, other negative emotions including fear, frustration, grief, shame, and loss may also be evoked.

Consistent with models of learned helplessness, a restricted ability to affect the outcome of a given situation may lead an individual to begin to make global and stable attributions (e.g., "this is my fate"), and consequently develop a sense of helplessness (Abramson, Seligman, & Teasdale, 1978). Studies support this notion, with research indicating that past experiences of racism are associated with lower levels of perceived mastery and elevated feelings of distress in Black adults (Broman et al., 2000), and with higher levels of hopelessness in Black adolescents (Nyborg & Curry, 2003). Eventually, as we discuss next, racism can become associated with negative mood states including depression. Depression itself reduces cognitive flexibility and energy, potentially limiting coping responses (Alexander, Hillier, Smith, Tivarus, & Beversdorf, 2007; Beversdorf, Hughes, Steinberg, Lewis, & Heilman, 1999).

In summary, racism is associated with changes in appraisal processes, influencing the tendency to view race-related events as personally relevant, and to appraise these events as potentially threatening and harmful. The effects appear to generalize to other experiences, such that individuals with past exposure to racism are more likely to view ongoing routine social interactions as harassing or unfair. Consequently, stress exposure may elicit more intense feelings of distress and a broader range of events may become capable of eliciting stress reactions. This more frequent exposure to stressors or to more intense distress may produce sustained changes in mood. Amelioration of these effects through coping activity is limited by the relative lack of effective coping strategies, and in some cases negative side effects of coping responses can exacerbate stress.

Distress

One of the most consistent findings in the literature on the health effects of racism are reports of the relationship of racism to depressive symptoms and other forms of distress. Racism has been associated with survey measures of depressive symptoms or distress in every ethnic group in which these issues have been studied, including Blacks (Bennett, Merritt, Edwards, & Sollers, 2004; Bowen-Reid & Harrell, 2002; Brondolo, Brady et al., 2008), Latinos (Brondolo, Kelly et al., 2005; Schneider, Hitlan, & Radhakrishnan, 2000), Filipinos (Mossakowski, 2003), Koreans (Lee, 2005; Noh & Kaspar, 2003), and South Asians (Lee, 2003). Racism has been associated with other negative mood states as well, including anger (Landrine & Klonoff, 1996).

Recently, we have reported that racism had significant effects on both trait and daily diary measures of negative mood in a community sample, and that these effects were independent of SES status and many indices of personality likely to affect mood (Brondolo, Brady

et al., 2008). Specifically, individuals with higher levels of exposure to racism reported higher levels of trait negative mood, as well as higher levels of daily sadness, nervousness, and anger in their diaries. The effects of racism on daily diary measures of anger persisted even when controlling for trait negative mood as well as levels of trait hostility and cynicism and individual and neighborhood levels of SES.

The unjust nature of race-based social exclusion or rejection may evoke a broader and more intense range of negative emotions than that elicited during other types of social exclusion. In a recent study, we inquired about responses to episodes of interpersonal maltreatment that varied in the degree to which racial bias was explicit. When the racial motivation was clear (e.g., the individual's race was mentioned) episodes of interpersonal maltreatment were associated with higher levels of negative affect, including sadness, anger, and fear, than when motivation was ambiguous (Brondolo, Brady, Beatty, Thompson, & Kumar, 2006).

The pain of depression can create a vicious cycle, impairing the ability to recover. Depression intensifies the pain associated with social exclusion and other negative events (Bäzner, Brömer, Hammelstein, & Meyer, 2006). This pain in itself may prove to be distracting, requiring individuals to focus attention on internal states instead of on the development of new skills or more effective coping strategies. Depression may also further impair the ability to self-regulate, as negative feedback is more painful or more problematic for depressed individuals than it is for nondepressed individuals (Compton et al., 2008).

Emotion-Focused Coping and Emotion Regulation

Given highly limited coping resources, individuals are likely to face the negative emotions aroused by racism without effective recourse. Consequently, this lack of resources may lead to the use of emotion regulation strategies that themselves prolong the negative consequences of exposure to ethnicity-related maltreatment. Both anger-suppression and rumination are emotion-focused coping strategies that appear to be linked to racism. In a community sample of African American and Latino adults (Brondolo, Thompson, et al., 2005), we have reported that the more individuals had been exposed to racism, the more they were likely to suppress or angrily express their anger when confronted by new experiences. They were more likely to suppress their anger if they had experienced high levels of workplace racism and more likely to express it if they experienced more social exclusion. Both the suppression and expression of anger may limit the potential to develop effective solutions and require effort that may tax coping resources (Baumeister & Alquist, 2009).

Inability to resolve a particular episode of ethnicity-related stress may make it more likely that individuals will ruminate about the experience. As a consequence, distress is sustained as individuals reexpose themselves to recollections of the event or engage in attempts to suppress recollections, both of which may require effort and expend self-regulatory strength (Brosschot, Gerin, & Thayer, 2006; Gerin, Davidson, Christenfeld, Goyal, & Schwartz, 2006).

In a sample consisting of community-dwelling adults and students, we asked participants to tell us about four different episodes of interpersonal maltreatment. The episodes differed according to the degree to which the race-based nature of the maltreatment would be clear to any observer. Higher levels of lifetime exposure made individuals more likely to ruminate about the episodes they reported. More explicit episodes evoked more rumination. The unjust and uncontrollable nature of the stressor appears to influence the tendency to continue to dwell on the event (Brondolo et al., 2006). Although rumination can at times lead to understanding and insight or the identification of new coping strategies, there is substantial evidence that rumination prolongs the stress response (Brosschot et al., 2006; Gerin et al., 2006).

PSYCHOPHYSIOLOGICAL RESPONSE: REACTIVITY, RECOVERY, AND TONIC EFFECTS

Racism may be associated with acute as well as more prolonged alterations in activity of the sympathetic-adrenomedullary and the HPA axes, through both direct and indirect pathways. Acute exposure to racism, like exposure to other stressors, elicits arousal of these neuroendocrine systems. Various laboratory tasks have been used to simulate exposure to race-related stressors (e.g., films depicting racist interactions, vignettes describing the experience of being accused of shoplifting). These tasks have been shown to elicit reactivity in blood pressure (Armstead, Lawler, Gorden, Cross, & Gibbons, 1989; Clark, 2000; Clark & Anderson, 2001; Fang & Myers, 2001; Lepore et al., 2006; Merritt, Bennett, Williams, Edwards, & Sollers, 2006), heart rate (Clark & Anderson, 2001; Sutherland & Harrell, 1986), electrodermal activity (Myers, Stokes, & Speight, 1989), and corrugator muscle tension (Jones, Harrell, Morris-Prather, Thomas, & Omowale, 1996; Sutherland & Harrell, 1986). Several investigators have compared cardiovascular reactivity in response to race- versus nonrace-related stressors, with most (Armstead et al., 1989; Guyll, Matthews, & Bromberger, 2001; Lepore et al., 2006; McNeilly et al., 1996; Myers et al., 1989) but not all (Fang & Myers, 2001; Sutherland & Harrell, 1986) finding greater physiological activation to racist stimuli.

The physiological effect of racism is not restricted to cases of overt racism. Several investigations have found that even covert racism, events in which the target believed that racial bias was a motivating force for maltreatment even though race was not explicitly mentioned, was associated with diastolic blood pressure elevations (Lepore et al., 2006; Merritt et al., 2006). In the study by Merritt and colleagues (2006), those participants who

perceived high levels of racism in a nonracist condition exhibited greater systolic and diastolic blood pressure reactivity than did those who perceived no racism in the nonracist condition or those in a condition in which the stimulus involved exposure to blatant racism.

Consistent with the notion that exposure to racism affects appraisals of new stressors (Gump & Matthews, 1999; Matthews, Gump, & Owens, 2001), both race- and nonrace-related, investigators have examined the relationship of past exposure to racism to the magnitude of reactivity during nonrace-related laboratory stressors (Clark, 2000; Guyll et al., 2001; Richman, Kohn-Wood, & Williams, 2007). The Clark (2000) study found that past exposure to perceived racism was associated with greater diastolic blood pressure reactivity and reduced diastolic blood pressure recovery during a nonracist laboratory social stressor. Guyll, Matthews, and Bromberger (2001) found higher basal heart rate and greater diastolic blood pressure reactivity in participants reporting past exposure to maltreatment attributed to racism, although some have found these effects to be moderated by personality factors (Richman et al., 2007).

Repeated exposure to events that are perceived as racist may result in more stable, long-term increases in cardiovascular activity. Therefore, several researchers have examined the relationship between perceived racism and ambulatory measures of physiological activity. These studies have demonstrated that perceived racism is related to higher levels of ambulatory blood pressure during waking (Hill, Kobayashi, & Hughes, 2007; Steffen et al., 2003) and nighttime hours (Brondolo, Libby et al., 2008) .

Exposure to racism has also been shown to affect HPA activity. For instance, Richman and Jonassaint (2008) exposed university-student participants to a laboratory stressor after a highly publicized, naturally occurring racial stressor affected the campus community. Results indicated heightened cortisol levels and blunted cortisol stress responses to the laboratory stressor.

Racism may affect physiological functioning specifically through its effects on depressed mood. Depression has been associated with a number of physiological alterations (for a review, see Belmaker & Agam, 2008), including altered basal cortisol levels (lower than nondepressed participants in the morning, higher in the afternoon), blunted cortisol reactivity to stress, and impaired cortisol recovery following exposure to a stressor (Burke, Davis, Otte, & Mohr, 2005; Gillespie & Nemeroff, 2005; Plotsky, Owens, & Nemeroff, 1998). Depression has also been associated with greater basal levels of plasma norepinephrine levels (Esler, 1982; Lake et al., 1982), an indication of heightened sympathetic-adrenomedullary activity, and with decreased heart rate variability at baseline (e.g., O'Connor, Allen, & Kaszniak, 2002; Rechlin, Weis, Spitzer, & Kaschka, 1994) and in response to stressor tasks (e.g., Hughes & Stoney, 2000), and greater heart rate reactivity (Kibler & Ma, 2004), which may reflect an imbalance between sympathetic and parasympathetic influences on the heart. Like depression, anger and hostility have also been associated with greater levels of HPA and sympathetic-adrenomedullary activation (Scalco, Scalco, Azul, & Lotufo Neto, 2005; Smith & Ruiz, 2002), as well as with decreased parasympathetic nervous system activity (McEwen, 1998).

Mays et al. (2007) reviewed the literature on race and changes in brain activation, particularly in the amgydala, prefrontal cortex, and anterior cingulate cortex. These areas are implicated in the control of ANS reactivity to stress. This is a growing research area, and one that may permit greater refinement of our understanding of the ways in which racism affects internal psychological structures, and consequently influences the development of sustained changes in brain activity.

Over time, increased neuroendocrine activity and impaired recovery may have deleterious effects on neurobiological, cardiovascular, and immunological systems. The chronic experience of stress is associated with sustained physiological changes that may remodel the brain, heart, vasculature, and other organ systems involved in stress-related disorders, may cause imbalances in the immune system, and may influence the expression of genes related to the development of both acute and chronic diseases, including respiratory infections, hypertension, and diabetes (McEwen, 1998). The evidence that racism is associated with long-term health effects is growing. Reviews by Paradies (2006) and others indicate that racism is related to objective indices of physical health, including ambulatory blood pressure (Brondolo, Libby et al., 2008; Hill et al., 2007; Steffen et al., 2003), low birthweight (Collins et al., 2000; Dole et al., 2003), and other medical conditions.

ANTECEDENTS AND MODERATORS OF THE EFFECTS OF ETHNICITY-RELATED MALTREATMENT ON PSYCHOLOGICAL AND PHYSICAL FUNCTIONING

Recent reviews have highlighted the importance of considering the effects of racism in context (Mays, Cochran, & Barnes, 2007; Williams, 1999). The interpersonal effects of racism do not exist in isolation. Individuals exposed to racism are also likely to encounter other stressors. For example, there is evidence that neighborhoods including large proportions of minority residents are often targets for environmental toxins and crime and are less likely to offer stable employment (Myers, 2009). These neighborhoods often lack the educational, supportive, and recreational resources that areas serving largely white populations enjoy. These additional stressors and the lack of resources may themselves be partly a function of racism. Residential segregation is likely to further exacerbate these effects (Williams & Mohammed, 2009).

These environmental deficits compound the effect of racism on self-regulation, appraisal processes,

depression, and autonomic functioning. For example, schools with inadequate resources will be less able to provide the types of activities which offer an opportunity to master new skills and refine one's self-knowledge. Overwhelmed teachers may be less likely to provide detailed feedback and corrective, supportive instruction. The cognitive skills gained through a rigorous course of study can also help individuals challenge over generalizations about their own competence and about other people's intentions.

Residential segregation can effectively create racially segregated schools, limiting the ability of the students to learn different ideas and skills and to challenge misconceptions, both about themselves and others. Neighborhood characteristics may compound these effects through multiple pathways. Neighborhood disorder and violence predict depression (Cutrona et al., 2006), and may add to the burden already imposed through individual-level racism. Residential racial segregation may highlight notions of in-group and out-group identity, fostering a "theory of group mind" (Abrams, Randsley de Moura, Hutchison, & Viki, 2005), and promoting intolerance toward those who deviate from the group's identified characteristics. As a consequence, those targeted individuals living within segregated communities may be less likely to challenge the nature of characteristics linked to identity and to explore multiple identities or diverse coping approaches.

SUMMARY AND CONCLUSIONS

Racism is a serious and pervasive social problem. In addition to direct environmental limitations on social, educational, and economic access, the psychological and biological effects of racism have the potential to rob individuals of self-determination and physical well-being. Understanding the mechanisms through which racism exerts its effects on individuals can reduce the risks for, and consequences of, exposure.

Racism can affect cognitive and motivational processes that influence the development of self-regulatory capacities that are necessary for achievement and health. Acquisition of an accurate base of knowledge about one's own capabilities and interests is restricted by limited opportunities and potentially biased interpersonal feedback. Targets of racism may further restrict their willingness to take risks and exploit opportunities when their own estimation of their competence is shaped by internalized racism, and when they are concerned that they will confirm racist stereotypes if they perform poorly. The reasonable fear of harm evoked by exposure to racism also influences the target's appraisals of their environment and new social interactions, undermining potential support, and shifting attention away from goal-directed activities.

These effects are compounded by the influence of race-based ostracism on self-awareness, making it difficult for individuals to fully evaluate the consequences of their actions.

However, if we understand these limitations, we can commit resources to increasing opportunities for participation in skill-building activities. We can help individuals consider the degree to which they are internalizing negative stereotypes and reducing their own expectations, a strategy Steele (1997) reported significantly improves performance. We can explicitly encourage individuals to participate in new activities and to explore their own individual ability, independent of racist stereotypes about their limitations. We can deliberately clarify concerns about racial bias during the process of providing feedback. We can generate support strategies that will help targets feel confident that they can focus on personal and professional goals without putting themselves in danger.

The injustice of racial and ethnic bias evokes a broad range of negative emotional reactions. Depression and sustained negative moods may further impair self-regulatory capacity, since depressed individuals respond more poorly to negative feedback. If negative moods are sustained, they can contribute to physiological changes that further undermine quality of life and growth. However, we can recognize that racism is painful and extend support across cultural divides to share the burden. We can intervene to prevent the deleterious consequences of sustained negative moods and negative social interactions on both cognitive and physiological processes. We can also address the cognitive and motivational costs of depression and hopelessness.

Most important, we can recognize that it is necessary to generate new options for coping with racism. Methods are needed to facilitate coping with racism both at the time ethnicity-related maltreatment occurs and as the target considers the possibility of encountering racism over their lifetime. These strategies are required as a means of avoiding the difficulties with anger-coping and rumination that are common responses to exposure to racism.

By considering race-based maltreatment from the target's perspective, we hope the reader will become aware of the ways in which targeted individuals may feel ostracized because of race or ethnicity. Greater clarity about the mechanisms of effect may help provide structure and support for inter- and intragroup conversations about the effects of racism. These conversations have the potential to generate new ideas for coping and new supports for coping efforts and for diminishing exposure to ethnicity-related maltreatment.

Racism is a complex phenomenon. Many different strategies will be needed to reduce exposure and address the consequences, and the most appropriate strategy to use at any time will vary depending on the individual and the circumstances. Developing these strategies is likely to be anxiety-producing and frustrating for all parties. But, ultimately, this joint effort is essential to achieve the goal of reducing racial disparities in health.

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14 Socioeconomic Status and Stress

Tarani Chandola and Michael G. Marmot

Large and persistent socioeconomic differences in health have been observed around the world. In the UK these social inequalities in health have persisted despite the existence of the National Health Service for more than 50 years providing universal access to health care. Early explanations for this health gap suggested these inequalities originated in material circumstances such as poverty and deprivation, as well as behavioral lifestyles such as smoking. However, the original Whitehall study, conducted among British civil servants, made clear that inequalities in health were not limited to the health consequences of poverty or conventional risk factors for ill health.(Marmot, Shipley, & Rose, 1984) Psychosocial factors such as stressors from work and family life were hypothesized to fill in the unexplained part of the social gradient in mortality, morbidity, and well being. This chapter reviews the evidence that such stressors are higher among lower socioeconomic status (SES) groups.

SES AND PERCEIVED STRESS

If stress is meant to account for some of the social gradient in health, people from lower socioeconomic groups should experience and report higher levels of stress. However, this runs counter to the popular perception that high-powered jobs at the top of the socioeconomic hierarchy are more stressful jobs. There is a stereotypical perception of a stressed person as a business executive with chronic work overload, (Furnham, 1997; Pollock, 1988) perhaps partly arising from early notions of a Type A personality type that was typically stressed and prone to coronary heart disease (CHD). This view may be strengthened by media reports of the stress levels experienced by political leaders (http://news.bbc.co.uk/1/hi/uk/4574750.stm), and the notion that such stress contributes to their accelerated ageing. (http://www.timesonline.co.uk/tol/news/uk/article641585.ece) This may lead to a general perception that higher SES jobs are associated with greater levels of stress.

This popular perception is corroborated by a British population survey showing higher levels of perceived work stress reported by those with more educational qualifications and by those with higher salaries. (Smith, Brice, Matthews, & McNamara, 2000) Perceived work stress in this study was measured by a single question on how stressful people found their jobs. People with the least qualifications, the lowest salaries, and in the manual unskilled occupational class reported the least amount of stress. It appears that higher SES correlates with higher levels of perceived stress.

However, perceived stress is just one of the many ways of measuring stress. As it is often measured by a single question, there are doubts about its validity and reliability. A single global question on stress confounds the exposure to the (work) stressor with the respondent's stressful reaction. Furthermore, the meaning of stress elicited by a single question may vary between SES groups, resulting in under-reporting of the stressors experienced by low SES groups. Other studies have examined the association of SES and stress by measuring stressors from validated questionnaires (mainly on work-related stressors) and from biological stress responses (such as elevated levels of diurnal cortisol secretion). These are reviewed below.

SES AND WORK-RELATED STRESSORS

The nature of working conditions has changed considerably in most industrial countries. A substantial part of the economically active population are now more likely than ever to work on temporary contracts, for a fixed term, and in insecure employment. There is some evidence that work environments are becoming more stressful, at least in the UK (Jones, Hodgson, Clegg, & Elliott, 1998). These adverse working conditions tend to be more prevalent in lower socioeconomic occupations and disadvantaged occupational classes—the lower the socioeconomic position, the higher the risk of exposure to adverse and stressful working conditions (Siegrist, 2002).

However, not all dimensions of stressful working conditions are more prevalent in lower SES occupations. Higher job demands, as characterized by the job-strain model, tend to be more prevalent in higher SES occupations (Bosma et al., 1997). In addition, workers in higher SES jobs may be exposed to greater work effort, a key factor in the effort–reward imbalance model

(Siegrist et al., 2004). On the other hand, lower job control (Bosma et al., 1997; Godin & Kittel, 2004) and fewer rewards (Siegrist et al., 2004) tend to characterize lower SES occupations. Furthermore, when the social gradient in the overall measure of stressful working conditions (job-strain and effort–reward imbalance) is analyzed, rather than its specific components, work stress tends to be reported primarily by those in lower SES occupations (Kouvonen et al., 2006; Tsutsumi, Kayaba, Tsutsumi, & Igarashi, 2001). Even when greater effort–reward imbalance is reported by higher SES workers earlier on in their career (Kuper, Singh-Manoux, Siegrist, & Marmot, 2002), lower SES workers tend to report a greater deterioration in their working conditions over their career lifetime (Chandola, Siegrist, & Marmot, 2005).

THE WHITEHALL II STUDY

The Whitehall II study is one of the main studies investigating the association between SES, stress, and cardiovascular disease (Marmot & Brunner, 2005). New results are presented here that explore the association between SES and different dimensions of stressors from work and family life, and the association of SES with longitudinal changes in work stress.

The Whitehall II study of 10,308 male and female civil servants was set up in 1985 to investigate and understand the causes of social inequalities in health. A major aim of the study has been to investigate occupational and other social influences on disease. All participants have undergone medical examinations and completed questionnaires covering a wide range of information including: health status, work stress, social supports, health behaviors, stressful life events, mental health, and more recently, information on job insecurity and retirement. The long-term aim of the study is to identify the specific psychosocial, behavioral, and pathophysiological pathways by which social circumstances affect health and disease. After the first wave (1986–1988), data collection was carried out in 1989–1990 (Wave 2), 1991–1993 (Wave 3) 1995 (Wave 4), 1997–1999 (Wave 5), 2001 (Wave 6) and 2002–2004 (Wave 7). Questions on work-related stressors were asked at nearly all the waves of data collection, and questions on stressors related to other domains of life were asked at some of the waves. A single global question on perceived stress was asked at Wave 3.

Civil service employment grade is the main measure of SES used in the Whitehall II study. The British civil service has a well defined social hierarchy and has traditionally been organized into hierarchical classes and grades. The clerical and support (messengers, guards, and supply carriers) staff are at the bottom of the hierarchy. Above them is the executive class, divided into hierarchical grades with clear lines of authority all the way from Executive Officers (the first management grade) up to the level of Permanent Secretary (Unified Grade 1). The salary levels of these civil service grades differ widely, with little overlap (Marmot & Brunner, 2005).

The measures of stressors in the Whitehall II study come from validated questionnaires, described below. As these stressor scores are measured in different units, they were transformed into z-scores to enable comparisons between the different measures of stressors.

A question on perceived stress was asked of participants in the third wave of Whitehall II study. The question was worded: In general, how much stress or pressure have you experienced in your daily living in the past four weeks? Participants were asked to choose from five ordinal categories ranging from "not at all" to "a great deal." The majority reported "a fair amount" or more stress (54%). Figure 14.1 shows that civil servants at the top of the civil service hierarchy (Unified grades 1–6) had the highest mean perceived stress levels. Furthermore, perceived stress levels declined lower down the civil service hierarchy. Executive Officers had lower than average levels of perceived stress and Clerical/Support workers had the lowest levels of perceived stress. This is a pattern that fits the popular perception that stress levels are higher among those at the top, the high flyers.

However, as we suggested earlier, this single global question on stress may not be a valid measure of stress. In the Whitehall II study, we can compare this association with the association of SES with stressors measured from other domains of life by validated questionnaires. These are shown below.

The most validated measure of work stress comes from the 42-item Job Content Questionnaire (Karasek & Theorell, 1990), from which a measure of job strain can be derived. Two scales are used to define job-strain-decision latitude (or job control) and job demands. Decision latitude is a combination of skill discretion (e.g., learning new things, task variety, job creativity), and decision authority (e.g., freedom to make decisions, how to perform work). Job demands are defined by five items (excessive work,

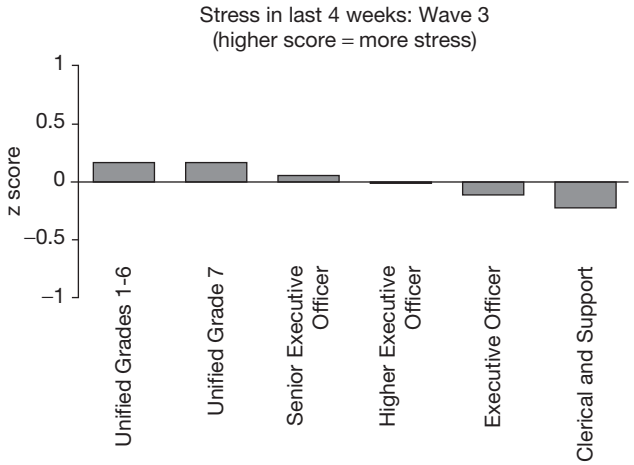

Figure 14.1 ■ Mean perceived stress and SES in the Whitehall II Study (Wave 3).

conflicting demands, insufficient time to work, working fast, and working hard).

Figure 14.2 shows that those at the top of the civil service hierarchy report the highest levels of job demands. Furthermore, those lower down the hierarchy report systematically lower job demands. The social gradient in job demands thus resembles the popular perception that those at the top of the SES ladder have the most stressful jobs. Also, the converse is seen in that those at the bottom of the SES ladder report the least stressful jobs, at least in terms of job demands.

However, job demands are just one dimension of work stress defined by the job-strain model. Decision latitude (or job control) is another dimension and Figure 14.3 shows that its relationship with the social gradient in working conditions is in the opposite direction to that of job demands. Those at the top report the highest levels of job control, while those at the bottom of the hierarchy report the lowest levels of job control. As lack of control is generally regarded as a stressor, the more stressful jobs (in terms of not being in control of your work environment) are found lower down the occupational hierarchy.

Job strain is the combination of having high job demands and low job control. There are a number of ways of deriving a measure of job strain from the job demands and job control scales. In order to facilitate the comparisons between the figures presented in this chapter, we chose to derive a continuous measure of job strain. Job strain was thus measured by taking the ratio of (standardized) job demands to (standardized) job control. A larger ratio will indicate greater job strain. In Figure 14.4, there is not much of a social gradient in job strain. The clerical and support workers report the highest levels of job strain. However, the lowest level of job strain is not reported by those at the top, but rather by those in the middle in the occupational hierarchy (Senior Executive Level civil servants).

Another conceptualization of job strain is the iso-strain model, which hypothesizes that the combination of socially isolation at work (i.e., without supportive coworkers or supervisors), in addition to job strain, is especially stressful and harmful to health, Figure 14.5 examines the job strain model by tertiles of social support at work. It is clear that there is a social gradient in job strain among those reporting low support at work. Among civil servants who report low support at work (those in the lowest tertile of support at work), those lower down the civil service hierarchy report higher levels of job strain. However, this association between SES and job strain disappears as civil servants report greater support at work. This suggests that greater support at work may help to reduce the social gradient in work stress, at least as defined by the job-strain model.

Work-related stressors are just one of the many potential stressors that people experience in daily life. Other common sources of stressors include family and

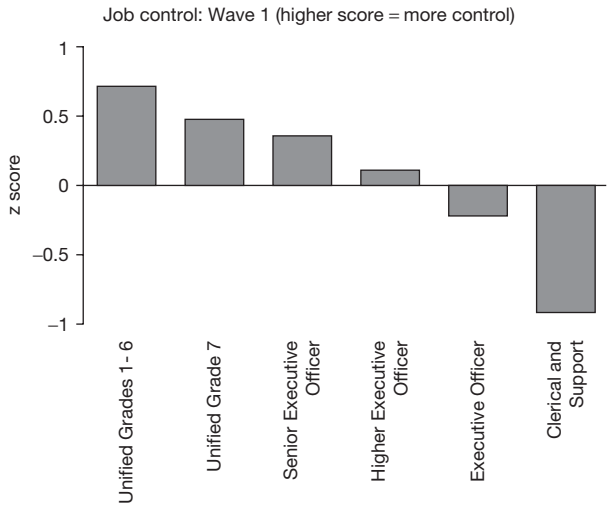

Figure 14.3 ■ Mean job control and SES in the Whitehall II Study (Wave 1).

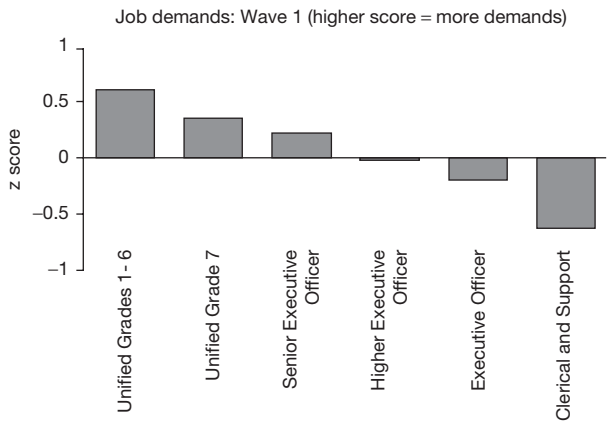

Figure 14.2 ■ Mean job demands and SES in the Whitehall II Study (Wave 1).

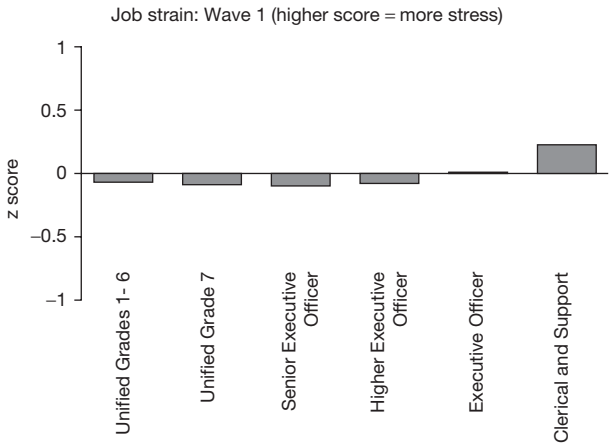

Figure 14.4 ■ Mean job strain and SES in the Whitehall II Study (Wave 1).

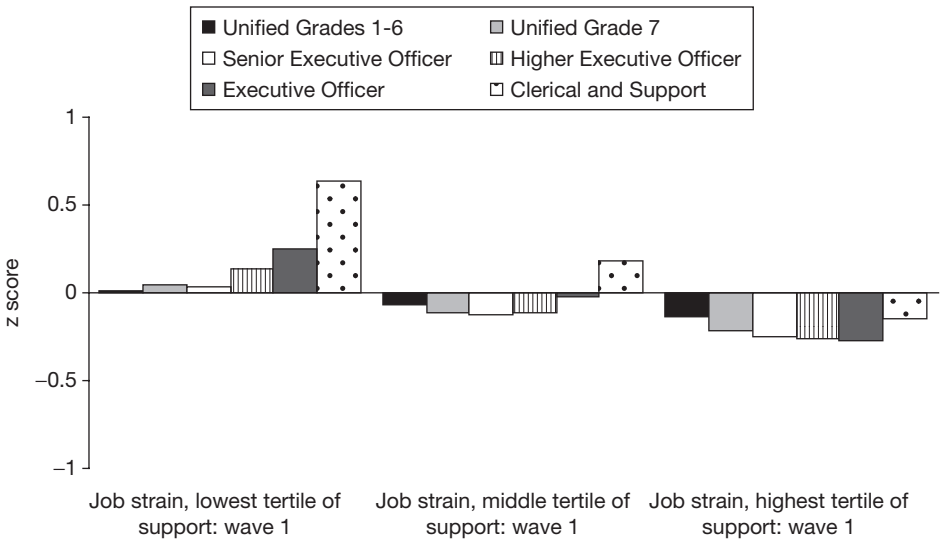

Figure 14.5 ■ Mean job strain and SES by tertiles of social support at work in the Whitehall II Study (Wave 1). (*See color insert.*)

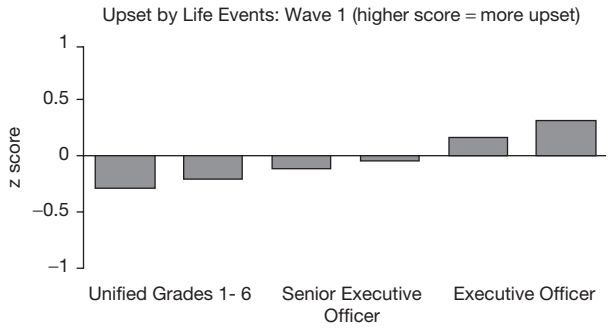

Figure 14.6 ■ Mean life event stress and SES in the Whitehall II Study (Wave 1).

financial stressors. Stressful life events were measured in the Whitehall II study by asking participants if they had experienced a list of eight events over the last 12 months (serious illness/injury, death or serious illness/injury of a close friend/relative, major financial difficulty, divorce/separation, other marital problems, crime, and change of job/residence), and how much they were upset or disturbed by the event (Marmot et al., 1991). Stressful interpersonal relationships were measured from the Close Persons Questionnaire, which includes four items about negative aspects of up to four close relationships (Stansfeld & Marmot, 1992).

Figure 14.6 shows that those at the top of the civil service hierarchy report the least life event stress and that life event stress increases lower down the civil service hierarchy. The clerical and support workers report the greatest life event stress. A similar pattern is observed in Figure 14.7 for stressful interpersonal relationships. This was measured using the Close Persons Questionnaire. Those at the top of the hierarchy report the least stressful relationships while those at the bottom report the most stressful relationships.

The Whitehall II study repeated questions about work stress in subsequent waves and is one of the few studies with several repeated measures of stressors. This allows us to examine changes in work stress levels. It is likely that working conditions and other stressors change as people age, get promoted, and/or change jobs. However, there is comparatively little evidence on how SES is associated with such changes in work stress as longitudinal data on work stress is uncommon. We asked the same Wave 1 job strain questionnaire at Waves 5 (1997–1999) and 7 (2002–2004). As many civil servants had already retired by Wave 7, we used their responses at Wave 5 if they did not have any response to the job-strain questionnaire at Wave 7. A difference score was calculated, subtracting their job demands or job control score at the first wave from their corresponding last wave score. So someone with a positive (or larger) difference score on job demands has greater job demands at the last wave compared to the first wave. Similarly, someone with a negative (or smaller) difference score on job control has lower job control at the last wave compared with the first wave.

Figure 14.8 shows that those at the top of the civil service hierarchy reported the greatest reduction in job demands, while those at the bottom of the civil service hierarchy reported, on average, an increase in their job demands. The social gradient in the difference score in job demands is clear—the lower down the civil service hierarchy, the greater the increase in job demands over time. So although lower SES workers report lower job demands to start with, over time their job demands increase. Conversely, those at the top of the SES hierarchy report higher job demands initially, but experience reduced levels of job demands over time.

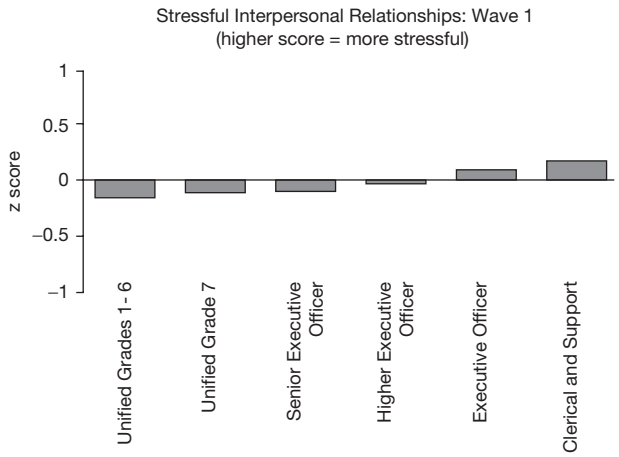

Figure 14.7 ■ Mean stressful interpersonal relationships and SES in the Whitehall II Study (Wave 1).

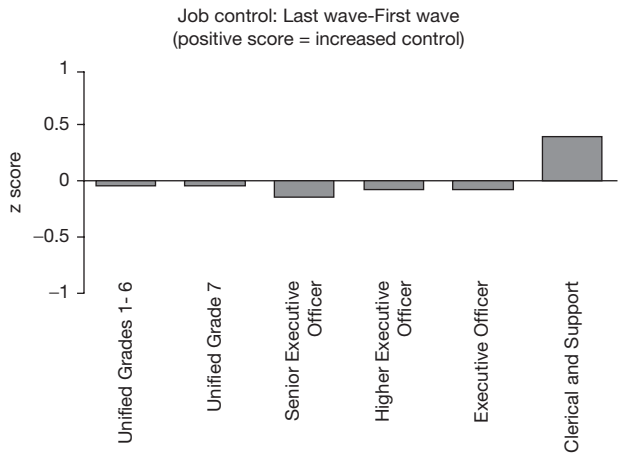

Figure 14.9 ■ Mean change in job control and SES in the Whitehall II Study (Last wave—Wave 1).

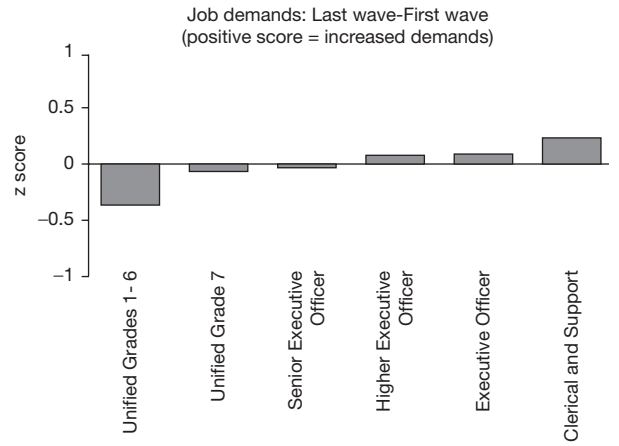

Figure 14.8 ■ Mean change in job demands and SES in the Whitehall II Study (Last wave—Wave 1).

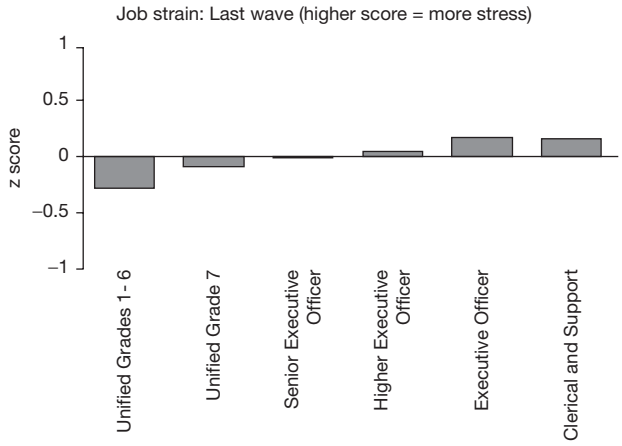

Figure 14.10 ■ Mean job strain and SES in the Whitehall II Study (Last wave).

Figure 14.9 shows that there is no clear social gradient in changes in job control. Clerical and support workers had the greatest increase in job control over time, however, the greatest decrease in job control was reported by those in the middle (Senior Executive Officers) rather than those at the very top.

Figure 14.10 shows a clear social gradient in job strain at the last recorded wave. Those at the top of the civil service hierarchy report the lowest average levels of job strain, while those at the bottom of the hierarchy report the highest levels. Furthermore, when broken down by levels of work social support (Figure 14.11), among those who report low support at work, there is a clear social gradient in job strain at the last recorded wave. However, with increasing levels of work support, this social gradient in job strain at the last wave diminishes. This resembles Figure 14.5 where there is a social gradient in job strain at the first wave among those with low support at work.

SUMMARY OF RESULTS FROM THE WHITEHALL II STUDY

Higher SES Is associated with higher levels of stressors from life events and close personal relationships. However, there appear to be different associations with SES for different dimensions of work stressors. Greater job demands (indicating greater work stress) is associated with higher SES, while lower job control (indicating greater work stress) is associated with lower SES. Moreover, over time, a higher SES person is likely to experience reduced job demands, while a lower SES person is likely to see an increase in their job demands. This results in a strong social gradient in job strain (work stress) at later stages of a person's career, with those in lower SES groups having higher rates of job strain. Furthermore, this social gradient in job strain is particularly marked for workers without supportive colleagues or managers. The overall

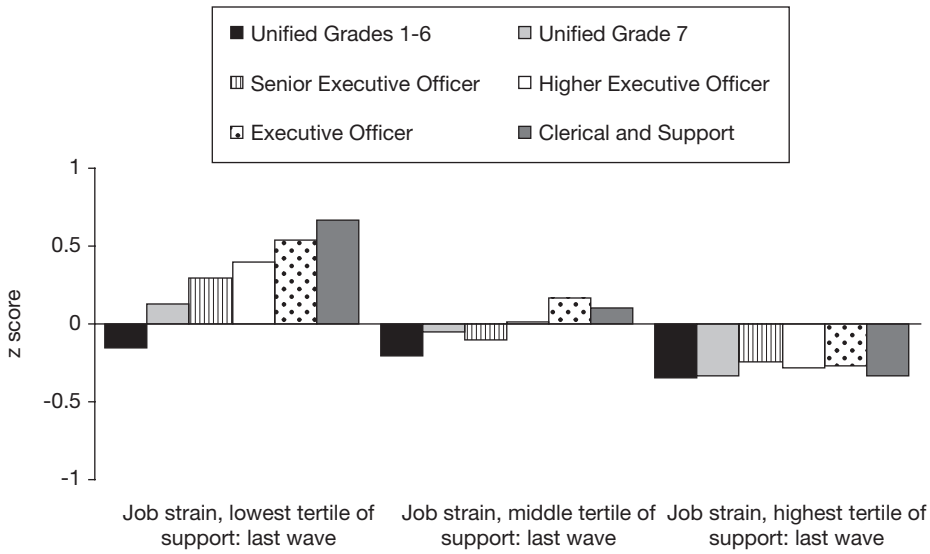

Figure 14.11 ■ Mean job strain and SES by tertiles of social support at work in the Whitehall II Study (Last wave). (*See color insert.*)

picture from the Whitehall II Study is that stressors from work, life events, and close personal relationships are more common in lower SES groups.

SES AND BIOLOGICAL STRESS MARKERS

Two biological systems, the sympathetic adrenomedullary system and the hypothalamic–pituitary–adrenocortical (HPA) axis, are hypothesized to link exposure to stressors to disease. The former results in increased levels of the stress hormones epinephrine and norepinephrine and activity of both systems can result in elevated levels of diurnal cortisol secretion. Evidence on the association of SES with cortisol has been mixed. In the 1958 British birth cohort (Li, Power, Kelly, Kirschbaum, & Hertzman, 2007), lower SES was associated with increased early morning cortisol secretion. In the Whitehall II study, higher SES was associated with lower working day cortisol levels among men, but higher working day levels among women (Steptoe et al., 2003). Some studies report no association between cortisol and SES (Dowd & Goldman, 2006), or associations between higher SES and higher levels of cortisol, epinephrine, and norepinephrine (Brandtstadter, Baltes-Gotz, Kirschbaum, & Hellhammer, 1991; Dowd & Goldman, 2006). Other studies find the reverse—lower SES is associated with higher cortisol levels in the late afternoon or evening (Cohen et al., 2006).

Some of the conflicting results regarding SES differences in stress hormone levels may arise because of differences between studies in protocols for data collection. As stress hormone levels vary widely during the day, there is strong possibility of measurement error. A study by Cohen, Doyle, and Baum (2006) takes account of such measurement error by repeated data collection of urinary catecholamines and salivary cortisol on different days. They found strong evidence that lower SES is associated with higher basal levels of cortisol and epinephrine.

"Allostatic load" refers to the price the body pays for being forced to adapt to adverse psychosocial or physical situations, representing either the presence of too much stress or the inefficient operation of the stress hormone response system (McEwen, 2000). It has been measured using indices of cardiovascular activity and risk, chronic levels of adipose tissue deposition, glucose metabolism, HPA axis functioning, and sympathetic nervous system activity. Allostatic load has been hypothesized to account for socioeconomic differences in health. A systematic review found evidence that allostatic load is elevated in low SES groups compared to high SES groups (Szanton, Gill, & Allen, 2005).

THE CONUNDRUM: OPPOSITE SOCIAL GRADIENTS IN PERCEIVED STRESS AND STRESSORS

There appear to be contradictory social gradients in perceived stress measured by a single global question on stress compared to stressors measured by questionnaires assessing specific aspects of life. Higher SES groups are more likely to report higher levels of perceived stress, while lower SES groups are more likely to report higher levels of stressors from life events, close personal relationships, and work characteristics. One of the clues to understanding this conundrum lies in understanding the meaning of perceived stress measured by a global question on stress.

Lay perceptions of stress are more likely to emphasize stressors from the work environment than other life domains (McCormick, 1997). A typical perception of stress is "Stress is being overworked and not having enough hours in the day" (Kinman & Jones, 2005).

There is some evidence that perceived work stress is most strongly correlated with job demands (Smith et al., 2000), and less correlated with other stressors from the working environment. This suggests that people, on average, tend to think about work stress mainly in terms of job demands such as their hours at work and may discount other sources of stressors when responding to a single question about perceived stress.

This is a similar pattern that is found in the Whitehall II Study. Figure 14.12 examines the mean of (z-transformed) job demands and job control by levels of perceived stress in Wave 3 of the Whitehall II Study. Unfortunately, questions on stressors from close relationships and life events were not asked at this wave. Higher levels of perceived stress are associated with higher job demands. However, higher levels of perceived stress are also associated with higher levels of job control. So lack of control at work is not perceived to be a stressor, even though it results in biological stress reactions.

Thus higher SES groups may report higher levels of perceived stress partly because they evaluate a global measure of stress in terms of their job demands. Lower SES groups may not perceive their lower levels of job control as a source of stress and so evaluate their perception of stress as lower than higher SES groups on the basis of lower job demands, rather than lower job control.

DOES STRESS EXPLAIN THE SOCIAL GRADIENT IN HEALTH?

There is some debate about whether stressful working conditions account for some of the social gradient in health. Some argue that the association between stressors and health is confounded by the effect of material factors (Adamson, Ebrahim, & Hunt, 2006; Macleod et al., 2001). In other words, stress does not lie on the causal pathway from socioeconomic position to poor health: Those with lower income and less advantaged employment conditions would be at higher risk regardless of how much stress they experience or report.

Some studies reduce the possibility of such confounding by using well-validated measures of stressors and taking into account relevant material factors. Most conclude that stressors do account for some of the social gradient in health. Low control (Bosma et al., 1997; Kunz-Ebrecht, Kirschbaum, & Steptoe, 2004; van Lenthe et al., 2004), skill discretion (Andersen et al., 2004), job strain (Chandola, Brunner, & Marmot, 2006), and effort reward imbalance (Chandola et al., 2005) have been found to account for some of the social gradient in different measures of health. In addition, the effect of effort reward imbalance may be greater in lower SES occupations (Siegrist et al., 2004).

On the other hand, not all dimensions of adverse psychosocial working conditions contribute to explaining social inequalities in CHD (Suadicani, Hein, & Gyntelberg, 1993) (although this particular study suffered from a lack of validated measures of psychosocial work stressors). Kuper, Adami, Theorell, and Weiderpass (2006) found that job strain did not explain the social gradient in CHD by years of education among Swedish middle aged women. However, they acknowledge that work stress may be relatively less important in women than in men, because of their additional family and social roles. Moreover, stressors from such family and social roles were not measured in the study and so little could be concluded about the role of stressors from all domains of life in explaining the social gradient in CHD.

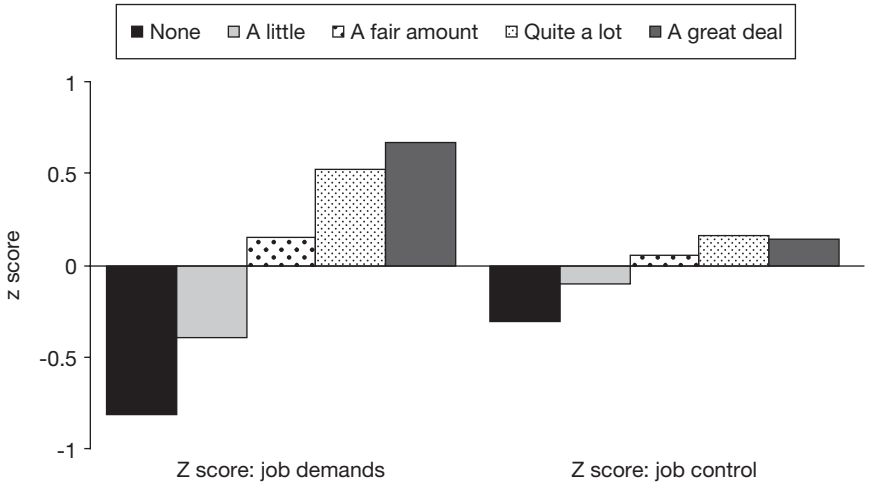

Figure 14.12 ■ Mean job demands and job control by levels of perceived stress in the Whitehall II Study (Wave 3). (*See color insert.*)

CONCLUSION

Lower SES is associated with greater reports of stressors from life events, close personal relationships, and work characteristics. Although higher SES groups perceive their stress levels to be higher than lower SES groups, they may be evaluating their stress on just one dimension of work-related stress, namely, job demands. When other work-related stressors are taken into account, such as job control and support at work, it is clear that lower SES groups have greater exposure to work-related stressors. However, there still remains some debate about the role of stress in explaining SES differences in health.

The evidence also suggests that lower SES groups manifest greater biological stress reactions in terms of release of stress hormones and allostatic load. These results challenge the popular notion that stress is the confined to those at the top of the social, political, or economic hierarchy. Rather, exposure to stressors from different aspects of life increases as one goes down the social hierarchy. Given its strong correlation with socioeconomic status, stress may play an important role in explaining the social gradient in health.

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15 The Role of Appraisal and Emotion in Coping and Adaptation

Craig A. Smith and Leslie D. Kirby

There is a puzzling bifurcation in the scientific literatures concerned with psychological stress, coping, and emotion. Robust, but largely separate, literatures have developed to focus on appraisal, stress, coping, and adaptation, on the one hand (e.g., Compas et al., 2006; Folkman & Lazarus, 1980; Lazarus, 1966; Lefebvre et al., 1999; Moskowitz, Hult, Bussolari, & Acree, 2009; Rasmussen, Wrosch, Scheier, & Carver, 2006; Taylor et al., 1992; Yi, Smith, & Vitaliano, 2005), and on appraisal and emotion, on the other (e.g., Frijda, 1986, 1993; Lazarus, 1968, 1991; Ortony, Clore, & Collins, 1988; Roseman, 2001; Roseman & Smith, 2001; Scherer, 2001; Smith & Ellsworth, 1985; Smith & Lazarus, 1990). Although the topics touched upon in these literatures are highly overlapping, the two literatures appear to have developed largely independently, and cross-references between them are rare.

This is especially puzzling because: (1) both literatures prominently share a common theoretical framework, *appraisal theory*; (2) the same individual, Richard Lazarus, was highly influential in the development of both (e.g., Lazarus, 1966, 1968, 1991; Lazarus & Folkman, 1984; Smith & Lazarus, 1990); and (3) in a number of his writings, Lazarus (1990, 1993a, 1993b, 1999, 2001) strongly urged the development of a unified theoretical perspective, arguing that "emotion" and "stress" were alternative conceptualizations of the same construct, and that replacing the construct of "stress" with that of "emotion" would greatly enrich the study of coping and adaptation.

In our own work, we have contributed to the literatures on both emotion (e.g., Smith & Ellsworth, 1985; Smith & Kirby, 2009b; Smith & Lazarus, 1990, 1993) and psychological stress and coping (e.g., Smith & Wallston, 1992, 1996; Smith, Wallston, & Dwyer, 2003; Walker, Smith, Garber, & Claar, 2005, 2007; Walker, Smith, Garber, & Van Slyke, 1997; Wright & Kirby, 2003). However, we have long subscribed to the type of unified theoretical framework that Lazarus envisioned, and we believe that such a framework provides a much more powerful perspective for studying issues of adaptation than the two seemingly separate literatures that currently exist.

In the present chapter we make the case for adopting a unified theoretical framework concerned with appraisal, emotion, coping, and adaptation. After providing an overview of psychological stress and coping theory, we consider the appraisal theory approach to studying emotion. We discuss some of the basic theoretical assumptions underlying this approach, and then describe a set of specific appraisal models of emotion that we have helped develop and test (e.g., Smith & Kirby, 2009b; Smith & Lazarus, 1990). In doing so, we illustrate how the development of these emotion models has been heavily dependent upon stress and coping theory. We then consider how current stress and coping theory might be informed by the advances we have described within emotion theory, and conclude by briefly considering some of the key benefits we believe a unified theoretical perspective has to offer the study both of emotion and of coping and adaptation.

AN OVERVIEW OF STRESS AND COPING THEORY

STRESS

Undoubtedly, the most influential theoretical perspective concerning psychological stress and coping has been that advanced by Lazarus and colleagues (e.g., Lazarus, 1966; Lazarus & Folkman., 1984; Lazarus & Launier, 1978). This perspective, which explicitly grew out of an effort to understand individual differences in stress and coping (cf. Lazarus, 2001; Lazarus & Folkman, 1984), is inherently *relational*. A primary focus of this perspective is on the psychological stress response, and a fundamental theoretical assumption is that psychological stress is neither a simple reflection of the properties of the individual's situation or circumstances, nor a simple function of the individual's personal characteristics. Instead, psychological stress is a function of the individual's circumstances considered *in relation to* the individual's personal characteristics.

More specifically, Lazarus and Folkman (1984, p. 19) define psychological stress as: "a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being." Central to this definition is the idea that the psychological stress response is based on an evaluation or "appraisal" by the person of what the person's circumstances imply

for his or her well-being. Thus, appraisal is a central construct in this conceptualization of stress, so much so, that the entire theoretical approach has become known as "appraisal theory."

TYPES OF APPRAISAL

As conceptualized by Lazarus and Folkman (1984, p. 31): "Cognitive appraisal can be most readily understood as the process of categorizing an encounter, and its various facets, with respect to its significance for well-being." In delineating this categorization process, Lazarus (1966), Lazarus and Folkman (1984), and Lazarus and Launier (1978) identified two major classes of appraisal: *primary appraisal*, which is an evaluation of what is at stake in the encounter, or as Lazarus and Folkman (1984, p. 31) describe it: "Am I in trouble or being benefitted, now or in the future, and in what way?"; and *secondary appraisal*, which is an evaluation of options and resources for coping with a stressful encounter, or as Lazarus and Folkman (1984, p. 31) describe it: "What if anything can be done about it?"[1]

Lazarus and Folkman (1984) further define three major potential outcomes of primary appraisal, which provide an initial classification of the implications for adaptation of the person's circumstances: They can be appraised as *irrelevant* to his or her personal well-being if the situation does not concern the person's needs or goals; they can be appraised as *benign/positive* if the situation is appraised as preserving or enhancing the person's well-being (or in other words, the person's needs or goals are implicated in the situation in a positive way); or they can be appraised as *stressful* if the person's needs or goals are implicated in the situation in a way that taxes or exceeds the person's resources.

The appraisal of one's circumstances as stressful is what produces a psychological stress response, which in turn mobilizes the person to respond to the stress-eliciting situation through coping. Thus, it is under conditions appraised as stressful that secondary appraisals of coping resources and options become especially relevant. Lazarus and Folkman (1984) further identify three subtypes of stressful appraisals, which provide a more fine-grained categorization of the nature of stress-eliciting conditions: *harm/loss, threat,* and *challenge*. Appraisals of harm/loss reflect situations in which the person has already sustained some sort of damage, be it through injury, illness, loss of self-esteem, or some other setback to one's goals and pursuits. Both threat and challenge are more future-oriented. However, in threat, the focus is on the potential in the situation for future harm or loss, whereas in challenge, the focus is on the potential for gain or growth in the situation.

Several things should be noted about this conceptualization. First, as Lazarus and Folkman (1984) have argued, the labeling of the two major subtypes of appraisal as "primary" and "secondary" has proven troublesome because these terms are often mistakenly interpreted as implying either that these appraisals occur in a fixed sequence, with primary appraisals preceding secondary appraisals in time; or that primary appraisal is more important for understanding stress. Neither of these implications was ever intended by these labels (Lazarus & Folkman, 1984). Instead, primary appraisal has been considered "primary" because it is through this type of appraisal that it is determined whether one's circumstances are appraised as stressful, and thus whether secondary appraisals are relevant, as they are only relevant under stressful conditions However, when conditions are appraised as stressful, secondary appraisals are considered to be as important to stress and coping as are primary appraisals.

Second, there are some potentially problematic ambiguities and logical inconsistencies in the above formulation. For one, the meaning of the phrase "taxing or exceeding" one's resources in the definition of psychological stress is somewhat unclear. How much of a demand must be placed on one's resources for them to be considered "taxed?" Our sense from reading the literature is that often this definition is interpreted too conservatively, such that stress is seen as arising only under rather extreme conditions in which the situational demands exceed resources. Similarly, the phrase "endangering his or her well-being" may also be overly restrictive, as this aspect of the definition would seem to preclude stress resulting from challenge appraisals in which the focus is on potential personal growth and gain. Not only is challenge-related stress important in Lazarus and Folkman's (1984) own formulation, but the distinction between harm- and threat-related stress on the one hand, and challenge-related stress on the other, accords with the distinction between distress (negative stress) versus eustress (positive stress) advanced by Selye (1974) in his highly influential physiological conception of stress. Thus, a definition that seems to preclude challenge-related stress is highly troublesome. Finally, there is ambiguity as to whether the three subtypes of stress-producing appraisals—harm/loss, threat, and challenge—are defined purely by primary appraisal, or by different combinations of both primary and secondary appraisals. Lazarus and Folkman (1984) seem to imply that these subtypes of "stress" are defined solely through primary

[1] It should be noted that Lazarus and colleagues (Lazarus & Folkman, 1984; Lazarus & Launier, 1978) often discuss a third appraisal construct, that of *reappraisal*. It is very easy to mistakenly assume that reappraisal represents a third type of appraisal that is qualitatively distinct from either primary or secondary appraisal. It is not. Instead, the reappraisal construct was introduced to emphasize the fact that the psychological stress process unfolds over time (Lazarus & Folkman, 1984; Lazarus & Launier, 1978), and that as it unfolds the person repeatedly appraises his or her circumstances. As the terms of the person's relationship to his or her circumstances change, the appraisals will change, and with them the person's subjective response and coping efforts. However, as the appraisals are repeated over time, their contents are still comprised of primary and secondary appraisals.

appraisal, and they have been clearly interpreted by others as implying this (e.g., Tomaka, Blascovich, Kelsey, & Leitten, 1993). However this assumption causes some logical problems for the model, as will be discussed in the following text. All three of these issues will be addressed in our consideration of appraisal as it has developed in the context of emotion theory, and for now we simply want to highlight their existence.

It should also be noted that relatively little is said in this theoretical formulation about the nature of secondary appraisal, or about the person or situational factors that influence appraisal. Evaluation of one's potential control over the stressful person–environment relationship is mentioned as one important form of secondary appraisal (Lazarus & Folkman, 1984), and Lazarus and Folkman (1984, p. 36) note that challenge as opposed to threat appraisals are especially likely when the person has a sense of personal control over the transaction.[2] In accord with this, ability and self-efficacy beliefs (e.g., Bandura, 1982) are cited as important antecedents of appraisal. Existential beliefs, "such as faith in God, fate, or some natural order in the Universe" (Lazarus & Folkman 1984, p. 77), have also been suggested as relevant to appraisal in that they help people to ascribe meaning to their lives. In addition, motivational commitments, which include the person's goals and values, and represent things that the person holds to be important (Lazarus & Folkman, 1984), have been identified as important antecedents of primary appraisals, as they help determine what is at stake in any given encounter. On the situational side, several formal properties of events, including their novelty, predictability, uncertainty, imminence, duration, and ambiguity, have been identified as likely relevant to appraisal (Lazarus & Folkman, 1984). However, the specific ways in which these situation factors contribute to particular appraisals have not been well characterized.

COPING

As implied by the phrase "stress and coping theory," in addition to stress and appraisal, *coping* is the third major construct in this theoretical approach. It is also the construct within this theoretical formulation that has been subject to the most theoretical development and empirical examination. As defined by Lazarus and Folkman (1984, p. 141), coping consists of "constantly changing cognitive and behavioral efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of the person." One key aspect of this definition that Lazarus and Folkman (1984) highlight is that coping efforts should not be confounded with the outcome or effectiveness of those efforts. This is in contrast to lay usage of the term, in which to say that someone "is coping" often implies that they are doing well in managing a difficult situation. Instead, a key theoretical assumption that Lazarus and Folkman (1984) advance is that no form of coping is inherently beneficial to adaptive outcomes. Instead, they argue that every form of coping can be effective or adaptive under certain circumstances but also can be ineffective or maladaptive under others. For instance, Lazarus (1983), has made a compelling case that denial, considered by many to be an unambiguously maladaptive form of coping, can be highly adaptive under certain circumstances (as one example, when a person is confronted with news that is simply too traumatic to be processed all at once, such as receiving a diagnosis of a terminal illness). In a similar manner, Rasmussen et al. (2006) have argued that persisting in active attempts to achieve a goal, considered by many to be the epitome of adaptive coping, can be highly maladaptive if the goal is, in fact, unobtainable. Rather than including effectiveness as part of the definition of coping, Lazarus and Folkman (1984) argue that coping be defined as the efforts to manage stressful situations, whether or not those efforts are effective, and that part of the research agenda in studying coping is to identify and describe the conditions under which various forms of coping are adaptive versus maladaptive.

In describing coping, Lazarus and Folkman (1984) and Folkman and Lazarus (1980) have differentiated between two basic functions, corresponding to two different types of coping: *Problem-focused coping* refers to "the management or alteration of the person–environment relationship that is the source of stress," whereas *emotion-focused coping* refers to "the regulation of stressful emotions" that arise in response to the problem (Folkman & Lazarus, 1980, p. 223).

As originally conceptualized, problem-focused coping was described as being broader than problem-solving attempts that involve acting on the situation to alter it to reduce its problematic nature. Although subsuming such problem-solving strategies, problem-focused coping was also proposed to include more intrapersonal strategies that would reduce the problem through motivational and cognitive changes, such as changing one's level of aspiration, developing new standards of behavior, reducing one's degree of investment in the situation, and the like (Lazarus & Folkman, 1984). Emotion-focused coping was described as consisting primarily of a number of cognitive processes directed at reducing emotional distress, including avoidance, minimization, reappraisal of the situation in a more positive manner without really changing it, and the like. However, it was also proposed that sometimes individuals might deliberately engage in strategies directed at *increasing* distress, such as self-blame or magnification of the problem. In making this proposal, it was noted that some individuals might seek to heighten their

[2] It should be noted that this assertion, that control, as a component of secondary appraisal, helps differentiate between threat and challenge appraisals, adds to the unclarity, discussed above, as to whether such challenge appraisals are conceptualized as primary appraisals or a combination of both primary and secondary appraisals.

distress to facilitate a subsequent sense of relief, whereas others might try to increase their distress to help motivate them to contend with the problem (i.e., to motivate problem-focused coping; Lazarus & Folkman, 1984).

This conceptualization of coping has been supplemented by alternative conceptualizations, including *active* versus *passive coping* (Brown & Nicassio, 1987), and *cognitive* versus *behavioral coping* (Jensen, Turner, Romano, & Strom, 1995), among others. One especially important alternative has been proposed by Compas and colleagues (e.g., Compas, Connor-Smith, Saltzman, Thomsen, & Wadsworth, 2001; Compas et al., 2006; Connor-Smith, Compas, Wadsworth, Thomsen, & Saltzman, 2000). In conceptualizing coping, they build on a distinction between *primary* and *secondary control* advanced by Rothbaum, Weisz, and Snyder (1982). As suggested by the main title of their seminal article, "Changing the world and changing the self," Rothbaum et al. (1982) differentiate between two different ways of exerting control over one's circumstances: Primary control represents efforts to act on the situation to bring it more in line with one's wishes or desires, whereas secondary control represents efforts to alter oneself to be more in line with the demands of the situation. Compas and colleagues (e.g., Compas et al., 2001; Connor-Smith et al., 2000) use this distinction to define what they describe as two distinct modes of *engagement coping*, representing active attempts to manage the stressful situation: *Primary-control engagement coping* represents efforts to change the situation, and includes such strategies as problem solving, and, interestingly, efforts at emotion regulation; *Secondary-control engagement coping* represents efforts to change aspects of oneself to accommodate to the situation, and includes such strategies as positive thinking, cognitive restructuring, acceptance, and distraction (Compas et al., 2006). In addition, they propose a third major mode of coping, disengagement coping, which represents efforts to avoid or distance oneself from the source of stress, and includes such strategies as denial, avoidance, and wishful thinking (Compas et al., 2006). Walker et al. (1997) have proposed a very similar tripartite conceptualization of coping, differentiating among *active, passive,* and *accommodative coping*, in which active and accommodative coping correspond closely to primary- and secondary-control engagement coping, respectively, and passive coping corresponds closely to disengagement coping.

A comparison of these major conceptualizations of coping indicates considerable overlap among the constructs of problem-focused coping, active coping, and primary-control engagement coping. At the core of each of these constructs are efforts toward problem solving, in which the person attempts to act on his or her circumstances to bring them more in line with his or her goals or desires. There is far less agreement on the nature of the second major dimension of coping, with emotion-focused coping placing an emphasis on emotion-regulation efforts, and both accommodative coping and secondary-control engagement coping emphasizing a second mode of regulating the stressful transaction itself—changing oneself to better fit the demands of the situation. Interestingly, in both conceptualizations, what one approach considers to be the second major type of coping, the other approach considers to be a facet of its first type of coping. Thus, in the conceptualization of Lazarus and Folkman (1984), accommodative strategies such as changing one's level of aspiration, or of adopting new standards of behavior, are considered to be facets of problem-focused coping, whereas in the conceptualization of Compas et al. (2001, 2006) efforts at emotion regulation are considered to be forms of primary-control engagement coping. A further difference between the two conceptualizations is that Compas et al. (2001, 2006) propose a third major type of coping, disengagement coping, which includes strategies such as denial and wishful thinking that Lazarus and Folkman (1984) would subsume under emotion-focused coping. Our consideration of the advantages of a unified conceptualization of emotion, stress, and coping (see below) will offer a principled means for selecting among these alternative models of coping.

The models described above attempt to differentiate coping in terms of a few broad, overarching categories that are taken to represent major coping functions (Compas et al., 2001; Lazarus & Folkman, 1984). However, as suggested by the foregoing discussion, each major mode of coping subsumes a number of distinct strategies a person might enact in attempting to manage a stressful situation, including planning and problem solving, use of humor, positive reinterpretation, acceptance, distraction, denial, seeking social support, quitting, and so forth. Although early research tended to examine coping in terms of the broad overarching categories (e.g., Brown, Nicassio, & Wallston, 1989; Folkman & Lazarus, 1980), there has been increasing recognition that not all the specific strategies subsumed by the same higher-order coping construct are interchangeable (e.g., Jensen, Turner, & Romano, 1992), and there has been a movement toward studying the implications for adaptation of more specific coping strategies underlying the broad strategies. Accordingly, a number of coping inventories have been developed that allow the study of these more specific coping strategies in the general context of coping with life stress (e.g., The Ways of Coping Scale [Folkman & Lazarus, 1980; Folkman, Lazarus, Dunkel-Schetter, Delongis, & Gruen, 1986], The COPE [Carver, Scheier, & Weintraub, 1989], The Responses to Stress Questionnaire [Connor-Smith et al., 2001]), and in the more specific context of coping with pain (e.g., The Chronic Pain Coping Inventory [Jensen et al., 1995], The Pain Response Inventory [Walker et al., 1997], The Vanderbilt Multidimensional Pain Coping Inventory [Smith, Wallston, Dwyer, & Dowdy, 1997]).

Research using these instruments has begun to reveal much regarding the relation of coping to adaptative outcomes, including both health outcomes and psychological adjustment. Much of this research has

focused on coping and adjustment at the dispositional level, and has revealed reliable links between chronic or habitual styles of reacting to stress in certain ways to long-term indictors of mental and physical well-being. Perhaps the clearest, most consistent finding has been that the chronic/habitual use of strategies corresponding to disengagement or passive coping is reliably associated with negative outcomes. This applies to coping both with psychosocial stressors (e.g., Yi et al., 2005) and health problems including rheumatoid arthritis (e.g., Smith et al., 2003), HIV/AIDS (e.g., Moskowitz et al., 2009; Taylor et al., 1992), and chronic pain (e.g., Compas et al., 2006; Walker et al., 2005).

Identifying strategies that are as consistently related to positive outcomes has been more difficult, and null findings involving both active or primary-control coping and accommodative or secondary-control coping have been more common than ones involving disengagement or avoidant coping (cf. Compas et al., 2001; Smith et al., 2003). Nonetheless, there are clear indications that, at least within certain contexts, both active/primary-control coping (e.g., Moskowitz et al., 2009; Yi et al., 2005) and accommodative/secondary-control coping (Compas et al., 2006; Walker et al., 2005) are associated with positive outcomes including both emotional well-being and physical health outcomes (e.g., Compas et al., 2006; Moskowitz et al., 2009; Walker et al., 2005).

These findings are characterized by a number of limitations, many of which have been discussed extensively elsewhere (Coyne & Gottlieb, 1996; Coyne & Racioppo, 2000). We would like to highlight two. First, the focus on the dispositional level, which has dominated coping research to date, necessarily obscures the potential context-sensitivity of these influences. From relatively early on in the study of coping (e.g., Folkman & Lazarus, 1980; Folkman et al., 1986), there have been clear indications that problem-focused, or primary-control coping strategies are more likely to be enacted in situations in which individuals believe they have some ability to alter the terms of the stressful person–environment relationship, whereas emotion-focused or secondary-control coping strategies are more likely in situations in which individuals do not feel they have this ability. These associations likely reflect context-specificity in coping effectiveness, such that the strategies are more efficacious under the conditions in which they are most likely to be enacted. Moreover, as already noted, there are clear indications that even the strategies that have been demonstrated to be highly deleterious when employed habitually can represent effective coping under certain circumscribed conditions. For instance, Lazarus (1983) has outlined a number of conditions under which denial is likely to be a highly efficacious short-term coping strategy, although these proposals still await empirical verification; and Rasmussen et al. (2006) have proposed and empirically demonstrated that disengagement from one's goals, a form of avoidant coping, can be highly adaptive when those goals prove to be unattainable. Very clearly, it is important to take into account the context in which one is coping when examining the contributions of coping to adaptive outcomes. However, context-specificity is very difficult to examine at the purely dispositional level (but see Moskowitz et al., 2009, for an example of a meta-analysis that does so). Thus, it remains important to increase the degree to which coping is studied in a more situated, context-specific manner in which coping and outcomes associated with individual incidents are examined.

Second, the major focus of most stress and coping research conducted to date has been on the relationships between coping and adaptive outcomes such as physical health and psychological adjustment. In line with their relative theoretical neglect, alluded to above, both appraisal and its dispositional and situational antecedents have not yet been extensively examined in the context of coping. In what has been examined, the findings have been consistent with theory. For instance, both optimism (e.g., Rasmussen et al., 2006; Taylor et al., 1992) and self-efficacy (e.g., Lefebvre et al., 1999) have been implicated as important antecedents of coping that, at the dispositional level, tend to promote various forms of engagement coping, and to inhibit various forms of disengagement coping. This is consistent with theoretical propositions (e.g., Folkman, 1984; Lazarus & Folkman, 1984) hypothesizing that these sorts of dispositional variables should promote appraisals of personal control, which in turn should be associated with higher levels of problem-focused coping and lower levels of emotion-focused coping. However, to our knowledge, the role of control-related appraisals mediating the relationship between these dispositional antecedents and coping behavior has not yet been explicitly examined. In addition, the range of potential dispositional and situational antecedents of appraisal and coping has not been extended much beyond these two constructs (for an exception, see Walker et al., 2005).

Notably, these two limitations to the study of stress and coping from an appraisal perspective are ones that have been firmly addressed in research directed toward developing and testing appraisal theories of emotion (e.g., Roseman, 1984, 1991; Smith & Ellsworth, 1985; Scherer, 1984, 1997; Smith & Lazarus, 1990, 1993). Within the appraisal approach to emotion there has been a concerted effort to describe the appraisals hypothesized to elicit different emotions in considerable detail, and then to examine the relationships between appraisal and emotion in highly situated, context-specific ways. There has been considerably less focus on how the emotions, once elicited, influence behavior, including coping activity, or on the linkages between emotions and adaptive outcomes. Thus, the development of appraisal-related stress and coping theory on the one hand, and appraisal-related emotion theory on the other, have been highly complementary. We turn now to a consideration of the appraisal approach to emotion, with an eye toward highlighting

the relevance of emerging appraisal-based emotion theories to the study of stress and coping.

AN OVERVIEW OF THE APPRAISAL APPROACH TO THE STUDY OF EMOTION

THEORETICAL BACKGROUND

As was the case with the appraisal approach to studying stress and coping, a primary motivation in developing the appraisal approach to emotion was to explain large, readily observable individual differences (Roseman & Smith, 2001; Smith, 1989). Not only do different individuals often respond to similar circumstances with different emotions, but also the same individual will often respond to the same circumstances quite differently over time. That both these types of variability can be readily documented causes grave difficulties for attempts to explain emotion through classic psychological approaches: Situationally oriented stimulus-response theories hold emotions to be systematic responses to particular situational contexts, and thus have difficulty accounting for individual differences in response to the same context; dispositionally oriented trait-based theories attribute emotional reactions to stable traits, and thus have difficulty explaining the cross-time variability that is often observed within persons. In fact, historically, the readily observed variability in emotional reactions across individuals, circumstances, and time has often led scholars to characterize emotion as chaotic, disorganized, and disorganizing (e.g., Angier, 1927; Darrow, 1935), a view that was fairly dominant within academic psychology during the first part of the 20th century (see Roseman & Smith, 2001; Smith, 1989).

Over the last half century or so (e.g., Ekman, 1984; Izard, 1977; Lazarus, 1968; Leeper, 1948; Tomkins, 1963), the dominant view of emotion has changed dramatically, and within academic psychology emotion is now almost universally viewed as a highly organized system that serves important motivational and adaptive functions. With this theoretical shift, efforts to explain the elicitation of emotion, and especially individual differences in this elicitation, became very important, and appraisal theories of emotion (e.g., Roseman, 1984; Scherer, 1984; Smith & Lazarus, 1990) developed to meet this need. In fact, the first appraisal theory of any kind (or, at least the first to go by that name) was proposed by Magda Arnold (1960) to explain the elicitation and differentiation of emotion. Lazarus drew upon the appraisal construct as articulated by Arnold (1960), but rather than applying the construct to emotion theory, he first further developed and modified it in formulating and testing his model of stress and coping (e.g., Lazarus, 1966; Lazarus & Folkman, 1984; Lazarus & Launier, 1978). He subsequently reapplied his version of the appraisal construct to the study of emotion (e.g., Lazarus, 1968, 1991; Lazarus, Averill, & Opton, 1970; Lazarus, Kanner, & Folkman, 1980; Smith & Lazarus, 1990). It should be noted, however, that from the outset it is evident from a careful reading of his writings that Lazarus viewed his work on emotion and on stress and coping to be highly interrelated.

Within emotion theory, the appraisal construct proved to be very useful for explaining the antecedents of emotion, and by the mid 1980s research on appraisal theories of emotion had begun to flourish (e.g., Frijda, Kuipers, & ter Schure, 1989; Roseman, 1984, 1991; Scherer, 1984; Smith & Ellsworth, 1985), with the result that appraisal theory has become the dominant perspective for understanding emotion elicitation and differentiation. Here, we would like to focus on the development and testing of two distinct types of appraisal model, both of which are designed to address a distinct set of theoretical issues: *structural models* of appraisal, which attempt to specify both the contents of appraisal and how these contents contribute to the differentiation of emotional experience (e.g., Roseman, 1984; Scherer, 1984; Smith & Ellsworth, 1985; Smith & Lazarus, 1990); and *relational models* of appraisal, which attempt to specify the personal and situational antecedents of appraisal (e.g., Smith & Kirby, 2009b; Smith & Pope, 1992).

STRUCTURAL MODELS OF APPRAISAL

The first set of issues confronted by emotion-relevant appraisal theories have concerned explication of the appraisal construct. The result has been the development and testing of several structural models that, first, attempt to identify and describe precisely what it is that is evaluated in appraisal, and second, attempt to describe how the evaluations made in appraisal contribute to the differentiation of emotional experience (e.g., Lazarus, 1991; Roseman, 2001; Scherer, 1984, 2001; Smith & Ellsworth, 1985; Smith & Lazarus, 1990). Although each of the individual models has unique properties to distinguish it from the others, in broad strokes the models have developed to become very similar to one another. In particular, they are very similar in terms of what they describe as being evaluated in appraisal, as well as how those evaluations contribute to the differentiation of emotional experience (Ellsworth & Scherer, 2003). Thus in describing the structural models, we focus primarily on the one proposed by Smith and Lazarus (1990), not only because it is the model with which we are most familiar and continue to work with, but also because this model grew, more directly than the others, out of the appraisal construct as developed by Lazarus and colleagues within stress and coping theory.

As such, this model shares with stress and coping theory the assumption that appraisal is inherently relational. Thus appraisals do not simply reflect either the circumstances confronting the individual or his or her characteristics, but rather they represent an evaluation of what those circumstances imply for the individual's personal well-being given his or her unique configuration of

needs, goals, values, abilities, and the like. In addition, the model uses as its starting point the constructs of primary and secondary appraisal as articulated by Lazarus and colleagues (e.g., Lazarus & Folkman, 1984) and described above. Specifically, the model presumes that primary appraisal reflects an evaluation of whether and how one's circumstances are relevant for personal well-being, and that secondary appraisal reflects an evaluation of one's resources and options for coping with those circumstances (Lazarus & Folkman, 1984). However, the model has developed the appraisal construct considerably further than has been done in the context of stress and coping theory, and attempts to describe explicitly both the "questions" or issues that are evaluated in appraisal (referred to in the model as the *components* of appraisal), and how the outcomes of these evaluations, or the potential answers to the appraisal questions, map onto emotional experience. At present, the model highlights six components of appraisal, two of primary appraisal, and four of secondary appraisal.

The two components of primary appraisal are: (1) motivational relevance, an evaluation of how important the situation is to the person; and (2) motivational congruence, an appraisal of the extent to which the situation is consistent or inconsistent with one's current goals (i.e., is desirable or undesirable). The four components of secondary appraisal are: (1) self-accountability, an assessment of the degree to which oneself is responsible for the situation; (2) other-accountability, an assessment of the degree to which someone or something else is responsible; (3) problem-focused coping potential, one's perceived ability to act on the situation to increase or maintain its desirability; and (4) emotion-focused coping potential, one's perceived ability to adjust psychologically to and deal with the situation should it turn out to not be as desired.[3]

Table 15.1 illustrates both how the outcomes of appraisals in terms of these components map onto the experience of different emotions (as proposed by Smith, 1991; Smith & Lazarus, 1990), and how they map onto the major appraisal outcomes (i.e., benefits, harms, threats, and challenges) as described by Lazarus and colleagues within stress and coping theory (e.g., Lazarus & Folkman, 1984). Considered by themselves, the two components of primary appraisal are sufficient to define one's circumstances as "irrelevant" to personal well-being, as "benefit" (or benign/positive), or as "stressful."

One's circumstances are appraised as "irrelevant" to personal well-being if motivational relevance is appraised as low. Very little emotion is hypothesized to be elicited under such circumstances—perhaps some level of contentment, if the circumstances tend toward being desirable, or some level of boredom, if they tend toward being undesirable. Emotional intensity is limited in this manner because when motivational relevance is appraised as low, appraisals of motivational congruence are assumed to be highly constrained, such that appraisals of desirability or undesirability will be very mild. This reflects an observation, first made by Ellsworth and Smith (1988), and recently more thoroughly scrutinized by Smallheer, Kirby, and Smith (2007), that component appraisals are not made in isolation, but rather, they can constrain one another. In the present case, it is proposed that appraisals of low motivational relevance are associated with appraisals of neutral or mild motivational congruence, and appraisals of high motivational relevance, which occur in circumstances that the person perceives to be important, accompany appraisals of either high or low motivational congruence, that is, one's circumstances are perceived to be either highly desirable or highly undesirable. A second constraint reflected in the table is the assumption that appraisals of high motivational congruence (that one's circumstances are highly desirable) implies appraisals of neutral to high coping potential for the components of both problem-focused and emotion-focused coping potential. The assumption here is that low coping potential (i.e., that one either cannot affect or cannot adjust to one's circumstances) is inherently undesirable (cf. Smallheer et al., 2007).

Appraisals of high motivational relevance in combination with high motivational congruence (i.e., as important and desirable) are sufficient to define one's circumstances as benign/positive, or beneficial, whereas combined appraisals of high motivational relevance and low motivational congruence (i.e., as important and undesirable) are sufficient to define one's circumstances as "stressful." However, in neither case are these appraisals, taken by themselves, sufficient to fully determine which specific emotions will be elicited.

Under circumstances appraised as beneficial, the combination of high motivational relevance with high motivational congruence appears to be sufficient to elicit feelings of happiness (Smith, 1991; Smith & Lazarus, 1990). Moreover, it follows from the constraints discussed above (i.e., those associated with appraisals of high motivational congruence), that in these circumstances appraisals of

[3] Although given the label of "emotion-focused coping potential" by Smith and Lazarus (1990) to correspond to the construct of emotion-focused coping as advanced by Lazarus and colleagues (Lazarus & Folkman, 1984), this construct, as defined and operationalized by Smith and Lazarus (1990, 1993), reflecting the individual's ability to adjust to his or her circumstances should they not turn out to be desired, actually corresponds more closely to one's self-evaluated potential to engage in secondary-control engagement/accommodative coping (e.g., Compas et al., 2001; Walker et al., 1997). Consequently, this appraisal construct might be better named "accommodation-focused coping potential." We simply raise this point here, but will return to it when we consider the implications of this structural appraisal model for the conceptualization of both stress and coping toward the end of the chapter.

In addition it should be noted that there is actually a fifth component of secondary appraisal, future expectancy, that is included in the model, which reflects an appraisal of whether and to what degree one's circumstances might improve for any reason. Across a broad array of circumstances, this appraisal tends to be highly correlated with appraisals of both problem- and emotion-focused coping potential (Smallheer et al., 2007). There may well be a range of circumstances (e.g., in contending with a terminal illness), associated with appraisals of low problem- and emotion-focused coping potential, in which appraisals of positive future expectancy might be important in sustaining hope, but an extended treatment of these possibilities is beyond the scope of the present contribution.

Table 15.1 ■ Relating Stress-Related Appraisals to Emotions

		Low Motivational Relevance		**High Motivational Relevance**		
Motivational Congruence		Congruent (Assumed to not be low)	Incongruent	Congruent (Assumed to not be low)	Incongruent (**"Stress"**)	
Problem-focused Coping Potential					High	Low
		"Irrelevant"		**"Benefit"**	**"Opportunity"**	**"Harm"**
		Contentment	Boredom	Happiness/joy	Challenge/ determination	Sadness
Accountability	Self	Undefined	Undefined	Pride	Undefined	Shame/guilt/ embarrassment
	Other			Gratitude		Anger
Emotion-focused Coping Potential	High	Contentment	Boredom	Same emotions as above	Same emotions as above	
	Low	(assumed to not be low)	(assumed to not be low)	(assumed to not be low)	Fear/Anxiety **"Threat"**	

both problem- and emotion-focused coping potential will be neutral to high, and therefore will not contribute appreciably to the differentiation of benefit-related emotions. However, appraisals of self- and other-accountability are hypothesized to further differentiate benefit-related emotional experiences, because they give direction to and a target for one's coping activities by identifying who or what is responsible for the initiating circumstances. Specifically, appraisals of self-accountability are hypothesized to elicit feelings of pride, whereas appraisals of other-accountability are hypothesized to elicit feelings of gratitude.

As indicated in Table 15.1, a broad range of emotions can be elicited when one's circumstances are appraised as "stressful" (i.e., important, but in some way not as desired). However, the primary appraisals of motivational relevance and motivational incongruence are inadequate by themselves to determine which emotion(s) will be experienced. Instead, under conditions appraised as "stressful," secondary appraisals always need to be combined with the primary appraisals to provide emotion-differentiation. It is this observation that provides the impetus for Lazarus' (e.g., 1990, 1993b, 1999) frequent argument that emotion is a richer, more differentiated construct than stress, and should therefore supplant stress in stress and coping theory. As with the benefit-related emotions, appraisals of accountability provide some of this differentiation, with appraisals of other-accountability combining with the stressful primary appraisals to elicit anger, and appraisals of self-accountability combining with them to elicit a range of self-directed negative emotions, including shame, guilt, and embarrassment.[4]

[4]At present, the appraisal model as articulated by Smith and Lazarus (1990) does not provide an appraisal mechanism for differentiating among these self-directed emotions (i.e., to determine whether one will experience shame vs guilt vs embarrassment). This represents a clear indication that although this structural appraisal model has developed considerably beyond the appraisal models represented in stress and coping theory, it remains to be fully explicated.

However, unlike benefit-related emotions, in which appraisals of coping potential do not appear to contribute much to emotion-differentiation, appraisals of both problem-focused and emotion-focused coping potential are very important contributors to emotion-differentiation under stressful circumstances. First, appraisals of high problem-focused coping potential combine with the primary appraisals of "stress" to define one's circumstances as a "challenge" (indicating that the person has the potential to change the circumstances to bring them more in line with his or her desires), which elicits feelings of challenge/determination that motivate the individual to stay engaged in the situation and work to make it more desirable (Smith, 1991; Smith & Lazarus, 1990). In contrast, appraisals of low problem-focused coping potential combine with the primary appraisals of "stress" to define one's circumstances as a "harm" (indicating that the person is in a bad situation about which he or she can do little to make it better), which elicits feelings of sadness and/or resignation that motivate the individual to seek help and possibly to disengage from the harmful situation, permitting reengagement elsewhere (Rasmussen et al., 2006; Smith & Lazarus, 1990). Appraisals of high emotion-focused coping potential (the evaluation that one will be able to adjust to circumstances should they not work out as desired) have seldom been explicitly discussed in the context of this appraisal model, but they likely serve to allow one to remain relatively calm in the face of the conditions appraised as stressful. In contrast, appraisals of low emotion-focused coping potential (the evaluation that one will not be able to adjust to the circumstances and/or handle them should then not work out as desired) combines with the stress-evoking primary appraisals to define the circumstances as a threat, which elicits feelings of anxiety that motivate the person to be vigilant and to use caution in an attempt to avoid undesired outcomes (Smith & Lazarus, 1990).

To date there has been considerable effort devoted to testing the predictions made by this and the other

structural appraisal models cited above. The results of this work provide considerable evidence in support of the specific models tested, and strongly support the general proposition that the experience of particular emotions is systematically related to specific appraisals (e.g., Frijda et al., 1989; Kuppens, Van Mechelen, Smits, & De Boek, 2003; Roseman, 1991; Roseman, Spindel, & Jose, 1990; Scherer, 1997; Smith & Ellsworth, 1985; Smith & Lazarus, 1993; Tong et al., 2007). Thus, these structural models provide a useful theoretical lens for understanding the elicitation of differentiated emotional experience.

RELATIONAL MODELS OF APPRAISAL

The development and testing of the structural appraisal models, as described above, represent clear advances both in the development of emotion theory, and in the development of the appraisal construct more generally. However, taken by themselves, the structural models do not yet deliver on one of the key goals of appraisal theory both with regard to stress and coping, and emotion—namely to account systematically for individual differences in appraisal that then can account for individual differences in emotion and coping. This is because the structural appraisal models typically begin with the individual appraising his or her circumstances a particular way, and then examine the emotional consequences of those appraisals. These models, taken by themselves, do not attempt to address the situation and/or person factors that gave rise to the appraisals.

To address this limitation, work on the structural appraisal models has been supplemented by work on a second class of appraisal model, *relational models of appraisal*, that was developed precisely to describe the situational and dispositional factors that contribute to appraisal as well as how these factors are combined to yield particular emotion-eliciting appraisals (e.g., Griner & Smith, 2000; Smith & Kirby, 2009a; Smith & Pope, 1992; reviewed in Smith & Kirby, 2009b). The promise of this approach is that when the relational models are sufficiently developed, one ought to be able to predict systematically how an individual with a particular configuration of personal characteristics will be likely to appraise, and hence respond emotionally, to a given situation with a particular configuration of appraisal-relevant properties. The approach taken to develop these models has been to consider each of the appraisal components proposed in the structural model of Smith and Lazarus (1990) individually, and for each to identify the relevant properties of the person and the situation that are considered in the appraisal, and describe how those properties are combined to determine particular outcomes. These models have largely been developed through a logical analysis of what an "appraiser" would need to know about the person and his or her circumstances, to evaluate the appraisal question represented by the particular appraisal component (e.g., Smith & Pope, 1992). To date, specific models have been proposed (Smith & Pope, 1992) and empirically supported for two of the appraisal components, motivational relevance (e.g., Griner & Smith, 2000; Smith & Pope, 1992), and problem-focused coping potential (Smith & Kirby, 2009a; Smith & Pope, 1992). Relational models for the remaining appraisal components await development.

For motivational relevance, the key question to be evaluated is "How important to me is what is happening (or what might happen) in this situation?" As discussed by Smith and Pope (1992), this question is inherently relational. To answer it one needs to refer both to one's own goals and to the implications of the situation for those goals. A situation could have implications for many things but would not be appraised as motivationally relevant if the person did not care about those things. Conversely, a person could be passionately committed to a particular issue but would appraise little motivational relevance if the circumstances were seen as unrelated to that issue. Thus, it is hypothesized that motivational relevance will be appraised as high, resulting in relatively intense emotions, to the extent to which an individual cares about a particular goal or issue and his or her circumstances are perceived as having implications for that goal or issue. Motivational relevance should be appraised as relatively low to the extent that either condition does not apply. These propositions have generally been supported in a series of studies in which individuals' goals and concerns have been assessed as their degree of commitment to affiliative versus achievement issues and then their appraisals and emotions in response to situations in which relevance to achievement and affiliative concerns was either manipulated or controlled. In the main, one's degree of commitment to achievement concerns predicted how motivationally relevant one would appraise situations having high achievement relevance, but not how motivationally relevant one would appraise situations having high affiliative relevance, and vice-versa (e.g., Smith & Pope, 1992). As one concrete example, Griner and Smith (2000) assessed appraisals and emotion in individuals who had been preselected to be relatively high or low in their degree of orientation to affiliative concerns while they waited to interact with another individual on a teaching task (a situation with potential relevance to both achievement and affiliative concerns). It was observed that, relative to individuals who were low on affiliative orientation, individuals selected to be high on this orientation were likely to interpret the upcoming situation as having higher affiliative relevance, and associated with this perception, to appraise the motivational relevance of the situation to be higher, and to report higher levels of interest and lower levels of boredom.

For appraisals of problem-focused coping potential, the key question to be assessed is: "Can I successfully do something that will make (or keep) this situation (more) the way I want it to be?" As discussed by Smith and Pope (1992), who based their analysis, in part, on the seminal work of Heider (1958), appraisals of this component would seem to require consideration not only of the

perceived difficulty of the "task" at hand (i.e., whatever might need to be done to make one's circumstances more desirable), but also of how this difficulty relates to one's perceived abilities. Specifically, to the extent to which the task demands are perceived as exceeding one's abilities, appraised problem-focused coping potential should be low, but to the extent to which they are perceived as being within one's abilities, appraised problem-focused coping potential should be high. This hypothesis has been largely validated in a sequence of studies in which participants selected to be high or low in both actual and self-perceived math ability confronted either easy or difficult math word problems (Smith & Kirby, 2009a; Smith & Pope, 1992). For instance, Smith and Kirby (2009a) found that when confronting an easy problem, one's self-perceived and actual abilities were largely unrelated to one's appraisals of problem-focused coping potential and its related emotions of challenge/determination and resignation, but that in response to an extremely difficult problem, at all but the highest levels of combined self-perceived and actual ability, appraisals of problem-focused coping potential increased as a function of both increasing actual ability (as assessed by the Math SAT) and self-reported ability. In addition, increasing levels of appraised problem-focused coping potential were associated with increased levels of challenge/determination and decreased levels of resignation in response to the difficult problem. That the appraisals and emotions of the highest ability group did not conform to these predictions suggests that the model advanced by Smith and Pope (1992) may be somewhat oversimplified (see Smith & Kirby, 2009a), but in the main the general hypotheses were supported.

For the present purposes, the key thing to note about these relational models is that within the domain of emotion, efforts are underway to develop and extend appraisal models so that they can begin to deliver meaningfully on the promise of being able to account systematically for individual differences in emotion, and by extension, coping.

TOWARD AN INTEGRATED PERSPECTIVE ON APPRAISAL, EMOTION, AND COPING

In reviewing side by side the separate literatures on appraisal, stress, and coping, and on appraisal and emotion, we hope that we have rather forcefully illustrated that, although the two literatures often appear to be largely independent, the study of appraisal, stress and coping, on the one hand, and of appraisal and emotion, on the other, are highly interdependent. In large part, through the influences of Lazarus and his colleagues, the two lines of study have always informed one another. This is especially evident when the development of the appraisal construct is considered. The original appraisal construct that Lazarus developed and applied to the study of stress and coping (e.g., Lazarus, 1966; Lazarus & Folkman, 1984), was borrowed from the work of Arnold (1960) in the study of emotion. Conversely, as partially illustrated in Table 15.1, the development of structural and relational models of appraisal within emotion theory (e.g., Smith & Kirby, 2009b; Smith & Lazarus, 1990) was informed by, is consistent with, and in many ways serves as an extension of the development of the appraisal construct within stress and coping theory. As can be seen in the table, it is not at all difficult to map the components of appraisal proposed by Smith and Lazarus (1990) and others to be important for understanding emotion elicitation and differentiation onto the appraisal-related constructs highlighted by Lazarus and colleagues (e.g., Lazarus & Folkman, 1984) in the study of stress and coping.

Although the appraisal construct has of late been somewhat neglected in the study of stress and coping, as much of the theoretical work has been directed at the conceptualization of coping within this framework, the development of the appraisal construct has flourished in the study of emotion, making the study of emotion quite complementary to the study of stress. In fact, we believe that the appraisal construct within emotion theory has matured to a point where a careful consideration of this construct as it is represented in emotion theory could help advance the study of stress and coping. In this final part of this chapter, we would like to consider a couple of specific instances where we believe this to be the case.

First, we believe that Table 15.1 vividly illustrates Lazarus' (1990, 1993b, 1999) claim that stress and emotion are closely related constructs, and in fact, can be considered opposite sides of the same coin, but that of the two, emotion is the broader, richer, and more informative construct. As the table illustrates, stress-related emotions are a subset of all emotions. There are a range of emotional states, most notably benefit-related emotions, such as happiness, pride, and gratitude, which fall outside of the domain of stress. At the same time, there is a very broad range of stress-related emotions, corresponding to challenges (e.g., challenge/determination), threats (e.g., anxiety), and harms (e.g., sadness, anger, and guilt), that are each characterized by their own distinctive eliciting appraisals, and that differ greatly in their motivational properties (e.g., challenge/determination motivates one to persevere on a difficult task, whereas sadness/resignation motivates one to disengage from it; Smith & Kirby, 2009a; Smith & Lazarus, 1990). Thus, as Lazarus (1990, 1999) and Smith and Lazarus (1990) have repeatedly argued, knowing a person's emotional state conveys much more information about how that person is appraising his or her circumstances and how he or she is likely to behave than does merely know that he or she is experiencing stress.

In addition, examination of this table clarifies an ambiguity in the Lazarus and Folkman (1984) formulation of stress that we identified in our review. We noted that it was unclear whether the major subtypes of stress identified by Lazarus and Folkman—challenges, threats,

and harms, were solely defined by primary appraisals, as Lazarus and Folkman seemed to imply in a number of places, or whether these subtypes of stress required a joint consideration of both primary and secondary appraisal. As indicated in the Table 15.1, just as the differentiation of stress-related emotions requires a joint consideration of both primary and secondary appraisal, the major subtypes of stress described by Lazarus and Folkman are clearly defined by the joint consideration of both primary and secondary appraisals. All three subtypes of stress are characterized by the *same* combination of primary appraisals—high motivational relevance and low motivational congruence. It is consideration of secondary appraisal components that differentiate the subtypes. Thus, challenges are further associated with appraisals of high problem-focused coping potential; in contrast, harms are further associated with appraisals of low problem-focused coping potential, and threats are further associated with appraisals of low emotion-focused coping potential. Therefore, just as the differentiation of stress-related emotions is heavily dependent upon secondary appraisal, so too are the definitions of the major subtypes of psychological stress.

At perhaps an even more fundamental theoretical level, we believe that a careful consideration of appraisal as it has developed in the study of emotion helps to address some difficult issues in the definition of stress and coping. In particular, in our review of stress and coping theory we noted some ambiguities in the very definition of stress, as well as considerable disagreement as to how to best conceptualize the major types of coping. With regard to the definition of stress, we noted that there are problems associated with defining stress as being based on appraisals that the situation "taxes or exceeds one's resources" due to ambiguities as to what that phrase means, and that further defining stress in terms of appraisals that the situation is "endangering" the person's well-being is too restrictive in that it seems to exclude challenges, identified by Lazarus and Folkman (1984) as an important subtype of stress, from the stress category. We believe that a careful consideration of the components of primary appraisal as represented by the model proposed by Smith and Lazarus (1990), and depicted in Table 15.1, offers a cleaner, less problematic definition of stress than that originally offered by Lazarus and Folkman (1980), and that this definition further provides a basis for selecting among the current alternative conceptualizations of the major types of coping.

As depicted in Table 15.1, stress is defined by the combined appraisals of high motivational relevance and of motivational incongruence or, in other words, it occurs when the person appraises his or her circumstances as important, but in someway not as desired. The motivational incongruence, itself, can be conceptualized as a discrepancy, or gap, between what one *wants* in the given situation (referred to by Roseman, 1984, in his appraisal model, as one's "motivational state"), and what the person *has* in the situation (referred to by Roseman, 1984, as one's "situational state"). Thus, in this view, psychological stress is defined as a subjectively important discrepancy, or gap, between what one wants and what one has in a given situation, and the strength of the subjective stress is hypothesized to be a function of the magnitude of the discrepancy. These intuitions are captured in Figure 15.1. This alternative conceptualization of stress seems cleaner than the original, as there is no need to appeal to the demands of the situation taxing or exceeding one's abilities, nor is there a need to require that the circumstances necessarily endanger the person's well-being.

Moreover, this alternative conceptualization of stress appears to provide a theoretical basis for selecting among the alternative conceptualizations of coping that were reviewed above. If psychological stress is defined as the magnitude of the discrepancy between one's motivational state and one's situational state, then coping can be defined as one's efforts to reduce the magnitude of this discrepancy. As Figure 15.1 illustrates, there are two basic routes for reducing the discrepancy. First, one can act on the circumstances to change them to bring them more in line with one's desires. This clearly corresponds to problem-focused coping (Lazarus & Folkman, 1984) or primary-control engagement coping (Compas

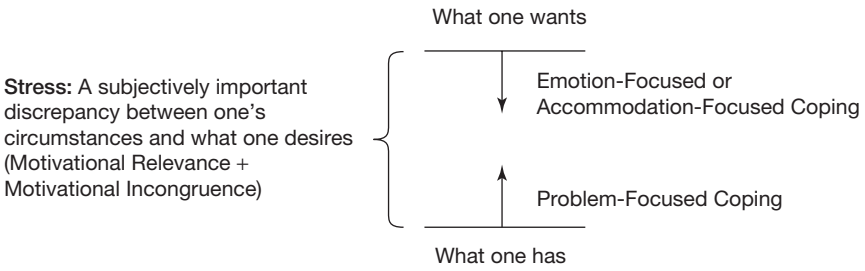

Figure 15.1 ■ Our theoretical conceptualization defines subjective stress as a perceived discrepancy between what one has in a given situation and what one wants in that situation. This gap is defined by the combined primary appraisals of high motivational relevance (importance) and high motivational incongruence (undesirability). Two major forms of coping are indicated as different routes to reducing the discrepancy, and hence, to reducing subjective stress: Problem-focused coping, which reflects efforts to change the situation to bring it more in line with what one wants; and emotion-focused or accommodative coping, which reflects efforts to alter one's goals and desires to bring them more in line with what one has.

et al., 2001), as depicted in the major conceptualizations of stress. Second, one can act on one's desires or beliefs in such a way that the circumstances are made more desirable without actually changing them. This can be accomplished through such strategies as reprioritizing ones goals (e.g., Rasmussen et al., 2006), appraising one's circumstances in a more positive light, reinterpreting the relevance of the circumstances to one's goals, and the like. These strategies are much more akin to secondary-control engagement coping as described by Compas et al. (2001) and accommodative coping as described by Walker et al. (1997) than they are to emotion-focused coping as described by Lazarus and Folkman (1984). Thus, if the emotion-based appraisal model of Smith and Lazarus (1990) is applied to stress and coping theory, an implication is that the second major mode of coping included in most theories might better be conceptualized as accommodative coping/secondary-control engagement coping than as emotion-focused coping. Further highlighting the interdependence between stress and coping theory and emotion theory, acceptance of this conclusion would imply that the appraisal component referred to as emotion-focused coping potential in the model of Smith and Lazarus (1990) might better be called something along the lines of accommodation-focused coping potential.

As we hope we have illustrated through this review and analysis, we believe there is much to be gained by adopting a combined theoretical perspective that integrates stress and coping theory with emotion theory. Even while evolving as seemingly independent literatures, both fields of study have benefitted, especially in the development of the appraisal construct, through the mutual influence of each field on the other. We believe that the mutual benefit would only be heightened if an integrated theoretical perspective were adopted. As Lazarus (1990, 1993b, 1999) has argued, and we have attempted to illustrate, a consideration of emotion enriches and clarifies the construct of stress, and helps to clarify the construct of coping. On the other side, much of the study of emotion within appraisal theory has been focused on describing the antecedents of emotion, and relatively little attention has been devoted to documenting the motivational effects of emotion on behavior and adaptation. We believe that the advances in stress and coping theory in conceptualizing coping and in relating it to adaptation and adjustment would prove very useful to emotion theorists as they attempt to map out the motivational and behavioral effects of various emotions. Our hope is that this review, by indicating the promise of adopting a combined theoretical perspective, will make the actual adoption of such a perspective more likely.

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16 The Dynamics of Emotion in Adaptation to Stress

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INTRODUCTION

What does it mean to say, "I'm stressed"? Early in the study of stress processes in humans, such a statement was thought to indicate that an individual had faced a physiological insult and was making efforts to return to what Cannon (1929) referred to as "homeostasis," or the body's state of balance (Goldstein & Kopin, 2007). The advent of Selye's (1956) concept of stress as any threat requiring some general adaptation had the ironic effect of both popularizing the notion of stress as a ubiquitous phenomenon and uniting many biomedical researchers in a common agenda to dismiss the idea of a generalized stress response altogether. Fortunately for the biobehavioral and social sciences, the stress construct proved to be resilient. There were too many empirical findings relating adverse events to physiological processes that could not be explained without reference to stress responses. However, with criticism came many refinements, including greater attention to identification of distinct responses to threat. Fast-forward to present-day and one can find an extensive literature identifying emotions as central organizing features in our response to stress. Throughout our lives, stress, in various forms, tests our adaptive capacity to regulate emotion and sustain well-being in the face of adversity. Importantly, as highlighted in the ensuing pages of this chapter, research has come to recognize emotions as both a reaction to a threat and an adaptive response that can help the individual maintain well-being and regain homeostasis despite systemic challenge.

The aim of this chapter is to explore the rich and growing body of literature on emotions as they relate to stress, to the health problems that result from failures in adaptation, and to resilient responses that promote positive adaptation. We begin by providing definitions of emotion and stress that allow researchers to make clear distinctions between these constructs. We then discuss evidence in support of a view that the relations between different emotions are dynamic and take on a particular importance in the face of stress. Finally, the chapter will discuss the various implications of emotion for health outcomes and how interventions may aid the individual in adaptation to emotionally charged events, whether illness-related stressors like pain or interpersonal difficulties such as marital conflict.

SOME USEFUL DEFINITIONS OF EMOTION AND STRESS

There are many ways to construe the properties of an emotion. We define emotion as a state comprising both a feeling (i.e., a sensation with a valence) and a motivation (i.e., an action tendency; Craig, 2003; Frijda, 1987) that drives behavior. Emotions are organized through a complex and highly specific series of neuronal pathways that facilitate the appraisal of environmental stimuli as well as of internal states of disequilibrium and allow for a designation of valence to the experienced emotion (LeDoux, 1998). Beginning in the periphery, the body can detect changes in autonomic nervous system activity and integrate that information into an emotional response that prepares the individual to approach or avoid a threat to homeostasis (Wiens, 2005). Reports of positive affect (PA) and negative affect (NA) provide direct evidence of underlying emotions. Both stable trait differences in level of emotion as well as emotional states formed in response to everyday events constitute forms of emotion.

As articulated by LeDoux (1998), emotions are the result of automatic processes governed by the brain and influenced by physiological feedback reflecting the current condition of the body relative to its homeostatic equilibrium. Top-down cognitive inputs can focus attention, augment the feeling, and shift the motivational component of automatically generated emotions (Schachter & Singer, 1962). Thus, the cognitive state of the organism at the time of emotional processing may determine the intensity and even the valence with which the emotion is expressed (Gross & Levenson, 1993). Emotions have been studied as adaptive responses to disturbances in equilibrium that can result in either maladaptive coping, in the case of depression, or adaptive coping, in the case of positive well-being (Schulkin, Thompson, & Rosen, 2003). In the tradition of William James (1884), current neurological research suggests a role for specific brain regions, such as the anterior insula and anterior cingulate

cortex, in integrating information received from the body's periphery with the emotional experience (Wiens, 2005). The interoceptive process of receiving and interpreting bodily feedback informs the brain of a range of solutions that can be used to negotiate the challenge of a stressor (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000) and motivate an adaptive response.

When studying emotion processes, it is useful to adopt a definition of stress that is not confounded with emotion. Some stress researchers have given little attention to emotion, and many emotion researchers have ignored the role of stress in their formulations, in part because of the apparent overlap in the constructs. The approach that we adopt is to define stress as uncertainty introduced by unexpected events (Ursin & Olff, 1993; Zautra, 2003). This disturbance in expectancies upsets homeostasis, and the degree of upset varies considerably depending on the level of threat to current adjustment provoked by the disturbance. Some, but not all, emotions reflect responses to uncertainty and threat that arise from stressful events, but they are not the stress itself. Furthermore, uncertainty and threat do not constitute emotional states in themselves. By making these distinctions, we hope to encourage theory and research that address how stress and emotions interact dynamically to influence health and well-being.

MEASUREMENT AND INDUCTION OF EMOTION

The measurement of emotion, by itself, deserves an entire chapter. Here we provide only a glance at some of the dominant approaches, focusing on a dimensional model of affective space (discussions of conceptual and measurement issues related to discrete emotions may be found in Ekman, 1982; and Russell & Feldman Barrett, 1999). Watson and colleagues (Watson, Clark, & Tellegen, 1988; Watson & Tellegen, 1985; Watson, Weise, Vaidya, & Tellegen, 1999) proposed a two-dimensional model of emotion based on self-report data that consisted of both a PA dimension and a NA dimension. This work led to the development of the Positive and Negative Affect Schedule (PANAS; Watson et al., 1988), through which 10 unique descriptors were found to load almost exclusively on a PA factor (e.g., attentive, excited, proud), whereas 10 others loaded on an NA factor (e.g., distressed, guilty, jittery). The result was a measure for stable characteristics of emotion that was internally consistent and reliably descriptive across different settings and over time (Watson & Clark, 1992). Importantly, the PANAS provided the field with a more reliable instrument than those that had previously been in use, such as Bradburn's (1969) NA and PA scales, and the scales of Stone and Hedges (Hedges, Jandorf, & Stone, 1985).

Since its introduction, this two-dimensional model of emotion has piqued the interest of personality researchers whose work concerned the overlap between personality traits and the affect systems. Tellegen (1985) introduced the link between personality and affect through the identification of "emotionality" dimensions. Positive emotionality refers to social aspects of well-being that are driven by extraversion and high positive activation. In contrast, negative emotionality refers to characteristics representative of neuroticism, such as anxiety and high stress-reactivity. The evidence for positive and negative emotionality traits supported earlier findings indicating that extraversion and neuroticism were correlated with PA and NA, respectively (Costa & McCrae, 1980).

A central question in the measurement of emotion is whether to treat the construct as a transient state reflective of direct environmental input or as a stable trait that predisposes individuals to make consistently similar appraisals of emotional stimuli. Although PA and NA do exhibit stability over time, Tellegen (1985) suggested that the personality dimensions of positive and negative emotionality may give rise to the experience of more transient PA and NA states. Thus, the high degree of correlation between personality traits and corresponding affects seems to reflect a confluence of both trait and state influences on emotional expression.

Russell and Feldman Barrett (1999) draw the distinction between core affect, which refers to basic elements of affective feelings, like pleasure versus displeasure, and prototypical emotional episodes, which refer to more complex and discrete emotions precipitated by some causal series of events. These authors note that discrete emotions included in the class of prototypical emotional episodes, such as anger, fear, and love, do not describe general states, but rather specific emotional categories that are experienced through a defined range of intensity (Russell & Feldman Barrett, 1999). Thus, a continuous scale of emotion intensity may be warranted even for the measurement of discrete emotions.

The two most commonly used methods for measuring emotion are single-occasion self-report and controlled laboratory measurement of reactivity to a stimulus. Single-occasion measurement is most effective when a researcher or clinician wishes to obtain a trait measure of emotion and does not have the luxury of repeated measurements or elaborate laboratory testing. The PANAS is a good example of a self-report instrument that can provide a window into an individual's general predisposition in appraising emotionally relevant stimuli. The extent to which this measure, and others like it, reflects state or trait characteristics of emotion depends on the temporal framing of the item stem. If individuals are asked to respond according to their feelings over the past hour, day, or even week, the interpretation may be different from that of a report in which individuals are asked to respond based on their general feelings over the past 6 months, for example.

Laboratory methods permit the induction of emotional states with a standard stimulus, providing greater experimental control at the possible loss of external

validity. Examples of laboratory designs used to measure emotion include measurement of emotional state following painful stimuli (Zubieta et al., 2003), hedonic cueing with an addictive substance (Sayette et al., 2000), measurement of physiological markers such as electrodermal response (Brenner et al., 2005), reflexive eye blink (Lang, Bradley, & Cuthbert, 1990) following the presentation of emotionally evocative material, examination of facial expression of emotion (Ekman, 1982; Ekman & Oster, 1979), and presentation of video clips known to elicit emotional reactions (Davis, Zautra, Johnson, Murray, & Okvat 2007; Rottenberg, Kasch, Gross, & Gotlib, 2002). Integral to the laboratory design is the appropriate pairing of an aversive or pleasant stimulus with a measure of emotional reactivity that is capable of being altered.

One major problem facing emotion researchers accustomed to self-report data is the propensity of people to inaccurately recollect their past emotional experiences by relying on heuristics and general rules (Kahneman, 1999). Tennen (2006) found that the recollection of emotional states, such as sadness and guilt, was systematically biased by errors based on preexisting schemas. Researchers are increasingly turning to another method for measuring emotion, known as the daily process design, in an effort to avoid the pitfalls of retrospective reports. Through a daily diary format, participants are asked to report over a series of consecutive days on emotional experiences as they occur throughout each day, enabling researchers to estimate changes in within-person slopes over time in addition to aggregated interindividual differences (Tennen & Affleck, 2002). To increase compliance rates, time-stamped electronic diaries can ensure participant fidelity to study protocol. An additional methodological option is the experience sampling method, in which participants are randomly alerted to self-report at multiple points within each day (Csikszentmihalyi & Larson, 1992). The advantage of this design is that emotional states can be reported within close proximity to the events that may have precipitated them, allowing for an estimate of the immediate trajectory of the emotional response to and/or recovery from a pleasant or aversive event.

DYNAMICS OF EMOTION AND STRESS

There has been some controversy over the degree to which oppositely valenced affects are related within an affective, or evaluative, space (Cacioppo, Gardner, & Bernston, 1999), and part of that controversy stems from fundamentally distinct views of how the space is organized. Russell and Carroll (1999) support the notion that affect exists on a bipolar continuum whereby, heuristically speaking, a unit gain in one valence should be met with a unit loss in its opposite valence. One can imagine a simple straight line in which each pole represents the extreme high end of the range of PA and NA, respectively. In this framework, as an individual's NA increases, his or her PA should decrease, thereby increasing the degree of correlation between the two affects in a negative direction.

Another conceptualization of affective space considers PA and NA as separate, bivariate dimensions (Cacioppo et al., 1999). In this view, a net predisposition to approach or avoid a stimulus target may theoretically result from the dual processing of positive and negative affective components. To visualize an affective space that allows for affective differentiation, one can imagine a two-dimensional space with two perpendicular lines intersecting at a single point. One axis represents PA, and the other, NA. As an individual's NA increases in this model, his or her PA may or may not change, reflecting a degree of independence between the two affects (Zautra, 2003). In support of this model, the PA and NA scales of the PANAS (Watson et al., 1988) are substantially uncorrelated, suggesting that states of high positive affectivity do not necessitate concurrent states of low negative affectivity.

Although evidence has been offered for both the bivariate and bipolar models of affect (Reich, Zautra, & Davis, 2003), the integrative perspective of the Dynamic Model of Affect (DMA) perhaps comes closest to representing what happens in daily life. The DMA (Zautra, Potter, & Reich, 1997; Zautra, Smith, Affleck, & Tennen, 2001) recognizes the relative independence of affective components but holds that, during periods of elevated uncertainty/threat from stressful events, emotional states become less differentiated. Zautra, Berkhof, and Nicolson (2002) tested the hypothesis that stress would narrow the affective space between PA and NA in a sample of healthy workers in the Netherlands. They utilized an experience sampling method, a daily process design that randomly alerted people to obtain affect and event ratings 10 times per day for five consecutive days. Zautra and colleagues discovered that within-person estimates of the correlation between PA and NA were higher during moments when a stressful event was reported than during nonstress moments. In addition, a contingency analysis indicated that most individuals had a higher proportion of inverse PA/NA correlations under stressful than nonstressful moments, rebuffing earlier suggestions (e.g., Russell & Carroll, 1999) that psychometric and other statistical factors (e.g., changes in mean levels and variance of PA and NA under stress) were responsible for observed changes in the degree of relation between the two affects.

Why would we expect stress to impact the PA/NA relation? Stress has been shown to increase uncertainty, which in turn puts attentional demands on information processing circuits (Ursin & Olff, 1993). When one's information processing abilities are taxed, one's affective focus becomes limited and, consequently, PA and NA become more inversely correlated (Linville, 1985). During times of acute stress, this is an adaptive solution; the body must recruit energy to escape the most pertinent threat it faces. Thus, our affective complexity diminishes to

minimize energy expenditure, escape threat, and regain homeostatic balance. Uncertainty facilitates this process by motivating the individual to cognitively attend to the emotion most closely tied to a stressor: NA.

The examination of affect in the context of the stress of episodic pain has provided another test of the DMA. According to the DMA, elevations in pain should be associated with a less affective differentiation, as patients must divert resources typically used for complex affective processing and instead employ them for other homeostatic regulatory purposes. In line with predictions derived from the DMA, Zautra et al. (2001) found that, during painful weeks, reduced levels of PA predicted heightened levels of NA in rheumatoid arthritis (RA) patients. Recent findings further suggest that elevations in pain were related to increases in NA and decreases in PA to a greater extent in fibromyalgia (FM) patients than in a control chronic pain group of osteoarthritis (OA) patients (Finan, Zautra, & Davis, 2009). Given prior evidence that pain uncertainty is more prevalent in FM patients, who have chronic widespread pain, than in OA patients, who have localized joint pain, these findings appear to be in line with predictions of the DMA.

Early criticism of approaches that incorporated a bivariate model of affective processing suggested that unmodeled individual differences could account for some of the findings that indicated separate dimensions for PA and NA (e.g., Russell & Carroll, 1999). Longitudinal naturalistic studies have tempered some of that criticism for several reasons. First, the calculation of within-person slopes allows for an examination of changes in the individual over time, irrespective of the data for sample peers. Second, repeated measurements over weeks, days, or even multiple times within a day provide a significant advantage in statistical power compared with cross-sectional designs. Finally, as mentioned earlier, measurements of stress, pain, and affect can be obtained exceptionally close to when events that influence such states actually occur. Future studies that make use of interactive voice response technology to collect data via cell phones or personal digital assistants multiple times within-day will likely lead the way in further advancing stress and emotion theory. In sum, there are several possible explanations for this "shrinkage" of affective space, including increased informational demands on emotion processing, regulation due to heightened uncertainty, and increased attention to resolution of NAs provoked by the disturbance of homeostasis. More work is needed to identify the underlying factors responsible for the observed effects of a significant increased inverse relationship between PA and NA following stressful events.

EMOTIONAL INTELLIGENCE AND STRESS

Investigators have also sought to identify individual differences in emotion regulation capacity. Emotional intelligence (EI) refers to an ability to process emotionally relevant information in the course of adaptation to environmental challenges (Mayer & Salovey, 1997; Gohm, Corser, & Dalsky, 2005). As we have shown in the current chapter, the maintenance of complex information processing abilities when presented with emotionally oriented stimuli is essential to successful adaptation in times of stress. A high level of EI requires not only the ability to reason cognitively about emotions but also an ability to access emotions at appropriate moments and regulate emotions in an effort to maintain an emotional homeostasis. Mayer and Salovey (1997) have divided the abilities represented by EI into four major categories: (1) awareness of emotional states in oneself and others; (2) use of feelings and other emotion data to facilitate decision making; (3) learning and retention of knowledge about one's emotions; and (4) emotion regulation.

Some recent studies have applied EI theory to explore the utility of EI abilities in the reduction of stress. Slaski and Cartwright (2003) conducted an EI training study in which they trained office managers on EI skills such as self-awareness, emotion regulation, and recognizing emotions in others, among other techniques. Perceived stress significantly decreased pre to post for individuals who received EI training compared with those who received no training at all. This study supported a previous finding (Slaski & Cartwright, 2002) indicating that office managers who scored higher on EI measures tended to report less perceived work stress than those scoring lower on EI. Other research has reported that a buffering effect of some EI indicators may reduce the impact of stress on depressive symptoms (Ciarrochi, Deane, & Anderson, 2002).

Comparing the research on EI and stress with the DMA literature raises interesting questions about the importance of processing emotionally oriented stimuli in adaptation to stress. The DMA is associated with a clear set of findings that indicate a narrowing of affective space and, thus, a reduction of emotional complexity in the face of stress. Other research (Ong et al., 2006; Fredrickson, 2001; Zautra, Johnson, & Davis, 2005) suggests that the maintenance of PA during stressful episodes is representative of sustained emotional complexity and should be considered indicative of resilience. In contrast, it is not clear if heightened EI abilities confer resilience to stress. For instance, it is not known if EI abilities develop independently of stress or are shaped through the experience of stress. Furthermore, the studies that have explored EI and stress, to date, have used a cross-sectional design. The implementation of longitudinal design, then, would be an appropriate next step for this line of work. Future research is also necessary to clarify the mechanisms associated with emotional complexity under stress. Imaging studies using functional magnetic resonance and/or positron emission tomography would be useful in determining which brain regions account for heightened abilities in maintaining emotional complexity through stress.

STRESS AND HEALTH

The effects of stress on health outcomes are well documented in the literature, and other authors of chapters in this volume have provided comprehensive reviews of the relationship between stress and illness. We will not attempt to duplicate those efforts, but here we simply introduce key concepts relevant to our larger focus on emotions and health. Under conditions of stress, the sympathetic nervous system is activated and prepares the body for fighting or fleeing. Epinephrine and norepinepherine are released, resulting in an increased heart rate and blood pressure, and a diversion of energy away from nonessential systems such as reproduction, digestion, and growth, and toward large muscles (Sapolsky, 1994). In addition to disrupting human health by affecting cardiovascular parameters, chronic stress can impair health through activation of the hypothalamic–pituitary–adrenal (HPA) axis. When production of cortisol, the primary human hormonal product of the HPA, is increased by chronic stress, certain components of the immune system become inhibited, and energy stores are released, elevating blood glucose levels (Dickerson, Gruenewald, & Kemeny, 2004). Here again we defer to the work of other authors in this volume on the complex relationships between stress, physiological activity, and physical health.

NEGATIVE EMOTIONS, STRESS, AND HEALTH

Perhaps because of the close relationship between negative emotions and stress, much research on emotions and health has tended to focus on the role of negative emotional states and health. Negative mood has been associated with reduced natural killer cell (NKC) activity (Valdimarsdottir & Bovbjerg, 1997) and with a reduction in the proliferative response to a T-cell mitogen (Futterman, Kemeny, Shapiro, & Fahey, 1994). Koh (1998) found that patients with depression, which is characterized by negative mood, showed inhibition in several immune system parameters. In addition, psychiatric in-patients with depression have been shown to have a poorer blastogenic response than nondepressed control patients (Stein, Keller, & Schleifer, 1985), a lower percentage of helper T-lymphocytes (Krueger, Levy, Cathcart, & Fox, 1984), and a 50% reduction in NKC cytotoxicity (Irwin et al., 1990). Immune suppression may occur in a graded fashion across a spectrum of negative emotion, as evidenced by findings that lymphocyte response to certain mitogens was much lower for psychotic and severely melancholic inpatients than for patients with minor depression (Maes, Bosmans, Suy, Minner, & Raus, 1989).

Depression is also a significant risk factor for cardiovascular problems. A meta-analysis of depression showed the relative risk of developing coronary heart disease to be 2.69 for people with clinical depression compared with controls (Rugulies, 2002). It is, perhaps, no surprise that depression is associated with increased incidence of all-cause mortality. Barefoot et al. (2000) found that trait depression was predictive of a 32% increase in mortality risk for depressed patients undergoing coronary angiography, as compared with nondepressed patients, over an 11-year follow-up. These results appear to hold up across study populations and methods, as a meta-analysis of 25 studies of mortality and depression (Cuijpers & Smit, 2002) found that the overall relative risk of dying for depressed subjects was 1.81 compared with nondepressed subjects.

The effects of depression on pain and inflammation outcomes have been studied by members of our own research group. Interpersonal stressors are related to greater pain in patients with pain-related autoimmune disorders such as RA (Affleck, Tennen, Urrows, & Higgins, 1994; Zautra & Smith, 2001). Furthermore, that relationship is moderated by current depressive episodes, such that current depression contributes to an increase in pain reactivity to stress (Zautra & Smith, 2001). A history of emotion dysregulation also bears significance for an individual's current health. In a recent study, RA patients with two or more past episodes of depression had more pain at baseline, as well as greater pain in response to a stress induction, than patients with either zero or one prior episode, supporting the hypothesis that multiple depression episodes can lead to a lasting sensitization to social stressors (Zautra et al., 2007). Evidence suggests a link between depression, stress, and immune markers that are related to the inflammatory process in RA (Evers, Kraaimaat, Geenen, Jacobs, & Bijlsma, 2003; Zautra et al., 2004), providing a possible physiological mechanism by which multiple depressive episodes can cause or exacerbate inflammation-related joint pain in RA patients.

As research into stress and health outcomes grows, both the emotional predictors and the outcomes can be examined with greater detail and specificity. The need for this specificity has become clear as studies have suggested that general classes of emotional upset, such as depression, can be misleading. To qualify for a diagnosis of major depression, for example, a participant must first report feeling depressed or "blue" for a period of 2 weeks or more. Alternatively he or she could have a period of 2 weeks or more suffering a loss of capacity to experience pleasure. These choices introduce ambiguity about the nature of the depressive episode reported: Is it due to pervasive NAs, or the absence of PAs?

Anxiety, a state of apprehension or fear that can be diagnosed as a clinical disorder, is often comorbid with depression (Bakish, 1999). Like depression, anxiety is associated with incidence of cardiovascular events (Hemingway & Marmot, 1999) and is predictive of mortality in people after coronary artery bypass surgery (Tully, Baker, & Knight, 2008). However, both Tully et al.'s (2008) study and others (e.g., Strik, van Praag, & Honig, 2003) suggest that the relationship between depression and some health outcomes might be explained partially

or wholly by anxiety. Strik et al. (2003) examined the effects of depression and anxiety on the risk of an incomplete recovery after a heart attack and found that anxiety accounted for the relationship between depression and future cardiac events. Similarly, Tully et al. (2008) found that for patients who had undergone open-heart surgery, depression approached, but it did not reach statistical significance for prediction of mortality, while anxiety nearly doubled the risk of mortality. These studies highlight the importance of distinguishing between types of negative emotions when assessing their effects on health outcomes.

One negative emotion in particular, anger, is gaining attention in the study of the health consequences of emotional expression. Although anger suppression has long been associated with heightened pain reactivity (Quartana & Burns, 2007), mounting evidence indicates that both trait anger expression styles and state anger expression episodes contribute to increases in pain sensitivity (for a review, see: Bruehl, Chung, & Burns, 2006). In one study, trait anger expression, known as "anger-out," produced elevated pain responses to an acute pain stimulus for chronic pain patients, suggesting that maladaptive anger regulation may be related to impaired endogenous opioid system functionality (Bruehl, Burns, Chung, Ward, & Johnson, 2002). That those effects were not significantly different for healthy subjects with a trait anger-out style suggests that the endogenous opioid dysfunction that accompanies chronic pain may be separate from that which is fostered by the expression of anger (Bruehl et al., 2002). The argument for an endogenous opioid pathway for anger-out effects on pain sensitivity was recently bolstered by findings that the A118G polymorphism of the μ-opioid receptor gene accounted for differences in pain sensitivity for high versus low anger-out participants (Bruehl, Chung, & Burns, 2008). In addition to its effect on the endogenous opioid system's modulation of the pain response, anger expression may indirectly contribute to the development of chronic pain symptoms through its effect on adipose tissue distribution and muscle tension (Bruehl et al., 2006; Burns, 1997; Raikkonen, Matthews, Kuller, Reiber, & Bunker, 1999), although further refinement and direct tests of these hypotheses are necessary. Other work concerning effects of anger on health is discussed elsewhere in this volume in connection with hostile personality.

In addition to increasing the amount of attention given to specific emotions as predictors of health outcomes, there is a need for greater specificity in identifying the stressors that precipitate those emotions. Social threats provoke unique responses compared with other stressors that are often used in a laboratory setting, such as mathematical or memory tasks (Dickerson et al., 2004). It has been suggested that shame, for example, serves a social function by being associated with submissive gestures found in both humans and primates (Gilbert, 2000). In humans, shame is associated with de-escalation of conflict and increased cooperation from interaction partners (Keltner, Young, & Buswell, 1997).

As a unique threat with a corresponding emotion, it follows that a social stressor may precipitate a unique health outcome. A meta-analysis of stressors with a social-evaluative aspect that might induce shame indicated that these stressors were associated with greater salivary cortisol response than stressors without a social component (Gruenewald, Kemeny, Aziz, & Fahey, 2004). Cortisol responses were further heightened when social threats were combined with uncontrollability, and cortisol levels took longer under these conditions to return to baseline. The immune system also seems to be affected differentially by social versus nonsocial threats; social-threat stressors lead to an increase in proinflammaory cytokines (Ackerman, Martino, Heyman, Moyna, & Rabin, 1998), whereas other stressors do not necessarily produce this increase (Peters et al., 1999). In addition, not only can a particular stressor specify an immune response, but so too can a specific emotional reaction paired with the stressor. Individuals exposed to a stressor designed to elicit self-blame showed greatest tumor necrosis factor-α activity if they endorsed the emotion shame, as opposed to guilt, anger, sadness, and other negative emotions (Peters et al., 1999).

POSITIVE EMOTIONS, STRESS, AND HEALTH

Although the lion's share of research on emotions and health has focused on the harmful impact of negative emotions, a growing chorus of researchers has turned the field's attention to the potential benefits of positive emotion (Chesney et al., 2005; Pressman & Cohen, 2005). The physiological correlates of highly arousing and negatively valenced emotions such as anger or fear are easily detected through examination of sympathetic nervous system activation. Some positive emotions, such as excitement and joy, also carry high-arousal signatures, whereas other positive emotions, such as feelings of calm and serenity, do not. Examination of parasympathetic activity during calming positive engagement may reveal the equilibrating influence of those kinds of positive emotions. For example, Bernardi et al. (2001) found that yoga mantras and rosary prayer induced healthier cardiovascular rhythms. The undoing model (Fredrickson, Mancuso, Branigan, & Tugade, 2000) may shed light on how positive emotions exert their influence on health outcomes. According to the model, positive emotions do not, themselves, lead to a specific action, but rather undo the stimulating effects of negative emotions and serve to return the body to homeostasis. Several studies by Fredrickson tested this hypothesis by experimentally inducing high-arousal negative emotions in participants, which resulted in increases in heart rate, blood pressure, and vasoconstriction. Participants were then instructed to view a film designed to elicit feelings of

joy, contentment, neutrality, or sadness. Participants who experienced more positive emotions showed quicker cardiovascular recovery than those who viewed the neutral or sad films (Fredrickson et al., 2000). More work is needed to identify the unique physiological signatures of positive experiences beyond recovery of homeostasis. More attention to opioidergic and dopaminergic pathways may provide the evidence needed to quantify neuroendocrine responses that accompany positive emotions that arise from goal attainment and approach motivation.

There is also substantial evidence that positive emotional states are associated with better immune regulation. Futterman et al. (1994) found that induction of PA led to a heightened proliferation in response to a T-cell mitogen from baseline. Other studies indicated that positive events led to significantly fewer respiratory infections over a 2-week period and that having significantly fewer positive events can predict the start of an infectious illness (Evers et al., 2003; Lyons & Chamberlain, 1994). A recent study found that PA also affects glycosylated hemoglobin, an indicator of glycemic control in people with diabetes and an independent predictor of cardiovascular health (Tsenkova, Dienberg Love, Singer, & Ryff, 2008).

Positive emotion has also been shown to influence mortality rates. Danner, Snowdon, and Friesen (2001) examined the autobiographies of nuns written before they took orders, some of them 50 years prior to the time of the study. Negative emotion expressed in the diaries did not predict mortality, but nuns who expressed the most positive emotion lived on average 10 years longer than the others. Moskowitz (2003) likewise found that PA, but not NA, was related to survival in patients with AIDS. Positive mood may, additionally, serve as a buffer of the effects of negative mood on immune function. In a study of NKC activity, immune activity for people with both high positive and high negative mood compared with that for those reporting no negative mood (Valdimarsdottir & Bovbjerg, 1997).

Optimism, conceived either as a situation-specific outcome expectancy or a personality trait, has often been associated with positive emotion (Aspinwall & Leaf, 2002; Scioli et al., 1997) and has been studied in relation to immunological response to stress. Segerstrom, Taylor, Kemeny, and Fahey (1998) found that situational optimism in law students during their first semester of law school was associated with higher numbers of helper T-cells and greater NKC cytotoxicity. In studies involving other health outcomes, optimistic and hopeful individuals were less likely to take sick days and were less likely to be diagnosed with common illnesses like hypertension, diabetes mellitus, and respiratory track infections than their counterparts (Kivimäki et al., 2005; Richman et al., 2005). Furthermore, a prospective study of elderly members of a Dutch community found that those reporting a high level of optimism showed a lower incidence of all-cause mortality and an even greater decrease in cardiovascular mortality than those low in optimism (Giltay, Geleijnse, Zitman, Hoekstra, & Schouten, 2004).

Researchers have also examined positive emotion through the study of well-being. Two types of well-being that have been distinguished are worth noting here: hedonic and eudaimonic well-being (Barak, 2006; Ryan & Deci, 2001). Hedonic well-being encompasses positive emotions such as pleasure, happiness, and PA and has been described as "subjective well-being" (Ryff, Singer, & Love, 2004). In contrast, eudaimonic well-being refers to personal growth and development, with components including self-acceptance, purpose in life, personal growth, positive relations with others, environmental mastery, and autonomy (Ryff et al., 2004). Ong and Zautra (2008) point out that these two approaches are best thought of as complementary. Eudaimonic efforts lead to, and are reinforced by, hedonic outcomes.

Resilience has been described as the ability to "bounce back" from stressful experiences (Carver, 1998) and has been linked to positive emotionality through a variety of pathways, including openness to experience (Block & Block, 1980) and coping mechanisms (Masten, 2001). Furthermore, it correlates primarily with PA, but not NA (Tugade, Fredrickson, & Barrett, 2004). Like PA, trait resilience is associated with faster cardiovascular recovery from negative emotions (Tugade et al., 2004) and a diminished negative affective reaction to pain exacerbations (Zautra, Johnson, Davis, & Fasman, 2005).

The theme of "resilience" is evident in recent studies of emotion regulation. For example, Fredrickson (1998, 2001) has proposed that positive emotions broaden an individual's resource portfolio in the face of stress. Specifically, adaptive cognitions and behaviors are thought to be more readily retrieved and employed in the face of a stressor when positive emotionality is high than when it is low. In the language of the DMA, positive emotions counteract the force of stress in shrinking affective space. Although stress serves to increase NA, individuals who can sustain PA through stressful times appear to maintain a high level of information processing and emotional complexity and avoid the potentially harmful consequences of chronic, unmitigated NA (Tugade & Fredrickson, 2004; Zautra, Davis, Affleck, Tennen, & Reich, 2005).

A recent study by Ong, Bergeman, Bisconti, and Wallace (2006) extended theory on affective differentiation and resilience by showing that positive emotion not only moderated the effect of daily stress on negative emotion but also significantly diminished the effects of stress on next-day negative emotion. In addition, no relationship was observed between daily positive and negative emotion among people who scored high on a trait resilience measure (Ong et al., 2006), suggesting that resilient people are characterized by greater differentiation in affective experiences.

Zautra, Hall, and Murray (2008) call for more study of cognitive–affective and social processes like positive engagement, optimism, and strong social ties that lead to resilience following stress. They also broaden the definition of resilience to include the study of the sustainability of positive engagements in the face of adversity. The capacity to endure under stressful conditions is likely influenced by cognitive–emotional and social processes different from those typically identified when examining recovery of homeostasis following distressing events. A greater focus on those processes may add considerably to the scope of work and utility of stress–diathesis models to predict long-term health outcomes like survival and physical functioning in aging populations.

IMPLICATIONS FOR TREATMENT

The dominant Western therapeutic approach to treating mood disorders over the past half century has been rooted in theory in which intractable negative mood results from a habitually irrational cognitive appraisal of emotional stimuli (Beck, 1967, 1987). Under the framework of the diathesis–stress model, a diathesis (e.g., cognitive vulnerability; Abramson, Metalsky, & Alloy, 1989) is thought to create a vulnerability to depression that may be actualized when the individual encounters a stressor with sufficient potency (e.g., negative life events; Kessler, 1997). Depression, for example, is thought to result from a dysfunction in cognitive processing brought about by acute or chronic activation of latent diatheses by psychological stressors (Monroe & Simons, 1991). Cognitive theories of psychopathology, then, contend that the treatment of mood disorders generally proceeds first through the identification of negative patterns of thinking, or self-schemata (Beck, 1967, 1987). These negative schemata promote a cascade of dysfunctional thoughts about one's self-worth, the world, and the future, known collectively as the "negative cognitive triad." Beck (1976) asserted that the cognitions responsible for the automaticity of negative appraisals of emotional stimuli are necessarily distorted and, thus, should be targeted for change in the therapeutic context. Ideally, the result of successful cognitive therapy should be a reduction in the frequency and intensity of negative emotions thought to be maintained by distorted cognitions.

Although cognitive therapy remains the gold standard for the psychological treatment of mood disorders, a growing body of evidence supports the notion that therapy need not focus principally on the reduction of negative cognitions and emotional states. Treatments that target the promotion of positive emotional resources are being viewed instead as excellent complementary, if not primary, treatment options (Folkman & Moskowitz, 2000; Hamilton, Kitzman, & Guyotte, 2006). Clinically, the technique for maximizing a patient's general fund of positive emotion and emphasizing its importance as a resilience resource in times of elevated stress may not differ substantively from that employed for the reduction of negative emotion in cognitive therapy. For example, Folkman and Moskowitz (2000) note the efficacy of positive reappraisal, a strategy used to reframe a situation with a positive tone, in bringing about increases in PA for caregivers of dying and recently deceased HIV patients (Moskowitz, Folkman, Collette, & Vittinghoff, 1996). In the same study, problem-focused coping, which involves the active management of conditions that cause distress (Folkman & Moskowitz, 2000), was associated with an increased sense of mastery and control during conditions in which caregivers had no ostensible control of their partner's declining health. Thus, strategies commonly employed in traditional cognitive-behavioral approaches to reducing negative emotion can with some success be modified to focus on enhancing positive emotion (see also: Aldwin, 1994). It appears that focus on the positive need not, and perhaps should not, neglect the negative in building interventions that enhance resilience.

As detailed earlier, chronic NA and stress can result in harmful health consequences, which, in turn, serve to promote and maintain further negative affective states. However, a substantial amount of literature indicates that PA can provide a buffer against these effects. As such, researchers have explored the utility of interventions designed to enhance PA in ill populations. Coping effectiveness training (CET; Chesney, Chambers, Taylor, Johnson, & Folkman, 2003), delivered in a group setting, encourages participants to log daily positive events in a diary format, share those positive experiences with the group, engage in benefit finding, and laugh with each other as a coping response. In a randomized controlled trial of CET with HIV-positive men, patients who received CET evidenced decreases in perceived stress, burnout, and anxiety, and increases in positive states of mind, compared with participants in control groups. It was found that coping efficacy mediated some of the CET effects.

Another therapeutic approach to enhancing PA, known as mindfulness-based stress reduction (MBSR; Kabat-Zinn, 1990), dispenses with the notion that coping with stress should involve active, approach-oriented problem solving. Instead, MBSR, which has its roots in Eastern meditation practice and philosophy, adopts an active but observant stance, whereby emotions, thoughts, and physical sensations are noticed and accepted as part of the flow of life. Meditations are encouraged to be practiced on a moment-to-moment basis throughout even the most mundane daily activities like gardening, exercising, or driving (Kabat-Zinn, 1990). Recent evidence indicates that within-day, moment-to-moment experience of PA, assessed through the ecological momentary assessment paradigm, buffers against genetic influences on NA (Wichers et al., 2007). Such evidence strengthens the position that mindfulness-oriented therapy might provide significant benefits to individuals suffering from depression and other disorders characterized by high NA

and low PA. Rather than guide the individual through a Socratic exploration of a problem and its origin, MBSR treats negative cognitive and emotional intrusions as transient occurrences and facilitates the accentuation of one's stable positive features, such as the ability to forgive, hope, or savor (Hamilton et al., 2006).

Engaging in MBSR has been shown to be a promising intervention for aiding adaptation to a variety of physical and psychological disorders. Specifically, reductions in pain (Goldenberg et al., 1994; Kabat-Zinn, 1982), stress (Astin, 1997), anxiety and depression symptoms (Shapiro, Schwartz, & Bonner, 1998; Teasdale et al., 2000), psoriasis symptoms (Kabat-Zinn et al., 1998), and disordered eating behaviors (Kristeller & Hallett, 1999), as well as increases in positive mood (Bishop, 2002), have all been reported following mindfulness-based interventions. Our research group recently conducted a randomized clinical trial comparing a mindfulness meditation-based intervention with an emphasis on the promotion of PA to cognitive-behavioral therapy for pain and an education control condition (Zautra et al., 2008). We found that the mindfulness-based intervention was most effective for RA patients with a history of recurrent depression. This group experienced greater elevations in positive emotion and vitality and larger decreases in NA and joint pain relative to participants in other intervention conditions, suggesting mindfulness-based methods are particularly valuable for those with difficulty in emotion regulation. As further support, two meta-analyses (Baer, 2003; Grossman, Niemann, Schmidt, & Walach, 2004) have concluded that MBSR confers a moderate to large effect across illness populations. More studies, however, are still needed to compare mindfulness-based interventions with another active treatment before verifying the potential for these methods to improve emotion regulation among the chronically ill.

CONCLUSION

In the exploration of stress and emotion, a good adage may be, "the deeper one looks, the more one finds." Emotions operate in specific, yet complex, capacities in human adaptation to stress. Individuals may simultaneously be motivated to act in accord with emotional predispositions and to respond to seemingly incompatible demands in the immediate environment. Clearly, differentiating between emotions requires a significant contribution of cognitive resources to maintain a high level of information processing. Under conditions of uncertainty, those resources can be depleted, and affective differentiation becomes more difficult.

By examining the influence of discrete emotions, it becomes clear that health outcomes resulting from stress are often emotion specific. Negative emotions experienced through clinical disorders like depression and anxiety, for example, decrease immune function and increase the risk of death. However, as recent research has indicated, the health benefits of positive emotion, independent of negative emotion, are real and are still being uncovered. With more attention to how people are able to be emotionally resilient, it is likely that pathways to adaptation will continue to be revealed, informing researchers and clinicians alike.

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17 Coping

Charles S. Carver

This chapter addresses the topic of coping, a concept about which there is an extensive literature (see, e.g., Carver & Connor-Smith, 2010; Folkman & Moskowitz, 2004; Skinner, Edge, Altman, & Sherwood, 2003). Given the wealth of available information, this chapter is limited to introducing some of the themes of this topic rather than providing a comprehensive review. The chapter is organized according to the logical flow of the experiences that induce and define coping. To understand coping (and its role in promoting or impeding health), one must ask why coping happens. For that reason the chapter begins with brief consideration of the concept of psychological stress. Then it turns to coping per se, addressing several key issues in how coping is conceptualized and distinctions among ways in which people cope with stress. Finally, it briefly considers issues in studying how these diverse ways of coping may influence health.

PSYCHOLOGICAL STRESS

Several theorists have proposed models of psychological stress over the years, with varying points of emphasis. Nearly all statements made in the past 40 years, however, orient in one way or another to the work of Richard Lazarus and Susan Folkman (e.g., Lazarus, 1966, 1999; Lazarus & Folkman, 1984). To Lazarus and Folkman, stress is a transaction between the person and the context. Stress exists when people confront circumstances that tax or exceed their ability to manage them.

APPRAISALS AND STRESS

Lazarus (1966) consistently emphasized that people's *appraisal* of the circumstance often matters more in the transaction than does the objective circumstance itself (see also Smith & Kirby, chapter 15). Appraisals are cognitive evaluative processes that incorporate both information from the stressor and information from the person. For example, most people are not alarmed by the approach of a small dog, but for people with phobias about dogs, that circumstance is appraised quite differently. As another example, a student who has been thoroughly engaged in a course will appraise the announcement of a surprise quiz very differently than will a student who has not yet done any of the readings.

A second kind of appraisal is the person's appraisal of whether he or she will be able to deal with the circumstance. Some people in a given circumstance will be able to bring to mind responses to the stressor that they expect to be useful, others will not. People who can easily bring to mind ways to avoid or minimize potential bad outcomes will have a very different experience than a person who can think of nothing useful to do.

The appraisal of an aversive outcome looming or at hand is called *primary appraisal*. The appraisal of whether there are ways to respond to it is called *secondary appraisal*. Obviously these appraisals influence one another. A person who is very confident about having useful strategies will see the circumstance as being less problematic than will a person who can bring no useful strategies to mind.

Several further labels have been applied to appraisals of stressors. *Threat* appraisal means that the person perceives an impending event that may have bad or harmful consequences. *Harm* appraisal is the perception that something bad has already happened. *Loss* appraisal is a specific kind of harm appraisal, in which something that is positively valued becomes inaccessible. That is, harm can mean either the bringing about of pain and punishment or the removal of something desirable. Loss, in contrast, tends to be restricted to the latter case.

Another appraisal of events is also mentioned in this context: *challenge* appraisal. This means seeing the situation as demanding, but also as something you can benefit from. Challenge implies an "optimal" obstacle—something that will be surmountable (with effort), and something that will allow a better state of affairs because of being surmounted. Challenge also seems to imply the expectation of a good outcome. The properties of challenge experiences are different enough from those of threat and loss that some doubt that challenge should be viewed as a form of stress appraisal (Blascovich, 2008; Tomaka, Blascovich, Kelsey, & Leitten, 1993).

Another popular analysis of stress makes extensive use of an economic metaphor (Hobfoll, 1989, 1998). It starts from the idea that people have resources that they try to protect, defend, and conserve. Resources can be physical

(e.g., house, car), conditions of life (e.g., having friends and relatives, stable employment), personal qualities (e.g., a positive world view, work skills), or other assets (e.g., money or knowledge). Resources are anything the person values. In this view, stress occurs when resources are threatened or lost. This viewpoint emphasizes the utility of the resources as being critical to stress. Ultimately, however, even in this view threat and loss remain crucial to the experience of stress.

PHYSIOLOGICAL RESPONSES

Confronting threat and loss produces negative emotions, which incorporate a variety of physiological changes within the body: cardiovascular, neuroendocrine, and immune. Many kinds of emotion (e.g., fear or anger) are intrinsically organized around preparing the body for sudden or sustained action. Fear prepares the body for escape, anger prepares it for attack. Given this functional focus, the physiological changes that occur are aimed at making energy available to muscles. Because the body cannot do everything at once, these changes also divert resources from other functions such as digestion or self-repair (Miller, Cohen, & Ritchey, 2002).

Some negative emotions tied to stress have a different character, however. This is particularly true of emotions related to loss. Dejection and sadness are not about preparing for action, but rather about giving up the effort to attain desired ends (Carver, 2004; Nesse, 2000). There are physiological changes associated with deep sadness, but they are different from those associated with fear or rage.

These various physiological responses are functional for the purposes to which they evolved. In the short term, it is critically important, for example, to escape from a predator or from falling rocks. Indeed, this need is so urgent that it can temporarily preempt longer-term necessities such as fighting off an infection.

Even functional and adaptive processes can produce problems if they occur too often or for too extended time. As an example, extensive and repeated cardiovascular responses can place physical strain on arteries. Over time, this creates small tears in the inner lining of the artery. Normally, the tears are repaired without negative consequences. So far, so good. However, over time, the formation of plaques at the sites of these tears eventually turns into atherosclerosis, clogging of the artery (e.g., Krantz & McCeney, 2002; Rozanski, Blumenthal, & Kaplan, 1999; Smith & Ruiz, 2002). In this example, a normal function is accelerated, compressed into a briefer time span, so that it reaches a maladaptive endpoint sooner than it otherwise would.

As another example, the processes that control blood pressure respond to situational demands by creating increases from baseline levels. If the increases occur too often or are too sustained, the internal regulatory process begins to adjust the baseline upward—for example, by causing functional and even structural changes in blood vessels. Now blood pressure returns not to its preexisting resting level, but to a slightly higher level. Over many iterations, the resting level itself becomes elevated, and now constitutes a case of hypertension (cf. Fredrikson & Matthews, 1990).

Cardiovascular responses are one part of the physiological component of stress. Underlying those responses, and to some extent driving them, is a set of neuroendocrine mechanisms that play a major role in the body's stress response: the sympathetic adrenomedullary (SAM) system and the hypothalamic–pituitary–adrenocortical (HPAC) axis (McEwen, 2006, 2008). SAM and HPAC activation are manifested in elevations of several hormones, including catecholamines (epinephrine and norepinephrine) and cortisol. Cortisol is considered a particularly important stress hormone because of its links to other elements in the overall stress response. For example, an increase in cortisol can suppress immune functioning (e.g., Choi, Fauce, & Effros, 2008; Kronfol, Madhavan, Zhang, Hill, & Brown, 1997). That is, as was noted earlier, when appraisals indicate a strong and lasting need for vigorous physical behavior, immune surveillance takes a lower priority and is suppressed (Miller et al., 2002). As a result of its central involvement, cortisol is a frequent object of research on stress.

The immune system is another favorite target of discussions of stress-related physiological responding (Kiecolt-Glaser, 2009; Segerstrom & Miller, 2004). The immune system obviously has important implications for health. It is the body's main line of defense against disease agents that range from bacteria to cancer cells. If immune functioning is impaired over a sustained period, rather than just temporarily, the person becomes more vulnerable both to opportunistic infectious agents and to agents of disease that had already been at work in the body. The immune system is far more complicated than was assumed two decades ago, and there are several distinct ways in which stress can influence immune function (Kiecolt-Glaser, McGuire, Robles, & Glaser, 2002; Robles, Glaser, & Kiecolt-Glaser, 2005).

In thinking about the psychophysiological patterns involved in responding to stress, one last point should be made. Stress can be acute (relatively short term) or chronic (existing over much longer periods of time). Short-term stress responses are generally adaptive, unless previous damage has set the body up for the failure of some system. However, chronic activation of the body's stress response can have damaging effects on the body. When you imagine an example of stress, it may be easiest to imagine a stressor that is time-limited. Many of the stressors that people confront in today's world, however, are relatively chronic and long-lasting.

COPING

Stress leads to coping. Coping is generally defined in language such as this: Coping is efforts to deal with a

threatening or harmful situation, either to remove the threat or to diminish the ways in which it can have an adverse impact on the person. Some prefer to limit the concept of coping to responses that are voluntary and intentional (Compas, Connor-Smith, Saltzman, Thomsen, & Wadsworth, 2001); others include automatic and involuntary responses within the construct (Eisenberg, Fabes, & Guthrie, 1997; Skinner & Zimmer-Gembeck, 2007). Of course, distinguishing between voluntary and involuntary responses to stress is not necessarily easy; indeed, responses that begin as intentional may become automatic with repetition.

Even limiting the definition to responses that are voluntary, the definition given above is very broad. Not surprisingly, a good many distinctions have been made within the broad concept of coping (see also Compas et al., 2001; Folkman & Moskowitz, 2004; Skinner et al., 2003). A few of them are described in the sections that follow.

EMOTION-FOCUSED AND PROBLEM-FOCUSED COPING

Early on, Lazarus and Folkman (1984) and their colleagues made a basic distinction between problem-focused coping and emotion-focused coping. Problem-focused coping is aimed at the stressor itself and its physical impact. Problem-focused coping may entail taking steps to remove the stressor or evade its arrival, or to reduce its physical impact. Problem-focused coping in the face of an impending hurricane, for example, would include such actions as leaving the city for a safer place, putting up hurricane shutters, and obtaining supplies for a potential period without electric power. Emotion-focused coping stems from the fact that stress experiences generally lead to emotional distress. Emotion-focused coping is aimed at preventing, minimizing, or reducing this distress. Because there are many ways to try to reduce distress, emotion-focused coping includes an extraordinarily wide range of potential responses.

Once this distinction is made between problem-focused and emotion-focused coping, a number of other points arise. First, although the distinction may be useful, it does not apply easily to all coping responses. That is, some coping responses do not fit neatly into either category. For example, self-blame is hardly an attempt to remove the stressor; it may be an attempt to alleviate distress, but it often has the opposite effect. In contrast to that example, some responses can fit into either category, depending on what effect is intended. For example, people can seek social support to help them out in problem-focused efforts or to help in soothing distress emotion.

A second point concerns the fit between properties of the stressor and the adaptive value of the response. It is generally believed that the controllability of the stressor influences whether the person tends to turn to problem-focused or emotion-focused coping and how effective these classes of coping responses are. Problem-focused coping is well-suited if the stressor seems controllable; emotion-focused coping is better-suited if the stressor seems uncontrollable (Park, Armeli, & Tennen, 2004).

Third, although problem-focused and emotion-focused coping have different immediate goals, they often facilitate one another. For example, engaging in effective problem-solving strategies tends (indirectly) to reduce emotional distress. Engaging in effective emotion-focused coping may help the person face a problem more calmly and generate better problem-focused strategies.

APPROACH AND AVOIDANCE COPING

Another very important distinction among responses is between approach and avoidance coping, also labeled engagement versus disengagement coping (Roth & Cohen, 1986; Skinner et al., 2003). Approach coping represents efforts to deal directly with the stressor or the emotions evoked by it (as described just above). Avoidance strategies are attempts to escape, in one way or another, from having to deal with the stressor.

Disengagement coping is often emotion-focused: an attempt to escape from feelings of distress. Sometimes this kind of coping is almost literally an effort to act as though the stressor does not exist, so that the person does not have to react. An example is wishful thinking and fantasy, which temporarily distance the person from the stressor. Another example is denial that creates a boundary between reality and the person's experience.

Avoidance coping can be useful in the short term, in that it often does provide an opportunity for emotions to calm. It is generally ineffective in the longer term, however, when the stressor the person is confronting poses a real threat that will have to be faced eventually. If you go shopping at the mall to avoid thinking about a problem, the problem will still be there when you get home. Indeed, for many stressors, the longer it is avoided, the more difficult and urgent the problem becomes. Finally, some kinds of disengagement coping create problems of their own. Excessive use of alcohol or drugs can create social and health problems, and shopping or gambling as an escape can create financial problems.

POSITIVE, MEANING-FOCUSED, AND SPIRITUAL COPING

It has become increasingly clear that positive as well as negative experiences occur during periods of stress and adversity. For example, people report both negative emotions and positive emotions during stressful periods (e.g., Andrykowski, Brady, & Hunt, 1993; Norekvål et al., 2008). Although the evidence is mixed (Pressman & Cohen, 2005), there is also some basis for holding that positive emotions per se can have beneficial effects on health (Folkman & Moskowitz, 2000, 2004; Frederickson, Mancuso, Branigan, & Tugade, 2000). Thus, there is reason

to try to cope with adversity by finding experiences that induce positive emotions.

Another positive occurrence that is sometimes associated with stress is experiencing positive life changes, or finding meaning, in response to stressors (e.g., Jim & Jacobsen, 2008; Park, Lechner, Antoni, & Stanton, 2009; Tomich & Helgeson, 2004). Several terms have been used to refer to this sort of experience. Labels include *stress-related growth* (Park, Cohen, & Murch, 1996), *post-traumatic growth* (Tedeschi & Calhoun, 2004), and *benefit finding* (Tomich & Helgeson, 2004). Finding benefits in adversity has been linked to other positive psychosocial outcomes (Carver & Antoni, 2004; Helgeson, Reynolds, & Tomich, 2006). The responses that fall under these category labels are often treated as equivalent, but the labels appear to capture several phenomena that are distinguishable from each other (Sears, Stanton, & Danoff-Burg, 2003; Weaver, Llabre, Lechner, Penedo, & Antoni, 2008).

Another class of coping that has drawn widespread interest in recent years is coping through spirituality or religiosity. Spirituality and religiosity are distinct concepts (Zinnbauer & Pargament, 2005), but they are often treated together. It is a little hard to pin down exactly what this kind of coping consists of. Use of spiritual or religious coping may mean attending religious services and activities; it may mean engaging in frequent prayer; it may mean taking strength in one's faith or convictions; it may mean turning oneself over to a higher power. These are not the same activities, though they do often co-occur.

This class of coping response appears to focus mostly on distress emotions. Religious or spiritual coping is generally aimed (at least partly) at producing a sense of peace. In some circumstances, however, it can be thought of as indirect problem-focused coping. For example, the coping may involve praying for a stressful situation to change. Spiritual/religious coping appears to be common among people with chronic illnesses, such as HIV/AIDS (Cotton et al., 2006), cancer (Vachon, 2008), and chronic pain (Büssing et al., 2009). This may reflect the fact that these diseases have an uncontrollable nature that may be amenable to spiritual/religious coping strategies (Baldacchino & Draper, 2001).

CONCLUSIONS AND METHODOLOGICAL ISSUES

This brief review of distinctions among types of coping has been far from exhaustive (Compas et al., 2001; Skinner et al., 2003). Even so, it makes clear that there are many ways to group coping responses. No single distinction fully captures the structure of coping. Various kinds of analyses indicate clearly that coping incorporates multiple dimensions (Skinner et al., 2003). Unfortunately, the various distinctions do not form a neat matrix into which specific coping responses can be sorted. The distinction that may matter most is the one made between approach (engagement) versus avoidance (disengagement) coping. In general, approach coping keeps the person engaged in the effort to deal with the stressor; avoidance coping amounts to a tacit admission of defeat.

Many people are interested in coping primarily because they are interested in whether coping influences well-being. As studies address that question, a large number of methodological issues arise (Carver, 2006). One of the most difficult is how, and how often, to assess coping. Conceptually, coping is an ever-changing response to constantly evolving situational demands. The procedures of most coping studies do not reflect this conceptualization very well, however. Many of the studies that would be widely viewed as relatively good representatives of research on this topic assessed coping only once a week, or once a month, across the span of adapting to some stressor. Usually the coping measure asks the extent to which the person has engaged in various responses over the past day (or week). Those studies tell us very little about how the timing, order, combination, or duration of coping influences the outcome of interest, but such factors may be quite important.

Tennen, Affleck, Armeli, and Carney (2000) have proposed that a great deal is lost when we study coping across large aggregations of people without looking at what goes on within the person over time. They argued that people use emotion-focused coping mostly after they have tried problem-focused coping and found that it did not take care of the problem. This position suggests an approach to research that is very different from the typical study of the past. In this view, the question is whether (and how) the person changes from one sort of coping to another, across assessment points, as a function of ineffectiveness of the first response. Tennen et al. (2000) argued quite convincingly that, in order to answer these questions, coping must be assessed online and repeatedly. Unfortunately, not much work of that sort has yet been done.

STRESS, COPING, AND HEALTH

As noted just above, in some ways the ultimate question regarding coping (at least for the intended audience of this book) is whether it has an impact on health. Much of the research on coping has focused on psychosocial outcomes—emotional well-being and quality of life—or on physiological responses that occur very early in the pathway toward illness. What can be said about how coping affects physical health per se is limited (much more is known about effects of stress on health than about coping and health). We can, however, point to some issues that lie hidden behind that question.

Relative health in this context is the presence versus absence of a diagnosable, verifiable illness. Outcomes pertaining to health, however, are more varied than might be immediately apparent. They include disease "promotion" (initiation of the disease versus not), disease

progression (how quickly an early form of the disease advances), recurrence of disease, and mortality or survival time. This diversity among outcomes raises more methodological issues. For example, it is possible that stress and coping affect some outcomes but not others (e.g., progression but not promotion). Indeed, it is possible that stress and coping affect outcomes for some diseases but not for others (e.g., cardiovascular disease but not cancer). This complexity among possibilities means that to generate a clear conclusion about the role of coping in health requires the study of coping effects regarding diverse outcomes for diverse diseases. It would be overstepping at this point to make sweeping statements about effects of stress or specific coping strategies on "health" or "disease" in general.

COPING AND HEALTH: BEHAVIORAL PATHWAYS

Another issue that must be considered in thinking about relations between coping and health concerns pathways of influence. It is often taken for granted that the pathway to illness is physiological reactivity and disease pathways that follow from that reactivity. However, there are also far simpler and more direct ways in which coping can influence health. For example, people sometimes cope by engaging in actions that are antithetical to health. This is a pathway to illness that sometimes is overlooked but is quite important.

As was noted when discussing the distinction between problem-focused and emotion-focused coping, there is great diversity among emotion-focused coping responses. Virtually anything a person does with the intent of diminishing distress can legitimately be called emotion-focused coping. Some of these behaviors have effects other than the desired one. Indeed, some of these behaviors can actively promote health problems.

Smoking, alcohol and drug use, and casual sex are all common ways to self-sooth, or to diminish negative emotions when under stress (cf. Cohen, Schwartz, Bromet, & Parkison, 1991; Holahan, Moos, Holahan, Cronkite, & Randall, 2003; Horowitz & White, 1991). Activities of this sort may reduce negative feelings over the short term, thereby serving a role as emotion-focused coping. However, in the longer term they can have adverse effects on health, including risk of lung cancer, automobile accidents, and HIV exposure.

One behavioral pathway by which maladaptive coping influences health is engaging in behaviors that are harmful. Another pathway is reducing or even abandoning health-supportive behaviors. For example, exercise and a well-balanced diet are important contributors to the maintenance of good health. Yet exercise and proper eating habits often fall by the wayside when people are under stress. Putting aside these health-promoting activities robs the person of the benefits he or she would otherwise experience (Smith & Leon, 1992). Abandoning these beneficial behaviors thus can be considered maladaptive coping.

PSYCHOPHYSIOLOGICAL PATHWAYS

Direct behavioral pathways to health or illness are clearly important. However, most discussions of stress, coping, and health proceed from a viewpoint that begins with negative events inducing distress emotions with all of their physiological concomitants. If the distress experienced is intense, prolonged, or repeated, one or another kind of disruption of one or more physiological system may develop. The physiological disruption then leads gradually to disease outcomes.

From this viewpoint, the main role of coping in health is to influence the intensity and longevity of the physiological responses. That is, coping is beneficial if it minimizes the initial distress or dampens or abbreviates the negative emotions, because it thereby constrains the opportunity for system disruption. Coping is ineffective if it in some way promotes, intensifies, or maintains distress and the associated physiological responses.

In addressing psychophysiological effects of stress and coping, one might focus at several levels of abstraction. The focus could be on the effects of episodic change in some endocrine or immune parameter. The focus could be on the emergence of an intermediate disease state such as atherosclerosis or the eventual emergence of full-blown clinical events such as heart attacks. Effect of coping on outcomes at all these levels has been examined, though certainly not exhaustively. Here are just a few relevant examples.

One set of physiological parameters that has received attention concerns the stress hormone cortisol. In general, problem-focused and approach coping styles both are related to lower overall levels of cortisol, more favorable diurnal cortisol rhythms, and faster recovery to normal patterns after a stressor (Mikolajczak, Roy, Luminet, Fillée, & de Timary, 2007; Nicolson, 1992; O'Donnell, Badrick, Kumari, & Steptoe, 2008; Sjogren, Leanderson, & Kristenson, 2006). Measures that reflect social integration and social support have also been linked to favorable cortisol profiles (O'Donnell et al., 2008). Social isolation (living alone and having little contact with friends and family, suggesting underutilization of social resources for coping in times of stress) predicts a greater cortisol response at awakening and greater cortisol output over the day (Grant, Hamer, & Steptoe, 2009). Higher levels of religiosity have also been associated with more favorable cortisol patterns in women with fibromyalgia (Dedert et al., 2004).

Coping responses have also been linked to variations in immune system functioning. For example, in studies of HIV patients, those who showed difficulty in recognizing and expressing their emotions had higher levels of an immune marker related to HIV disease progression (Temoshok et al., 2008). Also among HIV patients,

those expressing disengagement-coping tendencies had higher viral loads and lower immune cell counts (Wald, Dowling, & Temoshok, 2006). In a non-patient sample, instrumental coping was linked to better immune system functioning, along with lower HPA activation (Olff et al., 1995).

Another body of work examines disease progression. Studies have shown that denial coping and lower satisfaction with social support relate to the progression from HIV to AIDS (Leserman et al., 2000). Active coping and spirituality show some evidence of predicting slower disease progression (Ironson & Hayward, 2008). A meta-analysis of coping among men with prostate cancer found that approach coping (both problem-focused and emotion-focused) improved physical outcomes such as self-reported fatigue and physical well-being, and that avoidance coping was associated with lower self-reported physical functioning (Roesch et al., 2005).

Enough research has examined coping and health-related outcomes in nonclinical samples to warrant a meta-analysis (Penley, Tomaka, & Wiebe, 2002). This analysis found that certain kinds of problem-focused coping (self-control and use of social support) related positively to diverse kinds of good health outcomes (ranging from self-reports of symptoms to objective illness-related measures). Other types of coping (e.g., confrontive coping and wishful thinking) related to poorer health outcomes. There were also cases in which the controllability of the stressor and whether the stressor was acute or chronic moderated the relationship between coping and outcomes. For example, distancing was related to poorer health outcomes when the stressor was chronic and controllable; taking responsibility was related to poorer outcomes when the stressor was acute and uncontrollable.

Another meta-analysis was reported even more recently, on a more focused set of studies (Moskowitz, Hult, Bussolari, & Acree, 2009). All of these studies examined persons with HIV. Outcomes were categorized as emotional, health-related behavior, and physical. Coping that involved direct action and positive reappraisal (engagement types of coping) had consistently positive relations to better results across all categories of outcome. Disengagement coping was consistently associated with poorer outcomes.

CAUTIONS AND QUALIFICATIONS

Before concluding this brief discussion of coping and health, a bit more should be said about what the literature does and does not show. As was noted earlier, much more is known about effects of stress than about effects of coping. A good deal of research on coping, even research that bears on health, has other limitations. One limitation is that some of these studies rely on self-reported health outcomes. These are much less reliable as indicators of health than are objective outcomes, and must be interpreted much more cautiously.

Further, a good deal of the research on coping and health assesses coping tendencies in general rather than coping with a specific problem, or assesses at a single time point how people coped with a specific problem over an extended period. This research may be telling us about coping and health, but it also may be telling us about something different: personality and health. That is, personality is an important determinant of how a given person copes with a given stressor at a given moment (Carver & Connor-Smith, 2010; see also Smith & Kirby, Chapter 15 in this volume). Personality may be an important influence on outcomes even apart from coping.

As an example of how the line between these concepts can be blurred, consider the literature on optimism. Optimism is a personality trait, but the essence of this trait dimension has much in common with certain ways of coping (positive reframing, looking on the best side of things, moving forward with a positive outcome in mind). To the extent that optimism predicts favorable health-related outcomes (Chida & Steptoe, 2008; Ironson & Hayward, 2008; Segerstrom, 2005), an unanswered question remains. Are better outcomes a product of differences in coping, or are they a product of something else embedded in personality? This question actually pertains not just to optimism but to a good deal of the literature on coping and health.

COPING INTERVENTIONS

This chapter closes with a brief look at the possibility of changing one's coping responses in ways that may foster better health. An emerging literature, though limited, is suggesting that health benefits may follow from certain coping strategies. This has helped to encourage creation of interventions for people who already are suffering from various kinds of disease. Here are two examples (for a more thorough review, see de Ridder & Schreurs, 2001).

Antoni and his colleagues have developed a 10-week cognitive behavioral stress management intervention involving relaxation, cognitive restructuring, and coping skills training for women being treated for nonmetastatic breast cancer. This intervention is broad in focus, with the intention of enhancing skills for dealing effectively with all sorts of life stresses, not just those associated with cancer treatment. It has been shown to lead to improvement in a variety of psychosocial outcomes (Antoni et al., 2006a, 2006b). It also led to greater reductions in cortisol levels through a 12-month follow-up, compared with a control group (Phillips et al., 2008). Finally, it led to greater production of cytokines that are involved in tumor surveillance (Antoni et al., 2009). Many of these effects were also shown to be mediated by confidence in being able to use the techniques; the intervention had taught the women for relaxing when stressed.

Another research team developed a year-long intervention (4 months of weekly sessions and eight monthly

sessions), which trained breast cancer patients strategies to reduce stress, improve mood, and maintain treatment adherence. Again the intervention was broad in scope. This intervention improved symptoms and functional status, compared with what was seen in a control group (Andersen et al., 2007). A recent report indicated that it even increased survival rates (Andersen et al., 2008). This is a particularly encouraging result, given the substantial controversy about whether such interventions can influence survival.

A number of other coping-based interventions have been developed for other health populations. Examples include dyadic interventions for enhancing communication skills for persons with HIV and their partners (Fife, Scott, Fineberg, & Zwickl, 2008) and pain-specific coping skills for persons suffering from sickle cell anemia (Gil et al., 2000). Both of these are more focused than, for example, the Antoni et al.'s intervention. Yet both represent a kind of coping training, teaching people to handle specific aspects of difficult situation. It seems likely that further exploration of such coping-based interventions will be an important agenda for the future in behavioral medicine.

SUMMARY AND CONCLUSIONS

This chapter reviews some of the themes of the extensive literature on coping with stress. Psychological stress occurs when people confront situations that challenge their ability to deal with them. Psychological stress and the emotional reactions produced by that experience bring with them a host of physiological as well as behavioral reactions. Although behavioral reactions to stress sometimes influence health (e.g., they sometimes are health-impairing behaviors), most of the work linking stress to health focuses on how physiological reactions ultimately create damage or dysfunction in the body.

Coping is efforts to minimize the adverse reactions that stress can create. Some kinds of coping are aimed at diminishing the threat value of the stress-inducing event, thereby preventing or attenuating the physiological responses. Some kinds of coping are aimed at diminishing the emotional reactions to the threat, thereby either attenuating the physiological response or limiting its duration. Approach coping is making all of these kinds of efforts to limit the stressor's impact. Avoidant or disengagement coping, in contrast, is action that temporarily avoids dealing with the threat. Some kinds of avoidant coping are health-damaging in their own right; avoidant coping can also exacerbate the situation because it simply delays the inevitable—that is, the stressor generally has not gone away while the person was avoiding doing anything about it.

If certain kinds of coping are successful in reducing the physiological responses that yield health impairment, those ways of coping should be encouraged. If certain kinds of coping make reactions worse rather than better, those ways of coping should be discouraged. Efforts to link various aspects of coping to physical health generally address the physiological changes that do and do not follow from those various ways of coping. This research faces a number of obstacles, including the difficulty of separating the influences of various aspects of coping from each other in the complex world outside the lab, and including as well the difficulty of assessing rapid changes in coping across time and changing circumstances. Nonetheless, efforts to determine what are the least health-damaging ways to respond to adversity represent an important part of health science.

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18 Personality and Stress: Individual Differences in Exposure, Reactivity, Recovery, and Restoration

Paula G. Williams, Timothy W. Smith, Heather E. Gunn, and Bert N. Uchino

INTRODUCTION

Throughout its history, research on psychological stress has reflected the assumption that the magnitude, consequences, and perhaps even the nature of the stress response are shaped by enduring traits of the person. Individuals vary greatly in the extent to which they are exposed to stress, the magnitude and patterning of their physiological and emotional responses to potentially stressful life events and circumstances, the length of time it takes to recover from stressful events, and the extent to which there is adequate restoration during or following times of stress. Each of these stress processes—exposure, reactivity, recovery, and restoration—is a potential pathway to poor health (Hawkley & Cacioppo, 2003; Uchino, Smith, Holt-Lunstead, Campo, & Reblin, 2007). Variability in these processes is generally believed to reflect, at least in part, an individual's personality.

In this chapter, we examine how personality—characteristic ways of thinking, feeling, and behaving—influences each of these stress processes. Mechanisms for these associations are considered, including recent findings regarding the genetic and neurobiological underpinnings of temperament and personality that influence stress. We present a theoretical framework that may inform personality–stress associations and discuss the relevance for stress research of central conceptual perspectives on personality and related methodological issues in personality science. As an exhaustive review of these topics is beyond the scope of the chapter, an overview of relevant research is presented, along with a conceptual guide to the role of personality in stress.

CONCEPTUALIZATION AND MEASUREMENT OF PERSONALITY

Many challenges in the study of personality and stress would become more tractable through consistent incorporation of concepts and methods of current personality science. For example, many different personality characteristics have been studied, often with minimal attention to their overlap with previously studied traits. Further, basic issues in the measurement of personality, such as convergent and discriminant validity, are sometimes given minimal attention beyond an implicit assertion that scale labels and item content accurately and specifically identify the intended constructs. Hence, we echo prior warnings in noting that research in this area can unintentionally reinvent previously identified traits under new labels (Holroyd & Coyne, 1987) or fail to identify basic dimensions of risk and resilience within an illusory diversity of personality constructs (Smith & Williams, 1992). Personality constructs examined in the study of stress range from fundamental dimensions of personality (e.g., neuroticism) to much more specific traits (e.g., sense of coherence, rejection sensitivity), often without a conceptual framework to bridge the global-specific distinction. These constructs also range from broad elements of static personality structure (i.e., global traits) to more dynamic aspects of personality processes (e.g., appraisals, expectancies, goals). Personality variables included in studies of stress, therefore, vary widely in form as well as content. Finally, the study of personality and stress often suffers from a conceptual and empirical separation from research on interpersonal aspects of stress; examination of traits related to stress often involves the implicit removal of the person from the surrounding social context.

Three perspectives in current personality science are valuable in addressing these and other problems in conceptualization and measurement of personality in studies of stress. First, the five-factor model (FFM; see Table 18.1) is a widely accepted trait taxonomy (Digman, 1990) with well-validated measures (e.g., Costa & McCrae, 1992). As such, the FFM provides a nomological net (Cronbach & Meehl, 1955) for comparing, contrasting, validating, and integrating personality scales and concepts used to study stress (Marshall, Wortman, Vickers, Kusulas, & Hervig, 1994; Smith & Williams, 1992). The psychometric tradition in which the FFM is embedded includes well-established procedures for development and evaluation of measures (Ozer, 1999; West & Finch, 1997). Unfortunately, this essential aspect of personality science is used inconsistently in research on individual differences in aspects of stress. Examination of associations of individual scales used in stress research with the broad domains of the FFM and their components or facets (see Table 18.1) would help to

Table 18.1 ■ Elements of the Five-Factor Model of Personality

Trait	Opposite Pole	Facets
Neuroticism	Emotional stability	Anxiety, angry hostility, depression, self-consciousness, impulsiveness, vulnerability
Extraversion	Introversion	Warmth, gregariousness, assertiveness, activity, excitement-seeking, positive emotion
Openness	Closed mindedness	Fantasy, aesthetics, feelings, actions, ideas, values
Agreeableness	Antagonism	Trust, straightforwardness, altruism, compliance, modesty, tender-mindedness
Conscientiousness	Unreliability	Competence, order, dutifulness, achievement striving, self-discipline, deliberation

Note: Adapted from "Professional Manual: Revised NEO Personality Inventory (NEO-PI-R) and the NEO Five-Factor Inventory (NEO-FFI)" by Costa, P.T., Jr., and McCrae, R. R., 1992, Odessa, FL: Psychological Assessment Resources.

identify common dimensions of risk and resilience as well as more specific traits related to stress. This cataloging of scales and traits used in the study of personality and stress could help foster a more systematic, integrated, and cumulative literature.

In this chapter, the primary labels used to designate traits examined in stress research correspond to the domain labels of the Revised NEO Personality Inventory (NEO-PI-R) (Costa & McCrae, 1992), a frequently utilized measure of the FFM: neuroticism, extraversion, openness to experience, agreeableness, and conscientiousness (see Table 18.1). Because of its longstanding association with stress and health, the Type A behavior pattern (i.e., competitiveness, achievement striving, impatience, hostility, excessive job involvement, and emphatic speech) must also be considered. Although articulation of the Type A behavior pattern arose out of medical and epidemiological research, as opposed to the personality tradition, the hostility aspect of this construct has been characterized in relation to the FFM. Costa, McCrae, and Dembroski (1989) presented evidence that hostility is related to aspects of neuroticism (especially the "angry hostility" facet) and to low agreeableness (i.e., antagonism). Similarly, other important traits in research on personality and stress, such as optimism, were also developed outside of the FFM, but they can be usefully related to elements of the FFM taxonomy (Marshall, Wortman, Kusulas, Hervig, & Vickers, 1992; Smith, Pope, Rhodewalt, & Poulton, 1989).

The FFM is particularly useful in clarifying *which* aspects of personality influence stress; it less useful in describing *how* personality influences stress. That is, the traits of the FFM primarily describe characteristics that people *have* rather than things they *do* (Cantor, 1990). The latter type of analysis can be useful in understanding the processes that might link personality with stress. There have been important efforts to link FFM traits to dynamic personality processes (e.g., McCrae & Costa, 1996), but a second major aspect of personality science—the social–cognitive perspective (Mischel & Shoda, 1998)—is more useful in describing the processes through which enduring characteristics of individuals influence day-to-day stress and adaptation.

Theory and research within the social–cognitive perspective have not achieved the same level of consensus as the FFM in terms of a widely accepted taxonomy of these "middle units" of personality that lie between broad traits and specific behavior (McAdams, 1995). Yet, valuable descriptions of this domain have been offered (Mischel & Shoda, 1998). Examples of these more specific and active personality characteristics and processes include the following: mental representations of self, others, and relationships (i.e., schemas) or interaction sequences (i.e., scripts); appraisals, encodings, or attributions regarding people and situations; motivational constructs such as expectancies, goals, and life tasks; self-regulation and coping; and strategies, competencies, and tactics in goal-directed action.

In this perspective, personality is described through the content of such characteristics (e.g., positive versus negative representations of others) as well as the associations among them (i.e., easily and rapidly activated negative scripts and schemas following appraisals of threat). Beyond their relative emphases on personality structure versus process, a major difference between traditional trait approaches such as the FFM and the social–cognitive view involves the patterns of consistency in behavior that characterize personality. Rather than broad patterns described by trait approaches that essentially represent averages in the behavior that is displayed consistently across situations, the social–cognitive view focuses on patterns of variability in behavior that reflect consistent responses to variations in psychologically distinct situations (Mischel, 2004). "If . . . then . . ." patterns of situation-specific responses, or "behavioral signatures" (Mischel, 2004), are seen as more accurate descriptions of individual differences in behavior. The FFM traits generally describe broad regularities in behavior, or cross-situational main effects, in a person by situation interaction model of behavior. In contrast, elements of the social–cognitive approach provide a more contextualized and dynamic account of individual differences. For example, the personality of an individual who experiences considerable stress and anxiety when interacting with supervisors at work and while making presentations to coworkers, but not in interactions with significant others, clearly differs from that of someone who displays the opposite situational pattern of stress (i.e., tense in close relationships but relaxed at work)—even if on average they both experience similar overall levels of stress and anxiety.

The social–cognitive and trait (e.g., FFM) approaches are complementary rather than necessarily mutually exclusive, and there are a growing number of integrative efforts examining social–cognitive correlates of FFM

traits and similar personality dispositions (e.g., Gambone & Contrada, 2002; Graziano, Jensen-Campbell, & Hair, 1996). The social–cognitive perspective might be particularly useful in the development of stress-reducing interventions, by identifying psychological mechanisms linking personality traits to various aspects of stress.

Optimism versus pessimism is an example of a personality construct widely studied in the stress literature that falls within the social–cognitive perspective. Individual differences in optimism–pessimism reflect generalized outcome expectancies, such that optimists expect positive outcomes whereas pessimists generally expect negative outcomes. Based in social–cognitive models of behavioral self-regulation and related motivational processes (Scheier & Carver, 1992), this trait describes individual differences in responses to disruptions or difficulties in goal-directed behavior, such that optimists persist in goal-directed coping, whereas pessimists do not. This conceptual description is clearly more mechanistic or process-oriented than that of static trait constructs, and it involves a fairly specific, rather than global, individual difference.

Studies of personality are a major component of the broader study of psychosocial influences on stress. Generally, such psychosocial factors are separated into characteristics of people (i.e., personality traits) and characteristics of the social contexts they inhabit (e.g., social isolation, conflict in close relationships, chronic job stress). Yet personality characteristics and aspects of the social environment are reciprocally related; personality traits both influence and are influenced by experiences in personal relationships and at work (Roberts, Caspi, & Moffitt, 2003; Robins, Caspi, & Moffitt, 2002). Further, some social–environmental factors related to the experience and effects of stress, such as social support, demonstrate stability over time and across situations, significant correlations with personality traits, and evidence of heritability. In these ways, social–environmental characteristics examined in stress research often "behave" like personality variables. Traditionally, personality research conceptualizes personality and social circumstances as separate sources of influence on behavior, emotion, and stress, which interact only statistically (Endler & Magnusson, 1976). Yet, personality influences exposure to levels and types of stressors encountered at home and work, rather than only moderating responses to this hypothetically separate source of influence on stress responses. The conventional separation of social–environmental and personality variables could impede the development of integrative models of risk and resilience factors in stress research.

A third major perspective in current personality science—the interpersonal view (Kiesler, 1996; Pincus & Ansell, 2003)—can be valuable in this regard. Sullivan defined personality as "the relatively enduring pattern of interpersonal situations which characterize a human life" (1953, p. 111). In the interpersonal approach, personality and social situations are reciprocally related, as they are in the social–cognitive perspective (Bandura, 1978; Mischel & Shoda, 1998). In interpersonal theory, the concept that describes the mechanics of this reciprocal influence is the transactional cycle (see Figure 18.1) (Carson, 1969; Kiesler, 1996; Pincus & Ansell, 2003), in which intraindividual components of personality (e.g., schemas, affect, expectancies, goals, appraisals) guide overt interpersonal behavior, as is the case in the social–cognitive approach. The actor's behavior influences the covert or internal experience (e.g., affect, appraisals) of interaction partners, often specifically in ways that increase the likelihood that the partner's responses will confirm the initial actor's beliefs and expectations. Given their generally negative expectations, for example, characteristically cynical and distrusting persons are likely to behave in a cold, defensive, or quarrelsome manner, increasing the likelihood that interaction partners will respond similarly rather than disconfirm the initial actor's expectancies by expressing warmth (Wagner, Kiesler, & Schmidt, 1995). This transactional process promotes consistency in

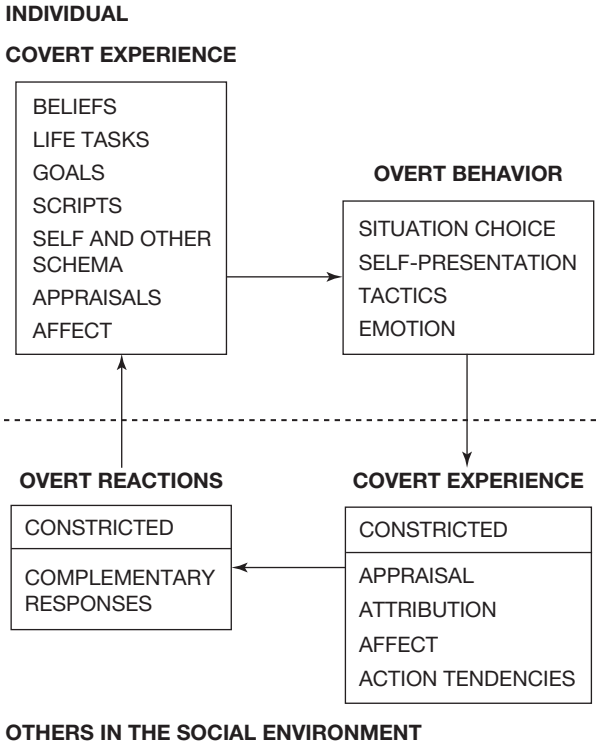

Figure 18.1 ■ *The transactional cycle*: An actor's covert experiences or internal responses influence his or her overt behavior. The actor's behavior, in turn, influences and restricts the interaction partner's covert experiences, leading that partner to behave overtly in response in ways that complement the initial actor's behavior, as when the actor's hostile expectations and overt behavior evoke hostility in return, or expressions of warmth evoke warm responses. Originally adapted from "Contemporary Interpersonal Theory and Research: Personality, Psychopathology, and Psychotherapy," by D. J. Kiesler (Ed.), 1996, New York: Wiley. Reprinted with permission from Gallo, L.C., & Smith, T.W. (1999). Patterns of hostility and social support: Conceptualizing psychosocial risk factors as a characteristic of the person and the environment. *Journal of Research in Personality*, *33*, 281–310.

social interactions that represents stability in personality in the interpersonal approach (Caspi, Bem, & Elder, 1989; Smith & Spiro, 2002). As described later, these same transactional processes can foster generally high or low levels of daily stress and stable levels of social support or isolation.

In the interpersonal perspective, individual differences in social behavior (i.e., personality traits) and the tone of social situations or interactions are described using two basic dimensions (see Figure 18.2). The affiliation axis of the interpersonal circumplex (IPC) (Kiesler, 1983; Wiggins, 1979) is defined by friendliness or warmth versus hostility, quarrelsomeness, or coldness. The control axis is defined by dominance versus submissiveness. The IPC can be used (Gurtman & Pincus, 2003) to compare, contrast, and integrate both personality traits (Gallo & Smith, 1998) and aspects of the social environment that are related to stress (Trobst, 2000). This integrative function of the interpersonal approach can be enhanced with a version of the IPC that also includes the FFM (Trapnell & Wiggins, 1990). The IPC affiliation and dominance axes are rotational equivalents of the FFM traits of agreeableness versus antagonism and extraversion versus introversion (McCrae & Costa, 1989); extraversion reflects somewhat warm dominance, whereas agreeableness reflects somewhat submissive friendliness.

Overall, the interpersonal approach combines assets of the FFM and social–cognitive approaches in facilitating integrative research on personality and stress by including both structural and dynamic concepts and methods. It further expands this integrative potential by means of its applicability to both personality factors and social–environmental influences on stress. Of particular relevance to understanding personality and stress, a socially dominant interpersonal style, including loud, rapid, and emphatic speech and a tendency to "cut off" and "talk over" others during social interaction, is associated with poorer health, particularly with regard to coronary heart disease (Houston, Chesney, Black, Cates, & Hecker, 1992), as are other indications of dominance (Smith et al., 2008). Further, effortful attempts to exert influence or control over others during social interaction evoke heightened physiological indicators of stress (Smith, Allred, Morrison, & Carlson, 1989; Smith, Ruiz, & Uchino, 2000), and subhuman primate models of atherosclerosis (e.g., Kaplan & Manuck, 1998) have demonstrated associations between social dominance, stress, and health. Hence, an additional potential contribution of the interpersonal perspective is its extension of influences on stress beyond the widely studied dimension of affiliation to the less frequently studied control or dominance dimension of personality and social life.

It is important to note that most studies of personality and stress have relied on self-report measures of personality. Hence, in addition to methodological issues involving convergent and discriminant validity of personality measures, recent research on the predictive utility of other methods of personality assessment could be usefully applied to stress research. Interview-based behavioral ratings or ratings provided by informants are used in some studies, but this is an exception to the general rule of self-reports. Importantly, interview-based or informant ratings are often better predictors of stress and health endpoints than are self-report measures (Miller, Smith, Turner, Guijarro, & Hallet, 1996; Smith et al., 2008). Self-report measures of personality and ratings by other informants or interviewers converge significantly, but only modestly, and often are differentially related to outcomes of interest (e.g., Oltmanns & Turkheimer, 2006). Hence, the nearly complete reliance on self-report assessments could be producing a misleading account of personality as an influence on stress, one that may underestimate the importance of personality variables.

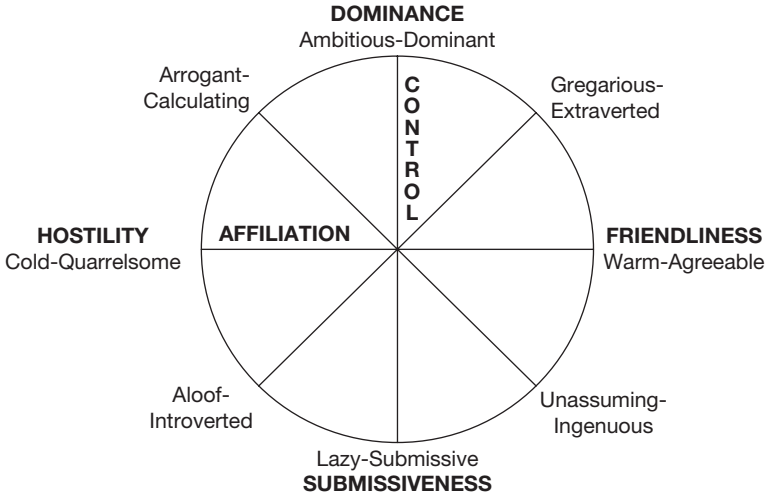

Figure 18.2 ■ *The interpersonal circumplex*: Individual differences in social behavior and specific interpersonal responses can be organized as blends of the two main dimensions of affiliation and control.

EMERGING PERSPECTIVES ON THE NEUROBIOLOGY OF PERSONALITY

Research on stress and adaptation has increasingly taken a brain-based approach (McEwen, 2007; Uchino et al., 2007). Similarly, our understanding of the associations between personality and stress processes can also be informed by recent developments in the neuroscience of personality and individual differences, through advances in molecular genetics, neuropsychological assessment, and functional neuroimaging techniques (Canli, 2006). In the modern era of neuroscience and behavioral genomics, research focuses on identifying specific biological pathways that contribute to complex cognitive and emotional behaviors. Research of this type contributes to our understanding of how individual differences in temperament and personality emerge and how such differences may confer vulnerability to poor stress regulation.

Temperament refers to individual differences in emotional, motor, and attentional reactivity and is often characterized as the initial state from which personality develops in interaction with experience (Rothbart, 2007). Importantly, temperament is considered to be biologically based, and identification of the underlying neural networks has become a focus of research (e.g., Posner, Rothbart, & Sheese, 2007). The FFM traits have been characterized with respect to the underlying temperament dimensions (Rothbart, 2007; Shiner & Caspi, 2003). Dimensions of temperament and FFM traits show significant heritability (e.g., Jang, McCrae, Angleitner, Riemann, & Livesley, 1998; Plomin et al., 1993), leading to research examining the genetic underpinnings of these individual differences. The "candidate gene association approach" involves testing the relationship between a particular phenotype (e.g., personality traits) and a specific allele of a gene. For example, relevant to personality associations with stress, variations in genes controlling serotonin are strongly implicated in individual differences in neuroticism–anxiety–depression. Moreover, variation in the serotonin transporter gene (5-HTTLPR) has been found to moderate the influence of stressful life events on major depression (Caspi et al., 2003), suggesting that this gene may underlie individual differences in stress responses.

Research utilizing neuroimaging techniques to examine brain activity among individuals with particular genetic variations and during particular cognitive–emotional tasks also holds promise for understanding personality associations with stress responses. For example, individuals with 5-HTTLPR S allele exhibit increased amygdala activity while processing emotional information (Hariri et al., 2002), suggesting that anxiety and fearfulness associated with the short allele may reflect hyperresponsiveness of the amygdala to relevant environmental stimuli. "Bottom-up" brain circuitry, mediated by the basal forebrain cholinergic system, has reciprocal connections with the amygdala and projections to the cerebral cortex (Berntson, Sarter, & Cacioppo, 2003)—important potential pathways for the exacerbation and amplification of stress-related responses (Uchino et al., 2007). Recent research has also highlighted the brain circuitry involving connections between the limbic system, particularly the amygdala, and the prefrontal cortex (PFC) in emotion regulation. Regions of the PFC are involved in "top-down" processing of emotion input and are central brain regions for executive functioning in general. Executive functioning constitutes a multifaceted construct comprising a number of basic neurocognitive processes, including conceptual reasoning; working memory; cognitive flexibility; response selection, inhibition, and initiation; set formation; and set maintenance (Suchy, 2009). Together, these processes allow us to generate goals and plans, modify our behavior in response to changes in the environment, and follow through and execute necessary actions in order to achieve goals. The fact that serotonergic functioning has been linked to both depressive vulnerabilities and impulsive aggressiveness—seemingly very distinct individual differences—may reflect the fact that a serotonergic neurotransmitter system that underpins executive functioning or self-regulation is a common contributing factor in both (Carver, Johnson, & Joorman, 2008).

Importantly, individual differences in executive functioning have been identified and are associated with stress regulation as well as with personality traits (Williams, Suchy, & Rau, 2009). These same PFC circuits, for example, are associated with parasympathetic activation that is important in both dampening sympathetically mediated stress responses and in the rapid and efficient mobilization of coping behavior and resources through temporary release of inhibition of those sympathetic responses (Porges, 2007; Thayer & Lane, 2000; 2007; 2009). Thus, some neural structures or circuits (e.g., amygdala) clearly contribute to stress reactivity, whereas others (e.g., underpinnings of executive functions in the PFC) may influence the modulation of these responses. To the extent that executive functioning and associated parasympathetic activation contribute to effective coping and attenuation of sympathetic responses, these factors could influence levels of stress exposure, recovery, and restoration, in addition to the more commonly examined endpoint of stress reactivity. Overall, the emerging understanding of the neuropsychological underpinnings of personality, including associations with executive functioning, may elucidate mechanisms for personality–stress relations.

PERSONALITY AND STRESS REGULATION

Personality characteristics make individuals more or less vulnerable to the deleterious effects of stress. Although this proposition appears simple at first blush, the interrelations among personality, stress, emotional

maladjustment, and physical illness are quite complex. Personality might influence the experience of and response to stressful circumstances in a number of ways. For example, personality style might be related to stress by increasing the tendency to be exposed to stressors, by influencing an individual's reaction to life events and circumstances, by shortening or extending the length of time it takes an individual to "recover" from the effects of stress, or by affecting the restorative processes that are crucial to the body's ability to repair itself in response to stress (Uchino et al., 2007). Collectively, these processes comprise stress regulation.

STRESS EXPOSURE

A transactional stress moderation perspective on relations between personality and stress suggests a reciprocal association between individuals and their environments, consistent with the social–cognitive and interpersonal perspectives in personality discussed earlier. In this view, personality traits and stressful events are not independent influences on health; life stressors are not randomly distributed across levels of various personality traits. Rather, by the nature of personality style, individuals may be more or less likely to find themselves in, or create for themselves, stressful circumstances. Stress exposure may take the form of external events, often measured as "major life events" (e.g., divorce) or "daily hassles" (e.g., argument with a coworker). However, exposure may also involve cognitive processes such as anticipation of a stressor (worry) and mentally reimagined stressors (rumination).

Associations with Personality

There is considerable evidence that personality factors are related to differential stress exposure. Characteristic ways of thinking, feeling, and behaving will increase or decrease the probability of stressful circumstances. Within the FFM, neuroticism is the factor most consistently associated with increased stress exposure. Individuals high in neuroticism are more frequently exposed to major life events, daily hassles, and chronic stressors such as conflict in close relationships (Affleck, Tennen, Urrows, & Higgins, 1994; Bolger & Zuckerman, 1995; David, Green, Martin, & Suls, 1997; Gunthert, Cohen, & Armeli, 1999; Magnus, Diener, Fugita, & Pavot, 1993; Suls, Martin, & David, 1998). Neuroticism is also strongly associated with a propensity for worry and rumination (Kotov, Watson, Robles, & Schmidt, 2007). Thus, even in the absence of external events, anticipating events that have not yet occurred, and "reliving" prior events, increase the total stress exposure for neurotic individuals. Trait hostility, often considered to comprise components of neuroticism and of antagonism, is associated with social isolation and inadequate social support (Siegler et al., 2003) and increases in marital conflict over time (Baron et al., 2007).

Conscientiousness is associated with a variety of factors suggestive of *reduced* stress exposure. For example, conscientiousness is related to lower rates of divorce (Roberts & Bogg, 2004), a major life stressor among adults. It is also associated with greater educational attainment and career success, factors comprising socioeconomic status which is, broadly speaking, related to reduced stress exposure. Importantly, conscientiousness may moderate the effects of other emotional traits, such as neuroticism. Optimism is also associated with decreased stress exposure, particularly of an interpersonal nature. For example, in a diary study, Raikkonen, Matthews, Flory, Owens, and Gump (1999) found that optimism was related to less exposure to negative social exchanges. Similarly, optimism is associated with increasing levels of social support over time (Brissette, Scheier, & Carver, 2002).

Potential Mechanisms

Consideration of the hypothesized behavioral motivation systems that underlie neuroticism/negative affectivity can inform our understanding of why this personality factor is so strongly associated with stress exposure. Neuroticism/negative affectivity is thought to derive from a highly active behavioral inhibition system (Gray, 1987), increasing sensitivity to signs of threat or punishment. This sensitivity can, in turn, lead to defensive behavior that may create stressful situations. Greater sensitivity to threat is also associated with anticipatory anxiety and rumination, which will increase total stress exposure in vulnerable individuals. Moreover, characteristic coping strategies may also serve to diminish or prolong stress exposure, such as when emotion-focused strategies lead to amplification of negative affective states.

The interpersonal perspective may also provide a framework for understanding personality associations with stress exposure. Characteristic styles of interacting with others may either enhance social support, potentially reducing stress exposure, or provoke conflict, increasing stress exposure. For example, hostile individuals may interact with others in a quarrelsome manner that thwarts the probability of receiving social support. Thus, a hostile individual's style may both increase the probability of stressful circumstances and reduce the likelihood of having access to stress-buffering resources (Smith, Glazer, Ruiz, & Gallo, 2004).

Individual differences in executive functioning that underlie personality may also play a role in associations with stress exposure. This may, in part, explain associations between conscientiousness and reduced stress exposure. Individuals who are able to override dominant emotional tendencies or impulses, stay on task, stay organized, and meet goals will reduce the probability of experiencing stressful circumstances. Individuals with poor executive functioning, on the other hand, may struggle with substance use, impulsivity, risk-taking behavior,

time management, planning, and organization—all of which have the potential to be stress generating.

STRESS REACTIVITY

The term stress reactivity describes the immediate response to a potentially stressful event and involves one's perception of the event (i.e., appraisal; Lazarus & Folkman, 1984), subjective distress, and physiological arousal (e.g., increased heart rate [HR] and release of stress hormones, such as cortisol). The onset or progression of disease may be influenced through repeated activation of the sympathetic adrenomedullary (SAM) system and the hypothalamic–pituitary–adrenocortical (HPA) axis, which are central to the body's characteristic responses to stress. Studies of stress reactivity, therefore, often focus on cortisol, the stress hormone indicative of HPA axis activation, and systolic and diastolic blood pressure and HR, indicative of SAM-mediated cardiovascular activation. More recently, phasic changes in high-frequency HR variability (HF-HRV) or respiratory sinus arrhythmia (RSA), indicative of parasympathetic activation, have also been studied. Additionally, there are a variety of anatomical and neuroendocrine links between the nervous and immune systems, including immune cell receptors for neurotransmitters and hormones that are either produced or regulated by the nervous system (Ader, Felten, & Cohen, 2001), indicating that physiological responses to stress also include immune system changes (Segerstrom & Miller, 2004; Uchino et al., 2007).

It is also important to consider subjective distress responses to events as a component of stress reactivity, even if they occur in the absence of enhanced physiological reactivity. Subjective distress, particularly if communicated in social interactions, may serve to increase exposure to interpersonal conflict or prolong stress responses. Additionally, recent advances in neuroimaging provide an alternate perspective on "reactivity." For example, enhanced amygdala activation during the processing negative emotional stimuli might also be considered stress reactivity.

Associations with Personality

Physiological reactivity to stress is reliably associated with traits reflecting propensity to negative affect. Anger, hostility, and depression have been associated with elevations of both SAM and HPA system activation in response to stress (Smith & Ruiz, 2002). Findings regarding relations between individual differences in hostility and cardiovascular reactivity to laboratory stressors are particularly robust (Smith et al., 2004), though the effects may be particular to interpersonal stress (Suls & Wan, 1993). A recent meta-analysis of laboratory stressor studies found that the constellation of hostility, aggression, or Type A behavior was significantly associated with cardiovascular reactivity, whereas the constellation of anxiety, neuroticism, or negative affect evidenced associations with *decreased* cardiovascular reactivity (Chida & Hamer, 2008). However, chronic anxiety and depressive symptoms are associated with altered autonomic regulation of the cardiovascular system (Berntson et al., 2003; Carney, Freedland, Rich, & Jaffe, 1995; Watkins, Grossman, Krishnan, & Sherwood, 1998), which may be manifest in poorer cardiovascular recovery, as discussed later. Each of these negative affective traits, in turn, has been found to be associated with various aspects of immune functioning, both in terms of response to stressors and more enduring levels of immune activity (Segerstrom & Smith, 2006).

Historically, associations between openness to experience and stress have not received much attention; however, recent findings regarding openness and health outcomes in chronically ill populations (Ironson, O'Cleirigh, Weiss, Schneiderman, & Costa, 2008; Jonassaint et al., 2007) suggest that this personality factor may influence stress responses. In support of this notion, Oswald et al. (2006) found that low openness was associated with blunted cortisol responses to laboratory stressors (i.e., speech task, mental arithmetic). Recent data also indicate that high-open individuals evidence lesser sympathetic activation (i.e., increased blood pressure) and greater parasympathetic activation (i.e., HF-HRV) in response to stress, whereas low-open individuals evidence parasympathetic withdrawal and greater sympathetic reactivity (Williams, Rau, Cribbet, & Gunn, 2009).

One concern about associations between personality traits and physiological responses to controlled presentations of laboratory stressors involves the extent to which they occur in "real life." Ambulatory studies are particularly valuable in this regard. For example, optimism has been associated with lower ambulatory blood pressure during daily activities (Raikkonen et al., 1999), whereas hostility has been associated with higher levels (Benotsch, Christensen, & McKelvey, 1997; Brondolo et al., 2003; Guyll & Contrada, 1998). Although it is often difficult to determine which stress processes are most pertinent in daily stress studies, it is possible to disentangle exposure and physiological versus affective reactivity if diaries are appropriately structured (e.g., Uchino, Berg, Smith, Pearce, & Skinner, 2006). As noted earlier, individuals high in neuroticism/negative affectivity demonstrate both greater exposure and greater affective reactivity to daily events (Bolger & Zuckerman, 1995; Mroczek & Almeida, 2004; Suls & Martin, 2005). Additionally, neuroticism appears to confer vulnerability to depression primarily under conditions of high life stress (Kendler, Kuhn, & Prescott, 2004), suggesting greater affective reactivity to adverse life events. Neuroticism has also been consistently associated with activation of the amygdala and anterior cingulate cortex (ACC), a brain region with connections to the superomedial PFC, during processing of negative emotional information, particularly emotionally negative faces (Haas, Omura, Constable, & Canli,

2007). Thus, although neuroticism appears to be associated with less cardiovascular reactivity to stressors, it is associated with greater *emotional* reactivity.

Potential Mechanisms

A multitude of mechanisms have been proposed to explain the associations linking together the constellation of traits including hostility, aggression, and other Type A behaviors. Although the legacy of the Type A pattern has primarily focused on anger, hostility, and aggressiveness, research indicates that descriptions of this construct contained a second unhealthy trait—social dominance. One hypothesis for greater reactivity among individuals with these characteristics is that they make effortful attempts to exert control, particularly in interpersonal situations. As noted earlier, such effortful attempts to exert control or influence over others evoke increases in sympathetically mediated cardiovascular reactivity (Smith et al., 2000). Hostile–dominant individuals may also perceive hostile intent and threat to social status in ambiguous situations and respond with heightened anger (Smith et al., 2004).

It has been suggested that decreased cardiovascular reactivity to laboratory stressors among individuals high in neuroticism may be due to a heightened orienting response, which would result in decreased HR (Chida & Hamer, 2008). Indeed, increased vigilance to threat has been demonstrated to result in enhanced parasympathetic activation and decreased HR (Somsen, Jennings, & Van der Molen, 2004). In addition to imaging studies demonstrating enhanced activity of the ACC during processing of negative emotional information (Haas et al., 2007), neuroticism is also associated with ACC activation during cognitive conflict detection tasks that *do not* contain an emotional component (Luu, Collins, & Tucker, 2000). Moreover, individuals scoring high on a self-report measure of the behavioral inhibition system (Carver & White, 1994) evidence greater event-related potentials in conflict trials of the Go/No-Go task (Amodio, Master, Yee, & Taylor, 2008), which has been demonstrated to reflect greater ACC activity (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Yeung, Cohen, & Botvinick, 2004). These findings suggest that neuroticism may reflect a cognitive vulnerability involving enhanced conflict monitoring.

STRESS RECOVERY

In the context of the stress response, recovery typically refers to levels of emotional or physiological arousal after termination of the stressor or to the time required for the individual to return to baseline levels after termination of the stressor. In the case of cardiovascular recovery, it has been hypothesized that the duration of stress-related cardiovascular responses may be as important as the magnitude of initial reactivity in the development of cardiovascular diseases (Brosschot, Gerin, & Thayer, 2006; Schwartz et al., 2003). Indeed, poor cardiovascular recovery has been associated with increases in blood pressure over several years (Mosely & Linden, 2006; Stewart, Janicki, & Kamarck, 2006). In addition to recovery, researchers have noted that physiological responses to stress may also occur in anticipation of a stressor (worry) and when a prior stressor is mentally reimagined (rumination), leading to the suggestion of a more inclusive construct termed *prolonged activation* (Pieper & Brosschot, 2005).

Associations with Personality

Individual differences in hostility have been associated with delayed recovery of cardiovascular responses to stress, particularly anger provocation (e.g., Anderson, Linden, & Habia, 2005). Neuroticism and other anxiety-related traits are also associated with poorer cardiovascular recovery to laboratory stressors (Chida & Hamer, 2008). Moreover, individuals high in neuroticism tend to experience "negative emotional spillover" after the experience of a negative event and concomitant negative mood, meaning that negative mood states tend to persist over time (Suls & Martin, 2005). Thus, it takes longer for these individuals to recover from negative daily events.

Potential Mechanisms

Central to cardiovascular stress recovery is the activity of the parasympathetic nervous system. Of particular importance, parasympathetic activation, as indexed by HF-HRV (or RSA), is associated with PFC activity (Lane, Reiman, Ahern, & Thayer, 2001). PFC functioning figures prominently in the recently proposed neurovisceral integration model (Thayer & Lane, 2007; 2009). Specifically, this region supports stress-dampening self-regulatory activity through parasympathetic mechanisms, as reflected in higher RSA. For example, increases in RSA have been associated with self-regulatory effort (Segerstrom & Solberg-Nes, 2007) and with attempts to modulate negative emotions during stress (Butler, Wilhelm, & Gross, 2006). Thus, to the extent that personality factors are associated with PFC functioning, this may provide a mechanism for associations with prolonged activation in response to stressful events.

An additional mechanism central to stress recovery involves known associations between prolonged stress exposure and down-regulation of glucocorticoid receptors in the hippocampus (e.g., Sapolsky, 1996), which serve to terminate cortisol responses to stress. Thus, under conditions of persistent stress, normal regulatory feedback mechanisms can be disrupted, resulting in longer recovery. Further, animal research suggests that chronic stress also leads to glucocorticoid receptor down-regulation in the PFC contributing to decreased dopaminergic transmission and associated PFC cognitive deficits (Mizoguchi, Ishige, Takeda, Aburada, & Tabira, 2004). Thus, personality factors associated with chronic stress

exposure, such as neuroticism, may also confer vulnerability to prolonged cortisol responses to stress and PFC cognitive deficits that may lead to further decrements in parasympathetic tone.

Related to physiological recovery are the characteristic coping styles that accompany personality traits. Some coping strategies, such as rumination (Brosschot et al., 2006), may impede recovery following stressful events. To the extent that personality is reliably associated with stress-coping patterns, this may be an additional mechanism for prolonged activation. Indeed, prior research suggests that each trait of the FFM is significantly and independently related to different coping strategies and that personality interacts with type of stressor to predict coping responses (Lee-Baggley, Preece, & DeLongis, 2005). For example, individuals high in openness tend to engage in more adaptive, flexible coping when faced with stressors, which may serve to enhance physiological recovery. Neuroticism, on the other hand, is associated with emotion-focused strategies that may serve to prolong emotional and physiological responses to stress.

PERI- AND POSTSTRESS RESTORATION

During and after the experience of stress, restorative processes operate to "refresh, buttress, and repair various forms of cellular damage" and to return an individual to baseline levels of physiological activity (Cacioppo & Berntson, 2007). In a related conceptualization, "allostatic load" refers to the disruption of homeostatic mechanisms by repeated stress and/or system dysregulation, and it is restored by "allostasis" or a dynamic process of maintaining system balance (McEwen, 2007). Sleep, wound healing, and humoral immunity are examples of restorative processes. Additionally, one aspect of restoration corresponds closely to illness behavior—the capacity for some individuals to retreat from daily stress to recuperate following a time of increased stress and/or illness. A weakened immunological state may increase stress resulting in a positive feedback loop that may foster the development of more frequent or chronic illness (Cacioppo & Berntson, 2006). Although it has been less the focus of research compared with other aspects of the stress response, personality is associated with restoration, particularly sleep quality, making this another potential pathway by which personality may influence stress regulation.

Sleep quality has emerged as a potent predictor of poor health. Poor sleep, especially sleep deprivation, is related to impaired immune functioning (Lange, Perras, Fehm, & Born, 2003) and predicts all-cause mortality (Dew et al., 2003). Recent research suggests that even modest reductions in restorative sleep are associated with increased susceptibility to illness (Cohen, Doyle, Alper, Janicki-Deverts, & Turner, 2009) and coronary artery calcification (King et al., 2008) in otherwise healthy individuals. Importantly, sleep disruption appears to have negative effects on emotion regulation (Dinges et al., 1997; Yoo, Gujar, Hu, Jolesz, & Walker, 2007) and cognitive functioning (Van Dongen, Maislin, Mullington, & Dinges, 2003), suggesting the potential for escalating stress regulation difficulties under conditions of poor sleep.

Associations with Personality

Of the traditional personality factors, neuroticism and other anxiety-related constructs have been most consistently implicated in the incidence of poor sleep (Gray & Watson, 2002). Moreover, high trait anxious individuals have been found to take longer to fall asleep, have greater percentage of and more frequent transitions to light sleep, and show lower rapid eye movement density compared with low trait anxious individuals (Fuller, Waters, Binks, & Anderson, 1997). Hostility is also associated with poorer reported sleep quality in response to interpersonal conflict (Brissette & Cohen, 2002). Individuals high in conscientiousness, on the other hand, report better sleep quality than their less conscientious counterparts (Gray & Watson, 2002). Moreover, conscientiousness appears to moderate the extent to which neuroticism is associated with adverse effects of poor sleep, such as depressive symptoms and functional impairment (Williams & Moroz, 2009).

Potential Mechanisms

The development of sleep problems is highly related to presleep arousal (Harvey, 2002), reflected in cognitive, affective, and/or somatic indications of anxiety or tension occurring during the period between when the individual goes to bed but before sleep onset. Thus, personality factors associated with presleep arousal will also predict the development of stress-related sleep disturbance. For example, prolonged recovery and perseverative cognition in response to stress may be a mechanism by which individuals high in neuroticism develop sleep problems. Relatedly, emotion-focused coping, which is associated with neuroticism, predicts greater stress-related sleep disruption (Sadeh, Keinan, & Daon, 2004).

The combination of propensity toward negative affect (underlying neuroticism) and poor effortful control (underlying conscientiousness) is hypothesized to be associated with poor emotion regulation. Thus, individuals with this personality profile are likely to have poorer self-regulatory abilities, with stress-related sleep disruption further limiting their regulatory capacity. Consistent with this notion, sleepiness (presumably reflecting poor sleep quality) is related to enhanced bias toward threatening interpretations in an information processing paradigm (Ree & Harvey, 2006). Thus, individuals who are particularly sensitive to signs of threat (i.e., high neuroticism) and have difficulty regulating this tendency (i.e., low conscientiousness) would be most vulnerable to an enhancement of this effect under conditions of poor sleep.

An Integrative, Developmental Model of Personality and Stress Regulation

It is clear that the components of stress—exposure, reactivity, recovery, and restoration—are not independent. An integrative model of personality and stress should consider the associations among various stress processes. Figure 18.3 provides a schematic for considering personality effects on stress regulation. Personality can be viewed as the phenotypic expression of genetic propensities to particular neurobiological characteristics that interact with environmental experience. Underpinning individual differences in personality and stress regulation at the phenotypic level are parallel individual differences in more basic psychobiological factors, or endophenotypes (Gottesman & Gould, 2003). These include individual differences in (1) cognitive processes (e.g., effortful control or executive functioning), (2) physiological processes (e.g., tonic parasympathetic tone, sleep architecture), (3) brain circuits (e.g., amygdala–PFC pathways), and (4) neurotransmitter systems (e.g., serotonergic or dopaminergic systems). Thus, personality reflects one level of a multilevel individual differences perspective.

As described earlier, personality characteristics act as risk or resilience factors for exposure to stress, a necessary precursor to stress reactivity (i.e., reactivity occurs in response to a real or imagined stressor). Personality factors also moderate the associations between exposure and reactivity. That is, given the occurrence of an event, personality influences appraisal processes and physiological responses. Personality also moderates the duration of recovery, once a reactivity process has begun. Importantly, recovery, in turn, influences restorative processes. For example, individuals who have difficulty recovering from a stressful event (e.g., who experience prolonged distress and rumination) will be prone to high cognitive and somatic presleep arousal, which will influence sleep quality. Although associations among the stress processes are presented in a "feed forward" fashion (i.e., exposure is associated with restoration via reactivity and recovery) in Figure 18.3, there may be other potential pathways. For example, stress exposure may lead to behavioral adaptations (e.g., obtaining additional employment to cope with financial difficulties) that influence sleep quality, bypassing reactivity and recovery pathways. Regardless, once poor sleep quality is present, emotion regulation abilities and daily functioning are adversely affected, thereby creating fertile ground for further stress and illness. Consistent with this notion, sleep-deprived individuals exhibit greatly enhanced amygdala activity in response to emotional imagery, but decreased activity of the medial PFC, suggesting a disruption of the emotional modulation circuitry (Yoo et al., 2007). Through these multiple processes, personality may be related to the propensity for escalating difficulties under stressful circumstances. For example, neuroticism is associated with stronger negative reactions to recurring problems over time, a process Suls and Martin (2005) term the "neurotic cascade."

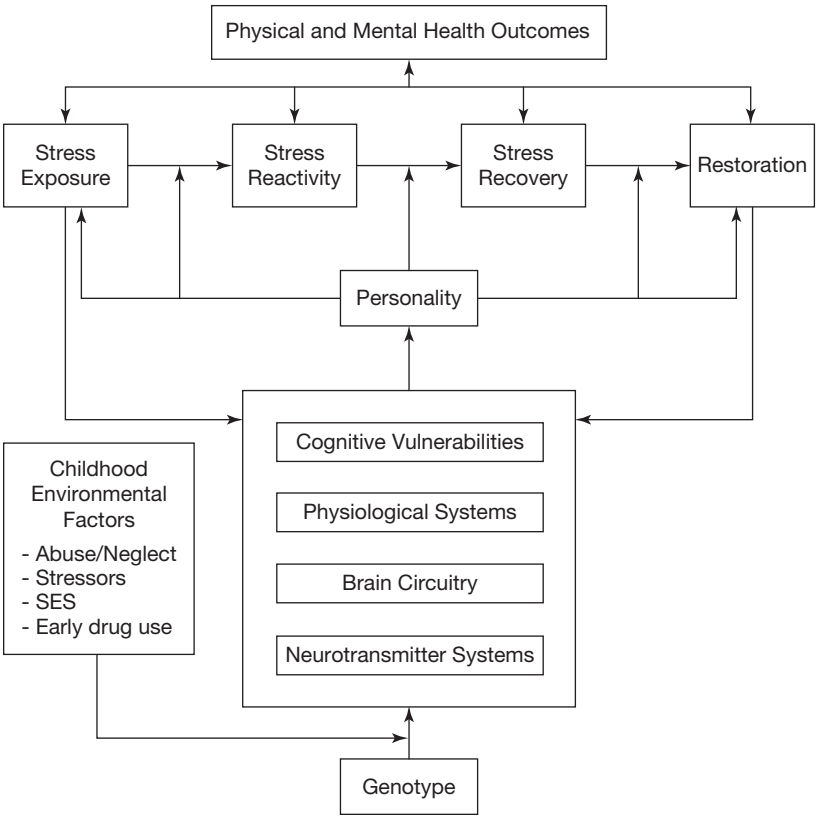

Figure 18.3 ■ *Schematic of individual differences in stress processes*: Personality is characterized as the phenotypic expression of genetic propensities to neurobiological characteristics that emerge in interaction with environmental experience over time. Dynamic reciprocal associations exist between these individual difference factors and stress exposure, reactivity, recovery, and restoration.

A developmental perspective is imperative to understanding personality associations with stress processes. Most studies examine personality–stress associations in a "slice" of time. As we have argued, particular personality profiles appear to place individuals at risk for negative stress-related trajectories, but the personality–stress relations may be different depending on when the association is measured. For example, early in the trajectory, individuals high in neuroticism may evidence increased cortisol reactivity. Later in the trajectory, after repeated exposure, enhanced mood response to events, prolonged recovery periods, and poor sleep quality, a level of allostatic load (and, potentially, depression) may be reached and anxiety-related traits will predict blunted cortisol responses.

Further, a growing body of evidence indicates that early-life experiences shape the physiological mechanisms identified as potentially linking personality and stress responses (Danese, Pariente, Caspi, Taylor, & Poulton, 2007; Gutman & Nemeroff, 2003; Luecken & Lemery, 2004; Taylor, Lerner, Sage, Lehman, & Seeman, 2004). For example, stress, particularly chronic traumatic stress, appears to undermine cognitive functioning though a variety of pathways including cortisol effects on the brain. Interestingly, Ellis and Boyce (2008) present evidence that highly protective environments may also result in high stress reactivity, in a process they term "biological sensitivity to context." That is, there may be a curvilinear relationship linking genetic vulnerability and environmental stress exposure to phenotypic expression of stress reactivity. Hence, research on personality and stress could also benefit from incorporation of recent developmental approaches to the emergence, continuity, and change of personality characteristics (Caspi, Harrington, Moffitt, Milne, & Poulton, 2006).

CONCLUSION

Early discussions of the role of personality in stress were primarily concerned with individual differences in the magnitude of stress reactivity (e.g., Cohen, 1980). That is, personality was conceptualized as accounting for variability in emotional and physiological responses to stressors. Later work examined the role of personality in stress exposure and reactivity (e.g., Bolger & Zuckerman, 1995). Yet, personality traits and processes are also clearly important in recovery and restoration. To fully capture and clarify these multiple roles of personality in stress and to best facilitate future research, at least three approaches to personality are needed. Well-established trait taxonomies such as the FFM and related well-validated assessment inventories are needed to compare, contrast, and ultimately integrate the plethora of personality characteristics studied in stress research. Without such comparative and integrative efforts to contend with an otherwise piecemeal literature, it will be virtually impossible to identify broad dimensions of risk and resilience. It will also be difficult to distinguish truly unique or specific personality influences on stress from those that seem unique on the basis of scale labels but are actually overlapping or redundant with similar traits studied under different names. In addition to the empirical referencing of personality variables used in stress research to established trait taxonomies such as the FFM, the further explication of associations of the FFM traits and their constituent facets with stress exposure, reactivity, recovery, and restoration constitutes an important agenda for both personality science and stress research.

In moving beyond evidence of associations between personality characteristics and aspects of the stress response to a more detailed understanding of underlying psychological mechanisms, the social–cognitive perspective in personality can be useful. The more dynamic and situation-specific individual difference concepts (e.g., schemas, scripts, appraisals) that comprise this perspective can help to clarify the proximal psychological influences on individual differences in various aspects of the stress response, perhaps in ways that facilitate the refinement of stress-reduction interventions.

The interpersonal perspective can also play a valuable role in explicating the specific and dynamic psychological influences on the stress response, especially because the most common sources of everyday stress involve social relationships and interactions (Bolger & Zuckerman, 1995). The interpersonal perspective also provides concepts and methods that facilitate the integration of personality and social influences on stress—two research domains that are often studied separately, to the detriment of both. Within the basic biopsychosocial framework underlying much of stress research, the interpersonal perspective can be seen as providing a bridge from the individual level of analysis in which most personality research typically occurs to the social level of analysis.

Similarly, emerging neuroscience perspectives on personality can provide a conceptual and empirical bridge between the psychological and biological levels of analysis. To the extent that the genetics and brain circuitry underlying personality constructs can be identified, along with individual differences in performance on cognitive and emotional tasks that reliably activate particular brain circuits, it will be possible to articulate neurobiological mechanisms for the effects of personality on stress responses over time. Individual differences in performance on such tasks and the patterns of neural activation that accompany them can be seen as endophenotypes underlying phenotypes involving personality and components of stress regulation. Yet, despite the promise of behavioral genetics and neuroscience in advancing our understanding of personality–stress relations, it is unlikely that single gene variations will have extensive explanatory value. Examining the contributions of multiple genes acting in response to environmental pressures is likely to be necessary for the development

of truly predictive markers that account for the majority of variance in any given phenotype, including personality factors related to stress.

Overall, a broad and inclusive view of personality science—ranging from the inherent and reciprocally determined social "embeddedness" of personality to its neurobiological underpinnings—has the potential to clarify individual differences in various aspects of the stress response. But this broader view of personality science also has the potential to provide an important integrative perspective on stress research in general. That is, while seemingly concerned exclusively with individual differences, the study of personality and stress can help identify the core biological, psychological, and social influences on stress by clarifying the nature and underpinnings of those individual differences (i.e., the study of "processes" and "individual differences" can exist together and inform one another in an integrative manner; see Posner & Rothbart, 2007). Thus, the concepts and methods in current personality science might prove to be useful in describing not just the individual differences in stress exposure, reactivity, recovery, and restoration that combine to characterize vulnerability and resilience but also the underlying nature of these key and universal components of human stress. A comprehensive perspective on personality includes accounts of both the universals of human nature and the myriad variations on this basic form (McAdams & Pals, 2006). Given this dual focus, personality science would seem to have much to offer in efforts to understand—and ultimately manage—human stress.

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19 Gender: Its Relationship to Stressor Exposure, Cognitive Appraisal/Coping Processes, Stress Responses, and Health Outcomes

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The puzzle of gender differences in stress continues to fascinate. In the search to understand how psychosocial factors influence health, focus has been brought to bear on elaborating the distinct experiences of stress in the lives of males and females. At least a part of this interest has grown out of the persuasive evidence linking stress to health (Cohen, Janicki-Deverts, & Miller, 2007; Hammen, 2005; Krantz & McCeney, 2002), coupled with the disparate patterns of gender differences in morbidity and mortality rates for stress-related conditions. The greater risk of men for the leading causes of death has led some to suggest that at least part of the health discrepancy is because men lead more stressful lives than do women (Davis, Matthews, & Twamley, 1999; Lawlor, Ebrahim, & Davey Smith, 2001). On the other hand, greater psychiatric morbidity for girls and women, particularly with respect to anxiety and depression, has led others to surmise that the burden of stress falls more heavily on females (Nolen-Hoeksema, 1987). A third perspective suggests that gender differences in stress may be more a matter of type rather than magnitude of stress, that is, males and females are exposed to or more vulnerable to stress in different life domains.

In this chapter, we review some of the evidence linking gender with the experience of stress. To frame the issue, we draw on the stress and coping model proposed by Lazarus and Folkman (1984), which distinguishes between exposure to objective events or circumstances and appraisal of those events or circumstances as stressful. Stress appraisal both fuels acute physiological changes and motivates coping responses that involve emotional, cognitive, and behavioral components. Gender may come into play at each phase of the stress experience, determining exposure to events and appraisal of those events as stressful as well as influencing physiological responses and coping efforts. It also may moderate the relation between stress and health outcomes, such that even when stress is comparable, one gender is more vulnerable to negative outcomes. We draw on work that has explicitly examined gender differences in stress exposure, appraisal, and responses, and focus particularly on adult samples. Finally, we conclude by proposing several areas ripe for future work to elaborate models linking gender and stress.

PSYCHOSOCIAL ACCOUNTS OF GENDER DIFFERENCES IN STRESS

Why would the sexes differ in their experience of stress? Some theorists have offered explanations for differences between males and females that emphasize biologically based factors (Hinojosa-Laborde, Chapa, Lange, & Haywood, 1999; Taylor et al., 2000), but gender is also a salient social category that profoundly influences how others regard us and how we view ourselves. Every society imposes a system of social rules and customs concerning what males and females are supposed to be and do, and people become embedded in gendered social roles that in turn mold their skills and beliefs about themselves. Here we consider two complementary explanations of gender differences in stress that point to psychosocial influences: a sociocultural account that highlights social roles and a gender-role socialization account that highlights person–situation interactions.

Social role theorists emphasize how the social structural conditions typical of the lives of boys and girls and of men and women determine their experience of stress (Eagly, 1987). Culture-specific, differential gender socialization practices lead to daily enactments of roles, responsibilities, and divisions of labor that shape exposure of males and females to particular kinds of stressors. Family and occupation represent the most salient roles for adults living in western industrialized countries and, despite substantial changes in the social roles of men and women in these countries over the past 50 years, those roles continue to be gender typed. Women are still more likely than men to fulfill the roles of homemaker and primary caretaker of children and aging parents, whereas men are more likely than women to be employed full time and to be the primary provider of the financial resources for the family (U.S. Bureau of Labor Statistics, 2001).

Social roles do more than shape individuals' exposure to particular kinds of stressful experiences; they also help to shape how individuals define and evaluate themselves. A body of evidence suggests that the content and structure of beliefs about self, or self-construals, differ between males and females (Cross & Madson, 1997; Markus & Oyserman, 1989). These self-construals

influence the types of information individuals attend to, how self-relevant information is processed and remembered, and what goals are most valued and pursued. Self-construals of women relative to men are more characterized by relational interdependence, wherein relationships are considered to be an integral part of one's self. According to this view, women's social information processing is heavily influenced by attention to the experiences of others in their social networks, and their goals are likely to include addressing others' needs. Consistent with a more interdependent self-construal, girls and women are more likely than boys and men to describe themselves in communal terms (e.g., sociable, attuned to others) and to value those attributes, in line with traditional gender roles for females (Rosenberg & Simmons, 1975; Twenge, 1997). In contrast, males' self-construals are characterized more by relational independence, wherein self identity is more tied to autonomy from others and social dominance. Based on differences in their self-construals, males and females should be inclined to find different types of circumstances stressful. For girls and women, events that occur to others in their networks or that threaten to damage significant relationships (e.g., family conflict) may be especially salient. For boys and men, on the other hand, events that threaten their autonomy or social position may be more problematic (e.g., job stress, financial strain).

These psychosocial accounts, emphasizing gender-linked social roles and psychological attributes, provide a theoretical basis for the expectation that males and females encounter, perceive, and respond differently to at least some common life circumstances. Although each account highlights particular aspects of a complex picture, in reality they are inextricably woven together and provide noncompeting predictions regarding how gender shapes the experience of stress. What does the evidence suggest?

GENDER DIFFERENCES IN STRESS EXPOSURE

When males and females are asked to report how affected they are by stress, girls and women typically say that they experience a greater impact than do boys and men (Davis et al., 1999). Women also are more likely than men to say that they are able to detect the distress of others and find it to be more "contagious" (Doherty & Orimoto, 1995). This is not especially surprising; females and males describe their general experience of stress in a way that is consistent with traditional gender-linked psychological attributes that emphasize sensitivity to emotional cues and expressivity for females and autonomy and dominance for males. Queries about the occurrence and perception of specific stressors or circumstances, however, yield a more varied picture and provide some clues about how gender-linked social roles shape gender differences in stress. Three classes of stress exposure have received the majority of attention: major life stressors, chronic stress, and episodic stress in daily life.

Major Life Events and Chronic Stress

Some of the earliest efforts to examine gender differences in a range of stressors relied on survey assessment to ask about the occurrence of past stressful major life events and their perceived stressfulness. Often incorporated into these inventories were items that assessed ongoing difficulty in important life domains, including family problems, financial stress, and work strain. The time frame covered in this assessment has varied, but generally spans the past several months to the past year, and counts of events are generally considered in aggregate. When individuals are presented with lists of discrete life events and chronic stressors, females indicate that they have experienced more stressors in the past than males. Nearly a decade ago, an extensive meta-analytic review of the literature evaluated findings generated from 119 survey studies of over 83,000 individuals and revealed that females did indeed report greater exposure to major and chronic stressors and were also more likely to rate stressors as intense compared to males (Davis et al., 1999). Although females were consistently disadvantaged, the gender differences tended to be quite modest in magnitude and were most pronounced for events classified as interpersonal versus other types of stressors.

More recent studies using similar survey methods also have suggested that the most consistent pattern may be greater self-reported exposure to interpersonal stressors among females. For example, Kendler, Thornton, and Prescott (2001) examined reports of the frequency of stressful life events over the preceding year in a sample of over 1,000 same- and opposite-sex twin pairs. Events related to interpersonal relations (e.g., loss of a confidant, problems getting along with others, crises of others) were more common in women. Events related to work, on the other hand, were equally common in men and women who were employed. Although most of the reports comparing life events in men and women have originated in samples drawn from the United States, the pattern of gender differences in the United States appears to hold for other western industrialized countries as well. In a random sample of over 6,000 adults from five European countries who were surveyed regarding the recent occurrence of life events, women reported encountering a greater number of life events overall, primarily due to their more frequent endorsement of stressful events having to do with close relatives, friends, and neighbors; by contrast, no gender differences were evident for job or financial problems (Dalgard et al., 2006).

When only the most extreme life events are considered, though, men appear to be at a disadvantage, consistently reporting a higher rate of exposure to potentially traumatic events than do women. On average, men are about 36% more likely than women to report that they

have experienced a traumatic event over their lifetimes (Tolin & Foa, 2006), and report a higher mean number of lifetime traumatic events (Breslau et al., 1998). Men and women also differ in the types of events they face. In their meta-analysis of 482 comparisons of the frequency of different types of traumatic events reported by males and females, Tolin and Foa (2006) found that males reported greater exposure to five of eight types: accidents, nonsexual assault, combat, disasters, witnessing death or injury, and illness or injury. Females were more likely than males to report having experienced two types of trauma: sexual abuse during childhood and sexual assault during adulthood. The sexes were similar in their reports of exposure to nonsexual abuse during childhood.

What explains sex differences in exposure to traumatic events? At least part of the increased overall prevalence for males relative to females may be due their greater rates of employment in gender-linked occupations that carry elevated risk. The most dangerous and injury-prone jobs are male dominated, including construction and transportation workers, firefighters, and police officers (Upson, 2004); men account for over 90% of job-related fatalities in the United States (U.S. Department of Labor, 2008). Elevated trauma exposure among men versus women may also be rooted in their greater propensity to engage in behaviors that increase the likelihood of trauma exposure, such as reckless driving, alcohol and drug use, and high-risk physical activities. Byrnes, Miller, and Schafer (1999) observed an average 6% higher rate of risk-taking among men compared to women across the 150 studies they reviewed. Gender-role attributes among males also may play a role in greater exposure to sexual traumas among females. Men who sexually assault or coerce women are more likely to describe themselves as high in traditional male-linked attributes like dominance and autonomy and low in traditional female-linked attributes like nurturance and compassion (Dean & Malamuth, 1997; Malamuth, Sockloskie, Koss, & Tanaka, 1991).

Daily Stress

Surveys that query individuals about past experiences have some important limitations, not the least of which is the potential error introduced by systematic recall biases and simple forgetting associated with retrospective reporting. Even interview-based assessments that provide prompts to enhance recall still rely on memory. Obtaining independent reports about life stressors from informants or archival records would address problems of accuracy, but these approaches are seldom practiced in research addressing gender and stress. Many of the problems of retrospective reporting inherent in the use of event inventories and interviews can be handled by repeated intensive measurement close in time to when the stressor or problem occurs through use of diary reports (Tennen, Affleck, Armeli, & Carney, 2000). Importantly, the advent of diary-based assessment represents more than a methodological fix for the problems inherent in retrospective reporting. Diary accounts, embedded as they are in the ebb and flow of everyday life, permit examination of gender differences not only in exposure to events but also in "reactivity" to events, in terms of either real-time perceptions of the severity of the stressors or emotional and coping responses to those events.

Data drawn from diary reports suggest daily stress reports for men and women vary in ways that are consistent with predictions based on gender-linked roles and psychological attributes. Perhaps the most extensive examination of daily events in men and women to date was conducted in the National Study of Daily Experiences (Almeida, Wethington, & Kessler, 2002), which included a sample of 1,031 individuals drawn from a nationally representative sample of adults in the United States. On eight consecutive evenings, individuals were interviewed by phone regarding any disagreements, work or school events, home events, discrimination, or events occurring to friends or family that had occurred during the previous 24 hours. Across all days, women reported slightly more days with at least one stressor than did men (41% vs. 37.5% of days for women and men, respectively) but a more similar proportion of days with more than one stressor (11.2% vs. 9.4% of days for women and men, respectively). Differences between the sexes in domains of stress were relatively uncommon but those that emerged were consistent with a gender-based account. Both sexes had arguments and tensions with others, but men reported more tensions at work, whereas women argued more over household chores and being treated with disrespect. Moreover, men reported more self-focused stressors involving financial and work problems, but women were more likely to report stressors related to network members.

A very similar pattern of gender differences in stress exposure emerged in work reported by Bolger, DeLongis, Kessler, and Wethington (1989) who examined daily work and home stress in a sample of married adults assessed daily for 6 weeks. Wives and husbands differed in reports on 4 of 10 event categories: Wives reported more daily home overloads and arguments with their children, whereas husbands reported more frequent work overloads and work arguments. Especially interesting were the "spillover effects" between work and home domains. Both husbands and wives experienced some modest carryover effects from work stress on one day to home stress on the next day. However, home stress spilled over to affect next-day work stress among husbands but not wives, a pattern that was not due to gender differences in number of hours worked, occupational prestige, or objective ratings of occupation demands. Thus women were able to avoid carrying over home stress into the workplace, and men were not. The authors speculated that gender-linked social roles for men do not include homemaking, which may leave them less skilled than women

at containing home-related stressors. These findings belie the commonly held view that women are especially vulnerable to conflicts between work and family roles on a day-to-day basis.

Clearly, reports of stress among men and women closely matched for important social roles can provide valuable clues about whether at least some of the gender differences in reports of daily stress are due primarily to differences in the social roles men and women occupy. In one of the few investigations to take this approach, Matthews and colleagues (2000) examined reports of interpersonal interactions across 3 days (2 workdays and 1 home day) in a sample of 100 employed men and women, matched for occupational prestige. At each query, individuals indicated whether an interpersonal interaction had occurred during the previous 30 minutes, the type of interaction (positive, neutral, conflictual), and their current mood state. They also reported on their end of day mood, the most stressful or difficult event that had happened to them that day, and the severity of that event. Men and women reported a similar number of conflictual interactions and a similar level of negative mood during the course of the day across all assessments. The sexes were also similar in their end-of-day ratings of mood and event severity for the worst event of the day. Occupational prestige, on the other hand, was related to daily conflict equally for men and women; those employed in lower compared to higher prestige positions reported more daily conflict. These findings suggest that not only occupational status (i.e., employed vs. unemployed) but also level of occupational prestige are critical, often overlooked features of the social context that shapes the experience of daily stress of men and women.

Even when they are employed in similar settings, men and women may have quite different perceptions of the stress associated with their work environment. Two models of work stress, the "job strain" and "effort–reward imbalance" models, have dominated the literature over the past three decades (Schnall & Landsbergis, 1994). The job strain model conceptualizes work stress as a job situation that is characterized by high psychological workload demands coupled with low decision latitude or control (Karasek, 1979), whereas the effort–reward imbalance approach construes work stress as a job situation in which the amount of personal effort expended outweighs the rewards that accrue (Siegrist, 1996). Do men and women differ in their experience of job stress? Some evidence gleaned from large epidemiological studies of employed adults suggests that when gender differences emerge, it is women who are at a disadvantage. For example, in a cohort of more than 10,000 British civil servants assessed in the Whitehall II study, 48% of women compared to 41% of men reported effort/reward imbalance at work (Kuper & Marmot, 2003). Likewise, among 3,000 employed men and women in the Framingham Offspring study, 29% of women and 16.4% of men reported conditions of high job strain at work (Eaker, Sullivan, Kelly-Hayes, D'Agostino, & Benjamin, 2004), rates that were roughly comparable to those reported in a large sample of male and female municipal employees in the Finnish Public Sector Study (Kouvonen et al., 2005). When external raters evaluate the demands and control associated with particular job positions, high job strain more often characterizes the positions occupied by women than by men (Kuper & Marmot, 2003). Thus women are more often employed in occupations that entail high demands and low control than are men and are more likely to report experiencing those stressful work conditions.

Taken together, the empirical evidence suggests differences in gender-linked social roles play a central role in determining the types of events and circumstances that men and women encounter. The most consistent gender differences to emerge from retrospective accounts of events are more frequent reports of interpersonal life events and greater stressfulness ratings of those events among females, but greater exposure overall to severe traumas among males. When ordinary, everyday stressors are assessed day-to-day or within-day, a more nuanced picture of gender differences takes shape. In general, men and women do report experiencing daily stressors consistent with the gender-linked social roles they occupy, such that women experience more family and network events, and men more work and financial events. Yet when gender comparisons are made in one particular domain, employment, women seem to encounter more job-related stress than do men in large part because they are more likely to be employed in lower status, high strain jobs. Matching men and women on occupational status appears to eradicate gender differences in the experience of stress. Moreover, men show greater evidence of spillover of stress from one day to the next, and from home to work.

GENDER AND RESPONSES TO STRESS

Does the experience of stress elicit different short- or long-term responses in men and women? Approaches to answering this question have varied widely, ranging from focus on immediate affective, coping, and physiological changes to more sustained shifts in mental and physical health that follow stressful experiences. And, not surprisingly, the extent of gender differences in responses to stress varies depending on the nature of the stressor and of the outcome.

Affective Responses

Diary reports provide a window into the changes in negative mood that accompany the occurrence of day-to-day stressors. A body of work suggests that men and women are generally similar in the affective responses to daily interpersonal contacts overall (Barrett, Robin, Pietromonaco, & Eyssell, 1998). However, men appear to be more vulnerable than women to stressors that fall

within male social roles. On days when they experience a work or financial stressor, for example, men show greater increases in negative affect than do women (Almeida et al., 2002; Bolger et al., 1989). Even for men and women who hold jobs of similar status, work strain is more strongly associated with end of day negative mood for men than for women (Matthews et al., 2000). The evidence regarding particular vulnerability of women to gender-linked stressors of daily life is much less consistent. Some findings suggest that on days when women and men report interpersonal conflict or other network events, women report greater increases in distress than do men (Bolger et al., 1989). In other instances, the findings suggest that the relation between increases in daily interpersonal stressors and same-day negative affect does not vary by gender (Matthews et al., 2000; Mohr et al., 2003), even for interpersonal events that may be particularly salient to women, like instances of sexism (Swim, Hyers, Cohen, & Ferguson, 2001) or child illness (Hobfoll, 1991).

For the most part, the effects of daily interpersonal events on mood are not sustained beyond the day on which they occur either for men or women. However, when gender differences in carryover effects emerge, it is men who appear to be more susceptible. For example, men experience an increase in negative affect on the days following increased conflict with their children, whereas women do not (Bolger et al., 1989). In a similar vein, interpersonal stress on one day is unrelated to negative affect on the next day for women and married men, but is related to increased next-day negative affect for unmarried men (Mohr et al., 2003).

Coping Strategies

Do males and females use different strategies to alleviate their experience of stress? Cognitive and behavioral responses to stress can include a wide array of approaches. Although coping responses have been clustered into distinct categories based on a variety of conceptual and empirical considerations, perhaps the most oft-used distinction for investigations of gender differences is one proposed by Lazarus and Folkman (1984). They classified coping responses as either problem focused or emotion focused. Problem-focused responses are those efforts aimed at altering the stressor itself, including taking action to change the situation and problem solving. Emotion-focused responses, in contrast, are directed toward altering one's emotional reaction to the stressor, and include a wide variety of strategies such as venting emotion, ruminating, and reframing the problem in a positive light. To the extent that coping responses align with gender-role stereotypes, men should be more inclined to confront a stressor directly, consistent with a problem-focused approach, whereas women should be more likely to try to manage the emotions elicited by the stressor and to seek social support. And, in fact, when individuals are asked about their usual responses to stress, the findings point to the view that men are more problem oriented and women more emotion oriented in their coping efforts (Billings & Moos, 1981; Folkman & Lazarus, 1980; Pearlin & Schooler, 1978).

Yet global reports of coping efforts seem to obscure rather than clarify whether and how males and females vary in their coping responses. Coping has been conceptualized as a dynamic process, set in motion by exposure to and appraisal of a particular event or situation, and evolving over time. In theory, then, coping efforts should be situation specific rather than dispositional. Because the nature of the stressor influences the selection of coping responses, examination of coping reports for men and women facing the same type of stressor is essential to identifying gender differences. Moreover, a fine-grained assessment of particular coping efforts, rather than broadly defined coping categories that include a host of different behaviors, provides the opportunity for a more nuanced evaluation of the evidence for gender difference in coping.

To address some of the limitations of earlier investigations of gender differences in coping, Tamres and colleagues (2002) conducted a quantitative review of 50 studies that have examined coping responses of men and women who faced similar stressors, ranging from chronic illness to dysphoric mood, infertility, and death of a child. Across all stressors, women reported that they used more coping strategies than men, including those categorized as problem or emotion focused. The most reliable overall difference between the sexes emerged for one strategy in particular: seeking social support for emotional reasons. Probing for gender differences in coping with gender role stereotypic stressors yielded a similar pattern of effects. That is, regardless of whether they faced relationship or achievement stress, women reported significantly greater use of problem-focused (e.g., active coping) and emotion-focused strategies (e.g., rumination), as well as social support seeking than did men. Women, then, endorse more strategies to cope with stress than do men, including those that might be considered gender-role consistent (i.e., emotion oriented; support seeking) and inconsistent (i.e., active, problem focused).

To what extent do gender differences in reports of general coping styles correspond with coping efforts in response to day-to-day stress? Measures of typical coping strategies do not appear to reflect the contemporaneous coping that occurs in response to specific current stressors. Among men and women reporting chronically high levels of work or marital stress, for example, women indicated that they typically cope with stress by seeking social support and using catharsis more than did men (Porter et al., 2000). When asked to report on their stress and coping multiple times per day over the course of 2 days, however, men and women were comparable in their experiences and behavior. There were no gender differences in reports of the total number of problems encountered, nor in the number of problems within work, marital, or other domains. Moreover, men and women did not differ in their appraisal of the stressfulness of the

problems, or in their diary reports of coping efforts. Men and women also report that they use similar approaches to deal with their day-to-day stressors in relationships, including arguing, avoiding, discussing, or ignoring the situation (Birditt, Fingerman, & Almeida, 2005).

In summary, gender differences in coping are especially likely to emerge when individuals are asked to report how they usually cope using more dispositional coping measures, rather than how they cope with particular situations on an ongoing basis using diary reports. This pattern seems to hold even in samples that include men and women who face similar types of stressors. What can account for this pattern of findings? One possibility is that global self-reports of coping are more likely than real time assessments to tap heuristics that guide how individuals recall their coping efforts (Porter et al., 2000). Thus individuals may be more inclined to recount coping efforts that are in line with gender role stereotypes when asked to provide global reports than when completing diary assessments in specific situations.

Physiological Responses

The contribution of gender to physiological responses to stress has been an explicit target of study for more than three decades (Collins & Frankenhaeuser, 1978; Frankenhaeuser, Dunne, & Lundberg, 1976). The most prominent early investigator in the area, Marianne Frankenhaeuser, proposed that gender differences in psychophysiological stress responses are determined primarily by the nature of the environmental demand (Frankenhaeuser, 1982). She asserted that responses to achievement demands should be more marked in men than women because such demands fall in a domain associated with a male gender role, and thus are more salient to men. She further predicted that sex differences in reactivity should disappear or even reverse in the face of demands that tap a domain falling within a female gender role. Her predictions rest on the assumption that when an individual's perceived competencies "match" environmental demands, he/she becomes highly engaged in the task, and consequently manifests heightened physiological activation. Situations that involve a "mismatch" between an individual's competencies and task demands, in contrast, should be less engaging and therefore elicit less pronounced physiological arousal.

Research probing gender differences in psychophysiological stress reactivity has tended to focus on a relatively limited set of markers of neuroendocrine arousal, particularly those reflecting hypothalamic-pituitary-adrenocortical axis (HPAC) and sympathetic-adrenomedullary axis (SAM) activity. HPAC activity has most often been assessed via changes in cortisol levels, whereas sympathetic activity has been assessed via changes in blood pressure and heart rate, as well as in catecholamine levels. A sizable body of evidence has accrued, much of it based on the examination of physiological responses to acute stressors with an achievement focus (e.g., mental arithmetic, academic examinations). In general, the findings point to more substantial stress-related increases in catecholamine, cortisol, and systolic blood pressure levels among men compared to women (Kudielka & Kirschbaum, 2005; Stoney, Davis, & Matthews, 1987), and suggest that heart rate responses to stressors may be higher in women compared to men (Kudielka, Buske-Kirschbaum, Hellhammer, & Kirschbaum, 2004; Stoney et al., 1987). Of course, because stressors that emphasize achievement are consistent with a male gender role, gender differences in psychophysiological arousal could be due at least in part to the extensive use of tasks that are more relevant and engaging for men.

To determine whether the magnitude of physiological arousal depends on the gender relevance of the stressor, a few investigations have contrasted responses of men and women to tasks selected a priori to be aligned with either a traditional male or female gender role. Much of the evidence is in line with Frankenhaueser's prediction that men and women are especially reactive to gender-relevant stress. For example, Stroud et al. reported that achievement tasks, which were perceived to require competitiveness and dominance to perform well, elicited increases in systolic blood pressure and cortisol that were more pronounced in men compared to women (Stroud, Niaura, & Stoney, 2001; Stroud, Salovey, & Epel, 2002). In contrast, socially oriented tasks involving social rejection and body image concerns, which were perceived to require emotionality and awareness of others' feelings for optimal performance, elicited heart rate (Stroud et al., 2001) and cortisol (Stroud et al., 2002) responses that were greater in women compared to men.

An alternative to examining wholly different tasks is to manipulate the gender relevance of the same task by altering task instructions to emphasize the importance of gender or gender-role related attributes for effective performance. This approach offers a significant methodological advantage by equating the task on all attributes except gender relevance. Smith, Limon, Gallo, and Ngu (1996) adopted this tack by examining how men and women responded to a scripted social task construed to emphasize the need to be either dominant and aggressive or communal and friendly for effective performance. Men showed greater increases in blood pressure than women to the dominance version of the task, whereas women showed greater increases in blood pressure than men to the communal version of the task. Although some null findings have been reported (Matthews, Davis, Stoney, Owens, & Caggiula, 1991), a similar pattern of findings linking gender relevant task instructions with reactivity has been reported by other investigators. For instance, when instructions for the cold pressor task emphasized the value of either male or female attributes for good performance, men showed greater blood pressure increases than women to the male-relevant version of the task, while women showed greater blood pressure increases

than men to the female-relevant version (Kolk & van Well, 2007; Lash, Eisler, & Southard, 1995; Lash, Gillespie, Eisler, & Southard, 1991). The difficulty of the challenge also comes into play as a determinant of how reactive men and women are to gender-relevant stress. Findings from a programmatic series of studies manipulating both the gender relevance and ostensible difficulty of a cognitive task showed that reactivity to gender-relevant stress is most pronounced when the task is perceived as moderately difficult (Wright, Murray, Storey, & Williams, 1997).

The cumulative evidence from laboratory-based research points to the malleability of gender differences in physiologic responses to stress, with most of the findings derived from investigations that focused on cardiovascular reactivity. The extent to which demands are perceived as gender- or gender-role relevant, in concert with the perceived difficulty of achieving success, appear to play a substantial role in determining the magnitude and direction of differences in reactivity between men and women. Whether the pattern of gender differences in response to laboratory-based stressors is also apparent in physiological reactivity to the types of recurring challenge faced in everyday life has not been extensively investigated. The limited data available from studies employing ambulatory assessment methods indicate that men and women do not differ appreciably in their blood pressure and heart rate changes in response to daily stressors, including social interactions and conflict (Guyll & Contrada, 1998; Matthews et al., 2000), and situations involving high perceived demands and low control (Kamarck et al., 1998).

HEALTH OUTCOMES

Health outcomes represent the last link in a chain of gender-linked differences in stress-related processes. An impressive body of research has elaborated the relations between stress and an array of health outcomes, including reproductive health (chapter 24), functional syndromes (chapter 29), and chronic pain (chapter 33). To examine the role of stress and gender in determining morbidity and mortality, we focus here on three common physical and mental health problems that disproportionately affect men or women: coronary heart disease (CHD), depression, and posttraumatic stress disorder (PTSD). Stress has been implicated in the development of CHD (for review see chapter 28; Kuper, Marmot, & Hemingway, 2002), depression (Kessler, 1997), and by definition, PTSD, and some empirical attention has been devoted to exploring whether stress exposure or responses mediate the relation between gender and risk for each of these health outcomes.

Coronary Heart Disease

CHD is the leading cause of death for both men and women, but as noted earlier, men have roughly twice the risk of women for CHD even after adjusting for conventional CHD risk factors, including smoking, obesity, and cholesterol (Barrett-Connor, 1997; Jousilahti, Vartiainen, Tuomilehto, & Puska, 1999). The extent to which gender differences in stress account for some of the excess CHD risk among men has been the target of speculation but relatively little empirical attention. In fact, research addressing this question has tended to focus on stress in one domain in particular: job-related stress.

A recent meta-analysis of prospective cohort studies reported that both job strain and effort-reward imbalance are risk factors for adverse cardiovascular clinical events (Kivimaki et al., 2006). Most of the evidence evidence relating job stress with CHD risk has been gleaned from samples of men, but a few studies have included men and women and conducted analyses that compare the sexes. Among the most widely cited investigations in this regard is the Whitehall II Study, which began following a cohort of over 10,000 British civil servants in 1985 (Marmot, Bosma, Hemingway, Brunner, & Stansfeld, 1997). After adjusting for age, employment grade, and conventional CHD risk factors, both high effort–reward imbalance and low job control were associated with roughly a twofold greater incidence of CHD at the 5-year follow-up, independent associations that held for both men and women (Bosma, Peter, Siegrist, & Marmot, 1998). Among employed individuals with established CHD, job strain also is related to increased risk of a future coronary event to a similar extent for men and women (Aboa-Eboule et al., 2007).

In contrast to findings linking job strain to poorer cardiovascular health, Eaker and her colleagues (2004) reported that job strain was unrelated to 10-year incidence of CHD in men or women in the Framingham Offspring Study. Somewhat surprisingly, it was the combination of high job demands and *high* (rather than low) levels of control that predicted nearly a threefold increase in risk of CHD compared to high demand-low control job strain, a relation that was evident only in women. The authors speculated that increased job control for women may collide with culturally based gender role expectations that highlight autonomy and dominance for men but not women. Thus, women in job positions with high decisional control may be faced with stress related to violating gender-role norms in the workplace. Only additional research that includes assessment of gender-linked attributes of individuals and their work environments can establish the validity of this account. In any event, the available evidence is not consistent with the notion that job stress confers greater CHD risk on men compared to women.

Attention to gender differences in stress-related CHD risk has broadened to include consideration of chronic strain in other important domains of life beyond work, in particular, home and family. As noted earlier, women continue to bear more responsibility than men for household maintenance and childcare, even when both spouses

are employed (Lundberg & Frankenhaeuser, 1999). Some investigators have proposed that because social roles related to family caretaking are more salient for women, the stress stemming from a lack of control over domestic conditions may be more deleterious to the cardiovascular health of women relative to men (Chandola, Kuper, Singh-Manoux, Bartley, & Marmot, 2004). In an initial test of this hypothesis in the Whitehall II Study data, Chandola and her colleagues (2004) found that women who perceived that they had little control at home were three times more likely to develop CHD compared to women with high control at home, even after adjusting for financial problems and conventional CHD risk factors. In contrast, control at home was unrelated to incident CHD among men.

Despite longstanding interest in the potential role of stress as a determinant of gender differences in CHD risk, relatively few investigations to date have compared men and women. None of the evidence accrued so far points to greater job stress-related vulnerability in terms of CHD outcomes of men relative to women. Indeed the most intriguing data hint that stress related to home life accounts for poorer cardiovascular outcomes only for women. The results highlight the potential value of broader and more thorough assessment of gender-relevant stress and its impact on cardiovascular health, and of attention to mechanisms that may account for gender differences between stress and CHD outcomes.

Depression

Perhaps the most oft-studied mental health outcome in response to stress is depression, a condition that will affect approximately 16% of adults during their lifetime. Depression exacts an enormous toll, accounting for not only markedly diminished psychological and social functioning but also greater morbidity from physical health conditions, including cardiovascular disease (Rugulies, 2002). Attempts to understand the roughly twofold greater risk of depression among females relative to males have focused on biological as well as psychosocial factors as potentially important. Research addressing biological factors has centered primarily on female reproductive hormones, in part because the gender difference in depression emerges during the pubertal transition and diminish postmenopause (Angold, Costello, & Worthman, 1998; Freeman et al., 2004). Accruing data suggest that fluctuations in reproductive hormones, particularly estrogen, may contribute to increased risk of depressive symptoms during puberty, the menstrual cycle, the postpartum period, and perimenopause in vulnerable women (Freeman et al., 2004; Payne, 2003). However, reproductive hormones alone account for only a small proportion of the variance in depressive symptoms in adolescent girls and women (Brooks-Gunn & Warren, 1989), suggesting that hormonal differences play a relatively minor role in explaining the greater risk of depression among females compared to males. In addition to reproductive hormones, genetic factors have also been proposed as a biological determinant of gender differences in depression. The majority of findings, though, suggest that heritability for depression is strong and equivalent for males and females (Eaves et al., 1997; Kendler & Prescott, 1999).

Of the psychosocial factors that have been proffered to explain greater depression risk among females relative to males, gender differences in the experience of stress is often cited as a likely culprit. In fact, aggregate measures of exposure to stressful life events and chronic strain have been linked to depression (Hammen, 2005), but they do not consistently explain the gender difference in risk (Dalgard et al., 2006; Kendler et al., 2001). The aggregation of diverse life events may obscure gender differences in the occurrence of stressors that are especially depressogenic, however (Kessler, 1997; Sherrill et al., 1997). One such stressor is childhood sexual abuse, which predisposes both men and women to depression but which occurs more commonly to girls than to boys (Tolin & Foa, 2006). In fact, roughly one third of the gender difference in rates of adult depression may be attributable to higher incidence of women's exposure to sexual assault and abuse, particularly during childhood and adolescence (Cutler & Nolen-Hoeksema, 1991). Relative to men, women also report more current ongoing role burdens and relationship strain, and these stressors partially mediate the link between gender and depression risk (Nolen-Hoeksema, Larson, & Grayson, 1999).

A second possible psychosocial mechanism accounting for gender differences in depression is greater vulnerability of women relative to men to the effects of similar stressors. The evidence has not been entirely consistent, but does suggest that men and women do not differ in their sensitivity to most types of stressful life events, including financial stressors, housing problems, illness, or marital problems (Dalgard et al., 2006; Kendler et al., 2001; Turner & Avison, 2003). Some data, though, point to several types of stress that may be especially depressogenic for one gender versus the other. Women appear to be more vulnerable to developing depression in the face of network conflict and events that occur to others in their networks, whereas men appear more at risk to the effects of job loss, divorce/separation, and widowhood (cf. Horwitz, White, & Howell-White, 1996; Kendler et al., 2001; Kessler & McLeod, 1984; Lee, DeMaris, Bavin, & Sullivan, 2001; Stroebe & Stroebe, 1983).

What might explain gender-specific vulnerability to depression associated with particular types of life events? One possibility is that women and men are particularly susceptible to events that confer a sense of loss or humiliation in a highly valued gender-linked social role (Brown, 2002). Based on this account, job loss may confer a more pronounced risk for depression among men compared with women partly because it represents the loss of a gender-linked role that at least traditionally has been

more highly valued for men (Eales, 1988; Weiss, 1990). For women, in contrast, social network events may pose a more serious threat. In a study of married couples exposed to similar life events, for example, women were more at risk than men for depression when they reported events involving children, housing, or reproduction (Nazroo, Edwards, & Brown, 1997). Importantly, the increased risk was only apparent for women who were more invested in their traditional roles as parent and homemaker; less traditional women did not experience increased risk of depression associated with these events.

Gender-linked social roles and/or personality attributes may also provide resources that mitigate the impact of the particular kinds of stress. For example, the lower risk of depression among women compared to men following the loss of a spouse may be due in part to their greater access to other sources of interpersonal intimacy and support (Siegel & Kuykendall, 1990; Stroebe & Stroebe, 1983). On a practical, day-to-day basis, wives are more engaged than their husbands in organizing social events and maintaining contact with family and friends, termed "kinkeeping" (Rosenthal, 1985). Wives are also more likely to consider someone other than their spouse as a confidant (Lowenthal & Clayton, 1968) and to have more diverse sources of emotional support than are husbands (Antonucci & Akiyama, 1987; Fuhrer & Stansfeld, 2002). When a spouse dies, their well-established, intimate social ties may leave women better equipped to weather the loss than are men. Compared to surviving husbands, surviving wives are more socially integrated, receive more emotional support, have more contact with their adult children, and are less lonely (Pinquart, 2003; Umberson, Wortman, & Kessler, 1992). The gender-linked expectation that men should be strong and stoic may also make it less likely that men ask for or are offered the social support that might alleviate some of the distress they experience during conjugal bereavement (Bennett, Hughes, & Smith, 2003).

In sum, the existing evidence hints that gender-linked social roles may confer both risk for and resistance to stress-related depression. On one hand, stressors that threaten valued gender-linked social roles may be especially depressogenic for men and women. On the other hand, psychosocial resources may accrue from occupying particular social roles that serve to buffer individuals from the affective impact of stressors. It is worth reiterating, however, that the links between gender-linked social roles and attributes, stress, and depression remain speculative in large measure because little of the existing empirical work has been theory driven.

Posttraumatic Stress Disorder

PTSD is a second mental health outcome, in addition to depression, that is precipitated by stress and linked to subsequent risk of health problems, including cardiovascular disease (Boscarino, 2004). Prospective evidence consistently points to lower exposure to traumatic events among females versus males, as noted earlier in this chapter. Yet despite less frequent exposure, females experience roughly twice the risk of developing PTSD following traumatic events compared to males (Breslau et al., 1998; Norris, 1992). Given this pattern of findings, some investigators have suggested that females have a general vulnerability to developing PTSD in response to all types of trauma (Gavranidou & Rosner, 2003). A recent review of several decades of work linking trauma exposure and PTSD, however, suggests that the magnitude of the gender difference in PTSD risk varies depending on the type of traumatic event. In their meta-analysis, Tolin and Foa (2006) found no gender differences in the conditional risk of PTSD associated with childhood sexual and nonsexual abuse, and adult sexual assault. In contrast, females were between 1.3 and 4.1 times more likely than males to develop PTSD in association with other types of events (e.g., accidents, disasters, combat, nonsexual assault); the most marked gender difference in conditional risk was associated with nonsexual assault. Males did not exhibit greater risk of PTSD compared to females for any type of event.

A number of possible explanations for the greater conditional probability of PTSD among females compared to males associated with most kinds of traumatic experiences have been explored, including gender differences in genetic contributions and in the prevalence of preexisting psychosocial risk factors for PTSD (Craske, 2003; McLean & Anderson, 2009; Olff, Langeland, Draijer, & Gersons, 2007; Saxe & Wolfe, 1999). PTSD symptoms after exposure to trauma, particularly assaultive trauma, are moderately heritable (Stein, Jang, Taylor, Vernon, & Livesley, 2002), but there is no evidence that the extent of heritability for anxiety disorders varies by gender (Hettema, Prescott, Myers, Neale, & Kendler, 2005). With regard to preexisting psychosocial risk factors, some evidence suggests that women are more likely than men to report a history of childhood abuse (Tolin & Foa, 2006), poor psychological adjustment prior to trauma exposure (Olff et al., 2007), and concurrent life stress (Davis et al., 1999). Controlling for known pretrauma risk factors diminishes but does not abolish the gender difference in PTSD risk, however (Breslau et al., 1998).

Much of the focus on understanding gender differences in PTSD vulnerability has centered on determining whether females are more likely than males to experience physiological, psychological, or social responses that increase the chance of developing PTSD. One line of work has explored gender differences in physiological arousal, particularly sympathetic nervous system activation, in the aftermath of exposure to trauma. Exaggerated or sustained sympathetic nervous system arousal following a traumatic event may facilitate an "overconsolidation" of the memory of the event, thereby increasing risk of subsequent PTSD (Pitman, 1989). Excessive sympathetic arousal may be particularly potent without the

counterregulating influence of cortisol (Resnick, Yehuda, Pitman, & Foy, 1995; Yehuda, McFarlane, & Shalev, 1998).

Do females show greater sympathetic arousal and/or less pronounced cortisol increases following exposure to traumatic events than do males? Findings gleaned from the small body of research comparing males and females suggest that gender differences in physiological activation shortly after exposure to traumatic events do not explain the greater PTSD morbidity among females. For example, higher heart rate levels in the hours to days following a traumatic event do indeed relate to increased risk of PTSD symptoms 4 to 12 months later in both children (Kassam-Adams, Garcia-Espana, Fein, & Winston, 2005) and adults (O'Donnell, Creamer, Elliott, & Bryant, 2007; Shalev et al., 1998; Zatzick et al., 2005). However, post-trauma heart rate levels shortly following the event are similar for males and females (Kassam-Adams et al., 2005; O'Donnell et al., 2007; Zatzick et al., 2005). Available evidence also suggests that women are not more likely than men to respond to trauma with a neuroendocrine profile reflecting heightened sympathetic and diminished HPA activity. A single study has assessed 15-hr samples of urinary epinephrine, norepinephrine, and cortisol levels of men and women 1 and 5 months following a motor vehicle accident (MVA: Hawk, Dougall, Ursano, & Baum, 2000). Women in the MVA group did not evince either elevations in catecholamine or decrements in cortisol levels compared to female controls at either time point. Rather, men involved in an MVA who also experienced PTSD symptoms tended to show elevated catecholamine levels (at both time points) and cortisol levels (at 1-month post-MVA) compared to male controls. The authors suggested that relations between heightened sympathetic activity and PTSD may apply to men but not to women.

Emotional, cognitive, and social responses following exposure to a traumatic event are among the most powerful predictors of PTSD (Brewin, Andrews, & Valentine, 2000), yet surprisingly little work has examined these proximal factors as potential mechanisms through which gender is linked to PTSD (Olff et al., 2007). The limited evidence does point to possible gender differences in responses to trauma that may help to explain why females appear to be more vulnerable. At least in retrospect, women more than men tend to report that they both viewed and responded to past traumatic events in ways that may heighten their ongoing sense of threat and inability to cope. When asked about their experience of a range of past traumatic events, for example, women report that they had more fear, shame, and anger associated with their most severe trauma (Bernat, Ronfeldt, Calhoun, & Arias, 1998), and that they were more likely to blame themselves and to see themselves in a more negative light (Tolin & Foa, 2002; Ullman & Filipas, 2005) compared to men. Females also retrospectively report that they view sexual trauma more negatively than do males. More than 70% of women but only 37% of men indicate that their experience of sexual abuse during childhood was negative, possibly because early abuse among women more often involved threat or force and occurred with close family members (Rind, Trowmovitch, & Bauserman, 1998). The pattern of gender differences in emotional evaluation of the trauma persists for assaults that occur during adulthood: 53% of women compared to 11% of men describe a past sexual assault as their worst-ever experience (Vrana & Lauterbach, 1994).

Because gender differences in evaluations of past events may be attributable to gender-related biases in recall, findings from investigations of contemporaneous responses to traumatic events can prove informative. In fact, some gender differences in negative evaluations of the trauma are evident when individuals are queried soon after the occurrence of a traumatic event. When assessed within the first several days after experiencing an MVA, for instance, women reported that the accident was more frightening than did men, despite the fact that women suffered less severe injuries (Ehlers, Mayou, & Bryant, 1998). These findings are in line with laboratory-based fear-conditioning studies, where women report greater levels of fear in response to standardized negative stimuli than do men, effects that are not accounted for by individual difference factors that are related to development of fear responses (e.g., anxiety sensitivity, trait anxiety; Kelly & Forsyth, 2007). However, it is not clear that gender differences in reports of fear generalize to other negative affects. For instance, when they were assessed within the first month after being the victim of a violent crime, women were not more likely than men to report feelings of shame and anger related to the trauma (Andrews, Brewin, Rose, & Kirk, 2000).

Some evidence suggests that gender differences in PTSD may be due to differences in the cognitive and behavioral strategies men and women employ to cope with the traumatic event. When asked how they coped with childhood abuse, for example, women were more likely than men to report that they used disengagement strategies, including social withdrawal and trying to forget the abuse, which were related to greater current PTSD symptom severity (Ullman & Filipas, 2005). A similar pattern emerged among ambulance workers exposed to repeated traumas, with more women than men indicating that they usually engaged in wishful thinking, mental disengagement, and suppression of trauma memories to deal with traumatic work-related incidents, all coping approaches that are typically linked to poorer outcomes (Clohessy & Ehlers, 1999). Among the most effective strategies for managing trauma-related emotions and memories is cognitive reappraisal, which involves reframing a traumatic event in less negative emotional terms (Bryant, Moulds, & Guthrie, 2001; Park & Blumberg, 2002). Little empirical attention has been directed toward addressing the possibility that women are less likely than men to attempt to reappraise a traumatic experience, but recent evidence gleaned from a sample of healthy adults provides some fuel for speculation. McCrae and colleagues (McRae, Ochsner, Mauss, Gabrieli, & Gross, 2008) used a

functional magnetic imaging paradigm to examine gender differences in reappraisal-related affect regulation in response to negatively valenced pictures. Their findings indicated that cognitive reappraisal appeared to be more automatic and less effortful for men. In particular, reappraisal was associated with less activation of the prefrontal cortex and greater decreases in amygdala activity in men compared with women. Thus, in the face of especially demanding circumstances, including trauma exposure, the ability to successfully down-regulate negative emotions via reappraisal may be compromised to a greater extent in women than in men.

The responses of social network members during and following trauma is among the strongest predictors of subsequent risk for PTSD (Brewin et al., 2000; Guay, Billette, & Marchand, 2006), and has been proffered as one potential factor explaining the link between gender and PTSD (Olff et al., 2007). Levels of social support following a trauma do not consistently vary by gender (Andrews, Brewin, & Rose, 2003), but a lack of support may be more deleterious for women than for men (Ahern et al., 2004; Andrews et al., 2003; King, King, Foy, Keane, & Fairbank, 1999). Moreover, women can experience more negative responses than men from family and friends in the aftermath of a traumatic event, a response that mediates at least part of the link between gender and subsequent PTSD (Andrews et al., 2003).

The available evidence, then, indicates that at least some of the increased risk of PTSD among women compared to men stems from their greater exposure to childhood trauma, their more negative evaluation of the trauma and of themselves, their use of less effective coping strategies, and less beneficial reactions from individuals in their social networks. Still unanswered is the question of how gender-linked attributes and social roles contribute to the greater vulnerability of women to PTSD. Programmatic work along this line has been relatively scarce, but several avenues have been proposed. One possibility is that gender-linked socialization fosters a greater willingness among women to acknowledge the experience of threat, fear, and uncontrollability, and to engage in more passive and avoidant coping strategies in response to traumatic events compared to men (McLean & Anderson, 2009; Norris, 1992; Olff et al., 2007). Further, their propensity to seek support from others in response to threat may diminish women's sense of self-efficacy (Craske, 2003), particularly if the support network does not respond adequately. On the other hand, traditional gender-role socialization for men may make it less acceptable for them than for women to avoid or withdraw from confronting their fears, resulting in a greater likelihood of exposure and habituation (McLean & Anderson, 2009). Undoubtedly, efforts to mitigate the deleterious effects of trauma will be strengthened by the elaboration and evaluation of comprehensive models that explicitly describe how gender comes into play (Olff et al., 2007).

CONCLUSIONS AND FUTURE DIRECTIONS

The field of stress research has advanced considerably over the past 30 years, and with it our understanding of the role of gender in the stress process. The shift from the use of survey methods that capture global self-reports to contemporaneous assessment of stress has provided both expected and surprising findings. Although women report more frequent exposure to childhood abuse and major and minor life events, men are more likely to experience traumatic events over their lifetimes. In their daily lives, women tend to report more network events and home-based stressors, whereas men report more work and job events, and stressors that are self-focused. Much of this difference, though, may be due to differences in employment and/or job status between women relative to men who are sampled. When women and men are well matched in employment status and occupational prestige, gender differences in stress tend to disappear. Moreover, there is little evidence of gender differences in coping or emotional reactivity to daily events, although some findings hint that it may be men rather than women who experience more emotional carryover from one day to the next, and from home to work. Men and women respond with heightened physiological arousal to standardized stressors that are gender relevant, but the limited evidence from ambulatory assessment in the field points to comparable autonomic arousal to the stressors of daily life. The most pronounced and consistent gender difference emerges in response to stressful and traumatic events, and particularly childhood abuse, where women are at much greater risk for depression and PTSD than are men.

Several avenues for continued exploration of the gender-stress relation hold promise. A pressing need in the literature is the assessment of broader, more diverse samples, which would provide important information regarding how social, cultural, and other environmental factors combine to shape gender differences in the experience of stress. Gender is not an isolated personal characteristic, but is intertwined with other aspects of one's identity, including social class, ethnicity, sexual orientation, and nationality. Yet nearly all of the research discussed here derives from heterosexual samples drawn from Western industrialized societies. Expansion of research populations would improve the validity and completeness of our models and their empirical support.

The field would benefit from continued focus on generating theory to connect the operation of gender and stress in everyday life. Models that explicitly incorporate gender-linked traits, cognitive factors, and social roles as mediators and moderators of the relations between gender and stress exposure, appraisal, coping, and outcomes would be especially valuable. One example in this regard is Nolen-Hoeksema's programmatic work examining how chronic role strain and a ruminative coping

style mediate the link between gender and depression (Nolen-Hoeksema, 1987; Nolen-Hoeksema & Girgus, 1994; Nolen-Hoeksema et al., 1999).

Emphasis on a lifespan development perspective would also extend our current conceptions of gender differences in the stress process. Life events and daily stressors have generally been assessed at very few points in time or within a relatively short time frame. Yet gender is an ongoing enactment rather than a stable, trait-like component of identity. For both males and females, environmental demands and role obligations shift over time, and interpretation of and coping with life circumstances take place in the context of an ever-growing body of life experience. The experience of stress must also shift as individuals mature and age, either as social roles change (e.g., from employee to retiree) or as individuals become more adept at regulating their exposure and responses to stress. For instance, the socioemotional selectivity theory proposed by Carstensen, Fung, and Charles (2003) suggests that as people age, they realize that their remaining years of life are limited and they invest more heavily in meaningful social relationships. To that end, they structure their social worlds to expand their opportunities for positive social contact and limit aversive social encounters. Thus, gender differences in exposure to stress, particularly to interpersonal stress, may diminish over a lifetime as men and women adopt more similar social goals. There also may be critical periods of development when gender differences in stress exposure, especially for traumatic events, have profound implications for later adaptation and functioning. As one example, differential exposure to sexual abuse between girls and boys in childhood may have a far reaching influence on stress exposure and responses into adulthood (Widom, 1989).

More frequent use of multiple methods and levels of assessment within individual investigations would also help to more fully elaborate models of gender and stress. Self-reports of stress and coping repeated over time have provided valuable clues about the role of gender in the stress process, and would be complemented by simultaneous assessment of more objective measures, such as physiological markers and behavioral observations. In a similar vein, examining the correspondence between gender differences that emerge in response to experimental manipulations of stress in the laboratory and those apparent in field assessments of daily stress would also illuminate when and how gender comes into play. By linking the day-to-day experiences of stress and coping assessed via diary and ambulatory approaches with subsequent psychological and physical health outcomes, we may be able to better discern how gender differences in the stress process affect longer term adaptation (e.g., Janicki, Kamarck, Shiffman, Sutton-Tyrrell, & Gwaltney, 2005). For example, contemporaneous assessment of day-to-day physiological activation, coping efforts, social network responses, and affective symptoms following the experience of a traumatic event would allow us to explore whether and how autonomic and effortful self-regulation varies by gender and predicts recovery. Such fine-grained evaluation can then be used to inform prevention and intervention efforts that may be tailored for men or women, if the evidence warrants it.

Few doubt that gender shapes how we experience the world, in obvious and subtle ways, and ultimately impacts our health. Developing more sophisticated conceptual models and methods is critical in our progress toward understanding the complex links between gender and stress. It is also needed to facilitate discovery of ways to prevent and treat some of the most prevalent and costly health problems we face.

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20 Stress, Coping, and Adult Development

Carolyn M. Aldwin and Loriena Yancura

> Coping and development seem inherently inter-connected. No account of coping is complete without acknowledging the central role that age-graded factors play in shaping an individual's adaptation to stress . . . Likewise, no account of development is complete without a consideration of how individuals respond to stress.
>
> *Skinner & Edge, 2002, p. 77*

Stress, coping, and development are inherently intertwined: Stress and coping processes are affected by age, and aging processes are influenced by stress and coping. Across the lifespan, there are changes in both the types of stressors that are experienced and in the strategies used to cope with those stressors. The different patterns of change that are often observed depend partly upon the conceptualization and measurement of stress and coping. In one sense, vulnerability to stress may increase in late life, yet stress may also contribute to late-life adaptability by instigating or forming the context for personal development in adulthood, through a process often called posttraumatic or stress-related growth (SRG). Thus, this chapter will not only review developmental trends in stress and coping processes but also discuss the positive and negative effects of stress, which depend in large part on the types of coping strategies that individuals use.

STRESS AND AGING

The four types of stressors most commonly assessed are trauma, life events, daily stressors, and chronic stress. All of these categories are relevant to the experience of stress in late life. To our knowledge, there are no stressors that are unique to old age. However, the frequency and impact of stressors do vary by age and form the focus of this section.

TRAUMA AND AGING

Trauma is defined by the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed. [*DSM–IV*]; American Psychiatric Association, 1994) as events that involve serious threat to life or physical integrity, which may occur either to the individual or to his or her significant others. Types of trauma include being a victim of crime or exposure to natural or man-made disasters. Experiencing trauma often results in posttraumatic stress disorder (PTSD), which is a syndrome characterized by startle reactions, irritability and numbness, sleep disorders, depressions, and flashbacks. In an early review, Norris (1992) identified car accidents as the most common sources of trauma in older adults. Weintraub and Ruskin (1999) found little evidence to suggest that older adults differ from younger adults in the development or patterns of PTSD.

However, older adults are clearly more vulnerable to the *physical* effects of traumatic events. In any massive population disruptions, both infants and the elderly have higher mortality rates. In late life, this is largely due to the fact that chronic illnesses become acute and life threatening, due to disruptions in medicines, food, water, and exposure to various pathogens (Mokdad et al., 2005). Thus, elders with chronic health conditions such as cardiovascular disease or diabetes may succumb to these illnesses due to lack of medicines, dehydration, malnutrition, and so on. Older adults with mobility problems or who lack transportation may also be unable to flee danger from natural disasters, as witnessed by the tragedy of Hurricane Katrina. Even events that are not generally considered natural disasters, such as heat waves, may prove to be physically traumatic to older adults. For example, nearly 30,000 older people died in Europe in the heat waves of the summer of 2003 (Haines, Kovats, Campbell-Lendrum, & Corvalan, 2006).

Most studies of trauma in later life examine the long-term effects of major traumas such as combat exposure or experiencing the Holocaust (Sadavoy, 2007). These types of traumas can have long-lasting effects that can be seen as much as 50 years or more after their occurrence (Spiro, Schnurr, & Aldwin, 1994; Cook & Niederehe, 2007; Kahana et al., 1998). Such effects include standard PTSD symptoms, such as nightmares, startle reactions, intrusive memories, and anhedonia, the inability to experience pleasure. Sadavoy (2007) suggested that Holocaust survivors may show better adaptation than individuals with heavy combat experience. This difference may be due in part to selective survivorship (survivor effects), given how few individuals survived the Nazi death camps.

Yet Aldwin, Levenson, and Spiro (1994) found that perceiving positive aspects of military service may decrease the long-term effects of combat on PTSD symptoms. Furthermore, individuals who experienced PTSD earlier in life may have more physical and psychological symptoms in retirement (Schnurr, Lunney, Sengupta, & Spiro, 2005). Experiencing trauma in earlier life may also complicate important developmental tasks in later life, such as the life-review process (Lomranz, 1990; Westwood & McLean, 2007).

The Kings and their colleagues (King, King, Vickers, Davison, & Spiro, 2007) developed a new measure of late onset stress symptomology (LOSS) to capture the distress that older combat veterans may face in later life. It assesses rumination about combat experience. They note that distress symptoms may manifest as cognitive confusion in late life, and discuss evidence suggesting that trauma earlier in life may accelerate cognitive declines, which may trigger psychological distress. There is some evidence that experiencing normative late-life stressors such as bereavement may be associated with LOSS scores.

Thus, older adults may be more vulnerable to the physical effects of trauma but do not seem to develop PTSD at different rates than younger adults. However, adults who exhibit PTSD in earlier life may have more difficulty in adaptation in later life.

LIFE EVENTS AND AGING

Stressful life event (SLE) scales typically assess a wide variety of events that require adaptational change. While early scales typically had both positive and negative events (e.g., Holmes & Rahe, 1967), most researchers agree that negative events are generally more likely to be associated with health symptoms (for a review, see Aldwin, 2007). However, the items on the scales often include some events that are better classified as traumas, and others, as daily stressors. The mixture of major and minor events on most SLE scales may contribute to their unreliability (Monroe, 2008). A more useful way of characterizing life events might be in terms of changes in social roles that they often involve, particularly negative events such as divorces, being convicted of a crime, or being laid off from work.

Aldwin (1990) noted a central paradox in aging and stress research. While it is generally assumed that late life is a highly stressful time due to the development of chronic illnesses and higher levels of bereavement and other losses, an early review by Rabkin and Struening (1976) showed that older adults report fewer life events than do young adults. Inspection of the items on the Holmes and Rahe (1967) scale often used in this research reveals that it contains items that occur mainly to younger individuals, such as marriages, births, divorces, graduations, job loss, and so on. Aldwin (1990) developed the Elders Life Stress Inventory to capture events that are more likely to occur to middle-aged and older adults, such as bereavement, other losses, family caregiving, and institutionalization of parents and spouses. Based on preliminary field work, network stressors (i.e., stressors occurring to those in one's social network), such as divorce of an adult child, were also included. Cross-sectional analyses suggested that there was little correlation with age in middle-aged and older samples, suggesting a fair amount of similarity in exposure to major stressors in later life. However, age differences might reflect differences between cohorts and/or their sociohistorical experiences, sometimes known as *period effects*, rather than age-related change per se. For example, the occurrence of a war or a major economic downturn may influence the number and types of SLEs experienced by a particular cohort (Elder & Shanahan, 2006), and longitudinal work—preferably using a cohort sequential research design—is necessary to determine whether stress really does change with age. Preliminary longitudinal work with the Normative Aging Study data for men suggested that there may be a nonlinear relationship, with SLEs increasing until age 65 and decreasing thereafter (Yancura, Aldwin, & Spiro, 1999).

Using data from the San Francisco Transitions Study, Chiriboga (1997) also found that there were no differences in the number of life events experienced by individuals in midlife and late life, but did find that young adults reported more life events. Given that young people are initiating new roles in life, it is not surprising that their lives are more unsettled. Young adults also reported more positive events. Chiriboga also examined longitudinal change in SLEs over the subsequent 12 years. However, the longitudinal data did not suggest a strict linear decrease with age. Rather, the differences between the cohorts were maintained, and the number of events fluctuated over time, suggesting both cohort and period effects on the occurrence of SLEs.

A handful of studies have examined change in stressors in adults using growth curve models (George & Lynch, 2003; Lorenz et al., 1997; Lynch & George, 2002; Shaw & Krause, 2002) over relatively short periods (e.g., 3–7 years). The results vary by age of the respondents, type of stressor, and context. For example, married women in their 30s have little change in stress over a 3-year period. However, recently divorced women typically have higher levels of stress that decrease to "normal levels" after 3 years, although stress levels of women with antisocial behavior patterns decreased less. In contrast, studies using large community-based data sets show increases in loss-related events in later life, especially in African Americans (George & Lynch, 2003; Lynch & George, 2002), although they do not show age differences in the effects of stress on outcomes.

Other studies have found weaker effects of life events in later life. For example, Johnson, Backlund, Sorlie, and Loveless (2000) found that widowhood had stronger effects on well-being in midlife than late life. Nolen-Hoeksema and Ahrens (2002) also found that loss events increase in later life, but these were correlated with depressive

symptoms primarily in midlife and not in later life. Thus, loss events may be more normative in later life and off-time in midlife, thus increasing their impact. Given that older adults are more vulnerable to physical stressors, it is odd that they appear to be less vulnerable to psychosocial stressors, a topic that will be explored later in a discussion of coping and aging.

HASSLES AND AGING

Daily stressors (hassles or microstressors) are generally defined as episodes of short duration, such as getting caught in a traffic jam or having an argument with a partner (DeLongis, Folkman, & Lazarus, 1988). They show clear developmental patterns with age (and life stage). For example, Aldwin, Sutton, Chiara, and Spiro (1996) found that both the frequency and type of hassles varied by age group. Overall, older men reported fewer hassles than middle-aged men. Not surprisingly, older men were less likely to report problems with work or children and, although they were more likely to report health-related hassles, the increase in these hassles did not fully offset the decrease in the work and parenting domains. Chiriboga (1997) found that older adults reported more health-related hassles whereas other types clearly decreased with age, such as problems with parents, children, spouses, work, relatives, and money.

In addition to differences in the number of hassles, there may also be differences in their impact among older and younger adults. In a cross-sectional study, Mroczek and Almeida (2004) found that older adults reported fewer daily stressors and less negative affect, but they were *more* likely to respond adversely to the stressors that they did report, especially if they scored high in neuroticism. Using the same data set, Birditt, Fingerman, and Almeida (2005) found that older adults reported fewer interpersonal daily stressors, with the exception of spouse-related events. However, in direct contrast to Mroczek and Almeida (2004), they reported that older adults were *less* reactive to these types of events. Stawski, Sliwinski, Almeida, and Smyth (2008) also found that daily stressors decreased with age but found no age differences in stress reactivity. They also found that global perceived stress was positively associated with reports of daily stressors but increased negative affect only in younger adults. Thus, it appears that the number of hassles decreases with age, but that age differences in reactivity to hassles may vary as a function of other factors.

Given the difficulties with health problems and loss in late life, it is surprising that hassles decrease, but this may reflect decreases in the number of social roles. Older adults are often retired and thus do not generally report stressors associated with work or parenting. However, findings are equivocal as to whether older adults show more or less reactivity to daily stressors. In part, this may reflect moderators such as neuroticism. While neuroticism was not found to moderate the impact of minor events in one study of very old adults (Klumb & Baltes, 2004), Neupert, Mroczek, and Spiro (2008) found that it did increase the effect of daily stressors on memory failures.

Uchino, Berg, Smith, Pearce, and Skinner (2006) investigated the conflicting results between reports of older adults' lower negative affect reactivity in response to daily stressors but greater cardiovascular reactivity to stressors in laboratory situations. In a daily diary study, they not only confirmed the finding of lower negative affective reactivity but also showed higher blood pressure reactivity than younger adults. Aldwin, Park, and Spiro (2007) hypothesized that older adults may appraise problems as less stressful in part because doing so may afford protection against their heightened physiologically reactivity to stress.

CHRONIC STRESS AND AGING

Pearlin and Schooler (1978) introduced the concept of chronic role strain. They argued that chronic disruptions in important social roles, such as marriage, work, and parenting, were particularly important in the stress–health relationship. To our knowledge, there is no consensus in the literature as to the definitive duration of chronic stress, but it generally refers to ongoing problems in individuals' lives.

Of all the stress categories, chronic stress is the one most studied in older adults. There are dozens of studies of older adults linking caregiving stress to adverse health outcomes (for a review, see Vitaliano, Young, & Zhang, 2004). The construct of chronic stress has played a prominent role in theories of stress and aging, with some arguing that chronic stress may accelerate the aging process by as much as 10 years through effects on chromosomes (e.g., telomere shortening) and on the immune system (e.g., inflammatory processes; Epel et al., 2006; Glaser & Kiecolt-Glaser, 2005; Simon et al., 2006). McEwen (2002) has argued that chronic stress results in allostatic load, a syndrome consisting of elevated risk factors for a variety of illnesses such as cardiovascular disease and diabetes that are associated with advancing age.

There is no doubt that chronic stress can have deleterious health effects. However, a search of the PsycINFO database failed to yield any articles that examined age differences in the prevalence or duration of chronic stress. While it may appear intuitively obvious that chronic stress increases with age, given the higher rates of loss and prevalence of chronic health problems in later life (see Aldwin, Spiro, & Park, 2006), there is as yet no hard evidence that chronic stress is more common in later adulthood than in younger adulthood. Indeed, some chronic stressors, such as poverty, job stress, incarceration, and caregiving for disabled children, may be more prevalent in earlier life. Preliminary findings obtained by Aldwin, Shiraishi, and Levenson (2002) in a study of college alumni suggested that middle-aged adults report

more chronic stressors, but this finding may not generalize to less-advantaged samples.

AGING AND THE PHYSIOLOGY OF STRESS

That stress can have profound effects on health is now widely accepted (Singer & Ryff, 2001). However, laboratory studies demonstrating impacts of stress on disease risk factors such as cortisol or blood pressure do not always translate neatly into field studies of the stress–illness relationships (Krantz & McCeney, 2002). In general, trauma and chronic stress tend to have more reliable effects on disease outcomes than do intermittent life events, whereas hassles or daily stressors are more likely to relate to outcomes that fluctuate more readily such as epinephrine or cortisol levels (see Aldwin, 2007 for a review).

As discussed elsewhere in this volume, it is likely that the stress–health link is mediated in part by stress reactivity, assessed by changes in heart rate, blood pressure, and cortisol, among other physiological parameters. Indeed, stress reactivity is thought to be a major aspect of biological aging. As Sapolsky (1999) has suggested, older organisms may have dysregulated reactions to stress, resulting in prolonged elevation of stress hormones that may have very toxic effects on a number of different organ systems. Thus, for biogerontologists, stress reactivity may hold the key to the aging process. However, whether there are age-related patterns of altered stress reactivity in humans has been more difficult to show.

We know that older adults are more vulnerable to physical stressors, but it is an open question whether they are more reactive to psychosocial stressors (Aldwin, Park, et al., 2007). In humans, the findings on age-related changes in the physiological stress responses are quite variable and somewhat contradictory (Wilkinson, Peskind, & Raskind, 1997). Some studies show age-related increases in baseline levels of cortisol in healthy older adults (Seeman, Singer, Wilkinson, & McEwen, 2001), but others do not (Kudielka, Schmidt-Reinwald, Hellhammer, & Kirschbaum, 1999). Artificial induction of cortisol responses using the dexamethasone-human corticotropin-releasing hormone challenge does have a stronger effect in older adults (Kudielka et al., 1999). In general, older adults also take longer to clear infused (injected) cortisol (Wilkinson et al., 1997).

Older adults do not necessarily show increased cortisol responses to psychosocial stress, however, and some studies suggest that there may be gender differences. Kudielka et al. (1998) showed that older men had greater responses to a public-speaking task, but Seeman, Singer, and Charpentier (1995) showed that older women had greater responses to a driving simulation task. Seeman et al. (2001) showed that young men and older women showed heightened cortisol responses to cognitive testing. Finally, studies by Kudielka, Buske-Kirschbaum, Hellhammer, and Kirschbaum (2004) and Adam, Hawkley, Kudielka, and Cacioppo (2007) showed flattened cortisol reactions to stress in older samples. Thus, there appear to be interactions between the effects of age and type of task on cortisol reactivity.

A handful of studies have examined longitudinal changes in cortisol levels and reactivity. Carlson and Sherwin (1999) examined longitudinal change in cortisol (CRT) and dehydroepiandrosterone sulfate (DHEAS) ratios in 63 people over an 18-month period. Generally, CRT was stable across this time period, although the 10 women who were not using estrogen did experience increases. DHEAS level, which is thought to be protective against the effects of CRT, did not change. However, this study did not examine reactivity.

Burleson et al. (2003) examined neuroendocrine reactivity to speech and mental math tests twice approximately 1 year apart in 35 women aged 49 to 83. Mean values changed on most measures, with epinephrine and norepinephrine increasing, and cortisol decreasing. Baseline, task, and recovery measures were highly correlated across time, but the measures of change in reactivity were largely unrelated to these other variables, suggesting individual differences in change in reactivity. Lupien et al. (2005) also examined change in CRT levels over several years and found three groups: high baseline levels, increasing slopes; moderate baseline levels, increasing slopes; and moderate baseline levels, decreasing slopes. Thus, the literature, based on small sample sizes, is highly inconsistent as to whether cortisol levels and reactivity change with age, perhaps reflecting individual differences in the aging process.

Diurnal rhythm patterns may be a more reliable indicator of stress-related perturbations in the hypothalamic-pituitary-adrenal (HPA) axis than either overall resting levels or stress reactivity. The release of CRT occurs in a predictable pattern of basal activity throughout the day characterized by peak early morning levels and a decline toward an afternoon/evening nadir. Circadian variation in HPA activity is evident in salivary CRT (Stone et al., 2001). Regular shifts in glucocorticoid HPA activity, as occurs in circadian rhythms, are considered essential for balancing stimulatory and inhibitory actions of glucocorticoids (Sapolsky, 1999). Failure to achieve the appropriate peak to trough variation in HPA activity can itself have deleterious health outcomes. For example, survival for breast cancer patients is not related to overall glucocorticoid levels but is related to circadian variation; patients with greater peak to trough variation in cortisol survive longer (Sephton, Sapolsky, Kraemer, & Spiegel, 2000).

Both chronic stress and PTSD can result in dysregulation of the HPA axis (Friedman & McEwen, 2004), although there is some controversy over the exact nature of these effects. While some studies find that PTSD results in heightened cortisol reactivity, others find flattened reactivity (Posener et al., 2000; Yehuda et al., 1995). Some studies suggest that diurnal rhythms flatten with age (Adam et al., 2007; Yehuda et al., 2003); thus, it is possible that chronic stress may interact with age by decreasing diurnal CRT variability in response to stress.

In part, the disagreements across studies on stress and cortisol reactivity in older adults stems from factors such as small sample sizes and differences in tasks (i.e., laboratory studies of discrete stressors vs. field studies using daily diaries). Furthermore, in most studies, the extent to which the researchers control for factors that might affect CRT reactivity and diurnal rhythms varies. These factors include medications such as corticosteroids and statins, illnesses, and even cognitive status (Fiocco, Wan, Weekes, Pim, & Lupien, 2006).

Thus, the physiology of stress in later life is highly complex. Although older adults may not show greater affective reactivity to stress, they may show greater cardiovascular and cortisol reactivity. However, differences in study design and analytical techniques can result in different outcomes, with older adults showing no age differences, enhanced reactivity, or lower reactivity. More studies are needed to disentangle these effects and to explain the contextual and individual differences in stress reactivity associated with age.

COPING AND AGING

A discussion of how coping changes with age depends upon how coping is defined. A precise definition of coping is complex and depends upon its theoretical conceptualization. Coping may be broadly defined as psychological and behavioral efforts that individuals use to manage stressors and the attendant negative affect. Psychological coping efforts modify thoughts or feelings; behavioral coping efforts are actions that directly affect stressors (Lazarus & Folkman, 1984). Three main approaches have been used to conceptualize coping in the academic literature: psychoanalytic approaches, coping styles, and process approaches.

PSYCHOANALYTIC APPROACHES

The earliest studies of coping were from the psychoanalytic tradition, which focuses on defense mechanisms. These are unconscious and hierarchically organized, with those in lower levels associated with more psychopathology. Vaillant (1977) arranged defense mechanisms into four hierarchical levels: projective mechanisms (e.g., denial, distortion), immature mechanisms (e.g., hypochondriasis, passive-aggressive behavior), neurotic mechanisms (e.g., intellectualization, repression), and mature mechanisms (e.g., suppression, humor). He examined 30 years of interviews from a longitudinal study and proposed a developmental progression along this hierarchy, with an increasing use of mature mechanisms with age. His findings also suggest that use of mature mechanisms is associated with happiness and longevity (Vaillant, 2002). Although this developmental trend was not replicated in two other longitudinal studies (Vaillant, Bond, & Vaillant, 1986; Vaillant, 1993), they did confirm the relationship between mature mechanisms and well-being. It would be interesting to see if there are individual differences in the developmental progress of coping strategies across the life span. Nonetheless, the psychoanalytic approach has been criticized, as the measurement of unconscious defense mechanisms is fraught with difficulty (Cramer, 2000).

COPING STYLES APPROACHES

As its name suggests, the coping styles approach assumes that there is intraindividual stability in the use of coping styles across various situations. This approach classifies individuals based upon typologies such as approach-avoidance (Roth & Cohen, 1986) or repression-sensitization (Byrne, 1964). Although one might think that coping styles, being personality based, would be stable and not show developmental change, life-span developmental theorists have often hypothesized that coping styles do change over the life span, and often involve changes in goals and how one achieves them. For example, some argue that aging is associated with decreased resources, and thus individuals must select the goals they wish to pursue, optimize their achievement of these goals, and compensate for any deficits blocking their efforts (Freund & Baltes, 2002). In contrast, Brandstädter (1999) argues that the nature of problems in later life changes, with young adulthood characterized by controllable stressors, such as job changes, and late life by uncontrollable stressors, such as death of a spouse. Thus, there is a shift from assimilative (problem-focused) to accommodative (emotion-focused) strategies in later life. In a cross-sectional study, Rothermund and Brandstädter (2003) provided evidence for this theory: Adults younger than 70 used assimilative strategies to cope with physical deficits, whereas those older than 70 used more accommodative ones. Carstensen, Mikels, and Mather (2006) also hypothesized that older adults' coping focuses more on self-regulation of both emotions and behaviors.

Another way of looking at the issue is that older adults may conserve resources when coping with problems, maximizing efficacy, and minimizing resource utilization (Aldwin, Park, et al., 2007; Baltes, Staudinger, & Lindenberger, 1999; Hobfoll, 2001). Evidence for this comes from a recent study comparing repressive coping and measures of psychopathology between a group of older adults (with a mean age of 73) and a group of younger adults (with a mean age of 20). Younger adults scored higher than older adults on psychopathology but lower on measures of repressive coping. The authors of this study suggested that this might be due to fewer intrusive and ruminative thoughts and greater positivity by older adults (Erskine, Kvavilashvili, Conway, & Myers, 2007). However, there may be limited relationship between coping styles measures and how individuals actually cope with problems in real life (Ptacek, Pierce, & Thompson, 2006), and so many researchers prefer to examine coping processes.

COPING PROCESS APPROACHES

The coping process approach examines how individuals respond to specific stressors. It considers coping as a product of both environmental demands and individual capacities (Lazarus & Folkman, 1984). Coping follows appraisal, an assessment of the possible impact of the stressor and of resources for dealing with it, and involves specific cognitive and behavioral efforts to manage stressors and their subject impact. Coping strategies are usually grouped into five main categories, problem-focused coping (thoughts and acts directed at solving the problem, such as creating and enacting a plan), emotion-focused coping (attempts to manage internal emotions about the problem, such as avoidance), social support coping (enlisting the help of others), religious coping (seeking help from a higher power), and cognitive reframing (trying to see the problem in a new light).

Studies examining changes in specific types of coping strategies with age have reported mixed results. The use of problem-focused coping has been found both to be unrelated to age (Aldwin, 1991) and to be less frequent in late life (Folkman, Lazarus, Pimley, & Novacek, 1987). However, simply assessing changes in the number of problem-focused coping strategies used may be too simplistic to understand changes in coping processes. Aldwin et al. (1996) found age differences in problem-focused coping using a self-report measure, but no age differences when coding semistructured interviews. Similar to Hobfoll (2001), they concluded that older adults may use fewer strategies but nonetheless be just as effective. For example, a middle-aged man may well attempt a home repair by himself, trying out different solutions, necessitating multiple trips to the hardware store, and so on. An 80-year-old is unlikely to engage in these activities but may simply hire someone (or ask his middle-aged son) to do the work. Thus, fewer problem-focused strategies may be used, but the net effect is the same. Furthermore, problem-focused coping strategies are believed to be more effective when stressors are controllable, whereas emotion-focused coping strategies are believed to be more effective when stressors are not controllable (Aldwin, 2007). Thus, a more appropriate way to examine age changes in coping processes might be by looking at coping efficacy, that is, whether the coping strategies used in a particular situation were perceived to be effective in dealing with the problem.

One positive aspect of the coping process approach is that it assumes that coping strategies are plastic, and presumably individuals learn to cope better through dealing with problems (Aldwin, 1991). One study suggests that individuals do learn from past coping attempts. Brennan, Schutte, and Moos (2006) examined longitudinal change in coping in adults aged 55 to 65. They found that directed coping (i.e., problem-solving and positive reappraisal responses that reflect behavioral and cognitive efforts to change a stressor) at age 55 to be positively predictive of stressor resolution at age 65. This suggests that older adults might become more effective in their coping strategies, and thus perhaps use fewer strategies.

However, studies of coping efficacy and age have also reported mixed results. Two studies have reported lower levels with age (Barry et al., 2004; Logan, Pelletier-Hibbert, & Hodgins, 2006), while two studies have found no age differences (Aldwin et al., 1996; Newth & DeLongis, 2004). However, nearly all of these studies (with the exception of Aldwin et al., 1996) examined older adults experiencing debilitating and uncontrollable stressors, such as chronic pain. Thus, the decreased coping efficacy of older adults may reflect stressor characteristics. In a sample of adults suffering chronic illness, Zautra and Wrabetz (1991) found that age was unrelated to coping efficacy after controlling for multiple confounds.

Thus, older adults appear to be just as effective copers as are younger adults, barring problems such as dementia. However, they may be more judicious in their energy expenditures, and, especially very late life, may shift the focus of their energies from the environment to self-regulation.

COPING AND HEALTH IN OLDER ADULTS

Much of the research on coping and disease outcomes in older adults has been done in the context of chronic diseases, such as arthritis and cardiovascular disease. Very few of these studies have specifically examined longitudinal changes in coping with age. However, a handful of studies have examined age differences in coping with disease. Several studies have found no age differences in coping with osteoarthritis (Rapp, Rejeski, & Miller, 2000), rheumatoid arthritis (Bartlett, Piedmont, Bilderback, Matsumoto, & Bathon, 2003), or cardiac problems (Shen, McCreary, & Myers, 2004). But other studies have found that older adults use fewer emotional expression-coping strategies (Felton & Revenson, 1987) and are more likely to discuss avoidance and acceptance of their disease (Buetow, Goodyear-Smith, & Coster, 2001). Thus, the inability to document effects of age differences in coping on disease outcomes may be due to the fact that severity of illness may overwhelm any age effects of coping (Aldwin, Yancura, & Boeninger, 2007). As suggested earlier, older adults may be more efficient at coping with chronic disease.

Most of what is known about coping and health in older adults comes from studies of self-report and laboratory health outcomes in family caregivers. Family caregivers provide physical, financial, and/or emotional care for relatives, often spouses, with severe chronic illnesses such as stroke or dementia. Caregiving duties may be extremely stressful; family caregivers are more likely to experience depressive and physical health symptoms than their non-caregiving peers. The severity of these symptoms is often associated with the functional capacity of the person to whom care is provided (Vitaliano, Zhang, & Scanlan, 2003). For example, caregivers for family

members with Alzheimer's disease experience high rates of burden, stress, and physical health problems. Health outcomes are also associated with individual characteristics; caregivers who are older, have lower socioeconomic status, and have less informal social support are likely to experience worse outcomes (Pinquart & Sorensen, 2003). Furthermore, there can be long-term immunosuppressive results from caregiving (Glaser & Kiecolt-Glaser, 2005; Robles, Glaser, & Kiecolt-Glaser, 2005).

For older caregivers, perceptions of the caregiving role have been found to be nearly as strongly predictive of burden as care recipient characteristics (Van Den Wijngaart, Vernooij-Dassen, & Felling, 2007), suggesting psychosocial factors as important contributors to relationships among stress and health. Furthermore, not all caregivers report burden; about 50% of caregivers report positive aspects of caregiving (Beach, Schulz, Yee, & Jackson, 2000).

The stress–health relationship in caregivers appears to be moderated by coping (Vitaliano et al., 2004). Coping has been shown to be protective against a wide variety of adverse physical and mental health outcomes in general populations (Penley, Tomaka, & Wiebe, 2002). Several studies have demonstrated relationships among coping and laboratory health outcomes in samples of older family caregivers. Vitaliano, Russo, and Niaura (1995) reported relationships among coping and lipid fractions. High-density lipoprotein, which is protective against coronary heart disease, showed negative associations with anger-control coping and positive associations with anger suppression. Similarly, triglycerides, a factor that contributes to coronary heart disease, showed negative associations with anger suppression and positive associations with avoidance coping.

Other biomarkers for cardiovascular disease also show relationships with coping and caregiving. For example, D-dimer is a hypercoagulability marker linked to increased risk of experiencing coronary events. Caregivers and non-caregivers have also been shown to differ in their recovery from increases in D-dimer in response to a public-speaking task (Aschbacher et al., 2005). Caregivers scoring low on the planful problem-solving scale of the BWOC were found to have greater increases in D-dimer from baseline to recovery than those scoring high on planful problem solving. Thus, certain types of coping may link stress to physical health outcomes in older adults.

Relationships between coping and health outcomes also appear to be influenced by contextual variables such as the physical health of caregivers and the amount of stress they are experiencing. One study classified caregivers into groups depending on whether their own health status increased, decreased, or remained stable over a 1-year period and reported that cluster membership was predicted by preexisting health status as well as coping style. Caregivers with declining health and weight loss over the course of the year had higher levels of avoidance coping and worse preexisting health outcomes than the other groups (Dew et al., 1998). Another study reported that active coping behavior in elderly caregivers was positively related to concavalin A and phytohemagglutinin, measures of general inflammatory immune response, during periods of high (but not low) stress (Stowell, Kiecolt-Glaser, & Glaser, 2001). These studies indicate not only that coping influences health but that its influence is also dependent upon health status and environmental context.

The context may also affect the impact of coping intervention programs and how their effectiveness may vary with age. For example, Smith and Toseland (2006) compared the effectiveness of a telephone support intervention in teaching coping strategies in two groups of caregivers: older adult caregivers who were providing support to their spouses and middle-aged caregivers who were providing support to their parents. The program was effective for the younger, but not the older, caregivers in reducing self-rated caregiver burden. However, using longitudinal data, Christakis and Iwashyna (2003) found that older spousal caregivers who used hospice care services were significantly less likely to die within 18 months of their spouses than those who did not use hospice care. Thus, coping interventions that provide tangible aid may be more effective in older adults than those that focus more on informational or emotional support.

STRESS, COPING, AND ADULT DEVELOPMENT

The notion of homeostasis underlies most coping theories—that is, coping is thought to buffer the effects of stress, returning the system to baseline (e.g., Carver & Scheier, 1999). From a developmental perspective, however, stress can evoke change, both in the short and in the long term. Sociologists often speak of turning points (Elder & Shanahan, 2006) that can change the trajectory of the life course. While resources provided by families and societies can help individuals negotiate turning points, whether that change is positive or negative depends in large part upon how individuals cope with the stressors (Park, 2009). Thus, Aldwin (1991) argued that stress forms a context for development in adulthood. Stress, especially major stressors, trauma, or loss, creates conditions of uncertainty, which can force individuals to reexamine their assumption system (Epstein, 1991; Janoff-Bulman, 2004) and challenge them to develop new resources with which to cope with future stressors (Aldwin, 2007). For example, widowhood, as devastating as it can be, evokes questions and changes. If you are no longer a wife, then who are you? Lieberman (1996) documented growth among widows, who returned to long-abandoned goals and pastimes after the deaths of their spouses.

In clinical and health psychology, this pattern is referred to as posttraumatic growth (PTG; Calhoun & Tedeschi, 2006) or SRG (Park, Cohen, & Murch, 1996). Calhoun and Tedeschi posited five basic dimensions of PTG. Individuals may report changes in values such as a greater appreciation of life and changed sense of priorities and perspectives, such as recognizing what is "really important" in life. There may also be changes in social relationships, such as closer ties with others. Increases in coping skills and mastery are also reported, and individuals can evince a greater sense of personal strength. As mentioned earlier, many people report stressors as turning points in which they recognize new possibilities or paths for their lives. Finally, some even report a greater sense of spirituality.

Aldwin, Levenson, and Kelly (2009) have argued that this is similar in many ways to themes posited in adult development. For example, an early study conducted by Aldwin et al. (1996) on SRG included one man who had experienced a terrible apartment fire in the dead of winter. He and his family were forced to mobilize to find new lodging. He shoveled paths to houses for his realtor and ended up buying a lovely but very dilapidated old house which had been used as a hippie commune. They moved into the house, taught themselves various home reconstruction skills, and eventually found themselves the proud owner of a beautiful house in which to raise their family. Thus, although coping consumes resources (Hobfoll, 2001), through the development of new coping skills, coping may develop resources as well.

In more systematic studies, PTG attained by coping with traumatic life events has been associated with the ability to cope with current life events. It is also associated with increased mental and physical health (Park, Mills-Baxter, & Fenster, 2005), and perhaps the development of wisdom as well. In a longitudinal study, Jennings, Levenson, Aldwin, Spiro, and Mroczek (2006) examined the relationships between combat exposure, perceived benefits of military experience, coping, and wisdom later in life. They found that perceiving benefits and problem-focused coping, but not combat exposure, predicted wisdom some 12 years later. Of course, it is likely that there are reciprocal relationships between these constructs. For example, Ardelt (1998) examined the long-term outcomes of going through the Great Depression. There were no differences between individuals high and those low on her wisdom measure on the likelihood of experiencing economic downturns. However, individuals initially high in wisdom grew in mental health between 1930 and 1944, while those low in wisdom developed worse mental health. Thus, coping with stress may lead to the development of positive resources such as wisdom, but wisdom may also affect the outcomes of stressful episodes, presumably through affecting the choice of coping strategies. It would seem that stress, coping, and development are closely intertwined in adulthood.

SUMMARY AND DISCUSSION: AGE AND WISDOM

In summary, stress and coping are not static in adulthood; rather, they are processes that change continually over the life span. The types of stressors may change with age, but there is little evidence that later life is necessarily more stressful than earlier stages. However, how individuals appraise and cope with stressors may change. Older adults may be less likely to appraise situations as stressful, in part because they may be more physiologically vulnerable to stressors and thus can little afford to become upset. With age, individuals may become more judicious in their deployment of resources, but older adults can be just as efficacious copers as younger adults. The process of coping with stress may lead to positive or negative long-term outcomes, but stressful situations can present opportunities for the development of more coping resources, such as wisdom.

Although wisdom is widely considered desirable, why is it important in old age? Ardelt (2000) defines wisdom as "the pinnacle of successful human development . . . . it comprises such positive qualities as ego integrity and maturity, judgment and interpersonal skills, and an exceptional understanding of life" (p. 360). Although data are sparse, one can speculate that it is important for a number of reasons. First, it is likely that wisdom—or at least wise behaviors—developed earlier in life may help individuals live into late life. For example, avoiding the excessive use of cigarettes, drugs, and alcohol definitely predicts longevity, as does personality characteristics such as conscientiousness (Friedman & Martin, 2007) and emotional stability (Aldwin, Spiro, Levenson, & Cupertino, 2001).

Second, for those who survive into late life, wisdom may help deal with the extremely difficult stressors and losses in late life. For example, in a longitudinal study of the Berkeley Guidance sample, Ardelt (2000) found that age was associated with poor self-reported health and lower levels of life satisfaction, but wisdom in late life was associated with better health and life satisfaction. While age was not associated with wisdom, it would make sense that the higher levels of self-regulation we hypothesize to be associated with wisdom would help individuals to cope better with problems.

Third, wisdom can be considered a form of "family capital" (Bourdieu, 1986). While we know of no study that directly examines whether wisdom in late life is transmitted across generations, it makes a certain amount of sense, given the emphasis on advice giving in current theories of wisdom (e.g., Baltes & Staudinger, 2000). Furthermore, there is indirect evidence. Simons, Whitbeck, Conger, and Chyi-In (1991) found that harsh grandparenting was transmitted across generations, which suggests that better parenting might also be transmitted. Also suggestive is the finding reported by Lamb et al. (1988) showing that

grandparents' support was associated with positive material characteristics and better social competence in the grandchildren. Moreover, Kessler and Staudinger (2007) found that generative older adults promoted prosocial behavior in adolescents, which is relevant because wisdom is thought to be associated with generativity (Helson & Srivastava, 2001). It would be extremely interesting to test this hypothesis directly.

Finally, it would also make intuitive sense that wise adults are a form of "cultural capital" for the community. Again, we know of no study that directly tests this, but the perennial call for "wise leaders" gives this credibility. Carey and Judge (2001) review evidence suggesting that the existence of grandparents apparently promotes longevity in a population. While older adults in preliterate communities were often viewed as repositories of knowledge, authors such as Thomas (2004) have argued that their wisdom is important to help solve problems facing many societies today.

Thus, wisdom in later life can be seen as a coping resource. It appears that it can facilitate coping with stress, even as it can develop through the coping process. Not only may wisdom benefit the individual but also it may well have the potential to benefit his or her family and community.

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21 Effects of Stress on Eating Behavior

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BACKGROUND

There is growing evidence to suggest that stress affects health directly through autonomic, neuroendocrine, and biological processes and also indirectly through changes to behaviors that influence health (Jones & Bright, 2001; Oliver, Wardle, & Gibson, 2000). Stress-induced modifications of habitual health behaviors such as food choice and eating behavior may be particularly important in understanding physical disease risk (O'Connor, Jones, Conner, McMillan, & Ferguson, 2008; Steptoe, Lipsey, & Wardle, 1998). Research has suggested that high levels of stress can be associated with both increased (e.g., saturated fat consumption) and decreased (e.g., overall calories) food intake (Wardle, Steptoe, Oliver, & Lipsey, 2000). Other research has found stress to be associated with an increase in food consumed as snacks in adults and adolescents, which may or may not influence health (Cartwright et al., 2003; Conner, Fitter, & Fletcher, 1999; O'Connor & O'Connor, 2004).

Over recent years, there has been increasing evidence to suggest a link between various aspects of diet and life-threatening diseases such as cardiovascular disease (CVD; Van Horn & Kavey, 1997) and cancer (Wong & Lam, 1999). The relationship between such diseases and various aspects of diet is a complex one. Nevertheless, three aspects of diet have been particularly implicated in relation to health outcomes: total fat and saturated fat in the diet, dietary fiber, and fruit and vegetable consumption (see Kumanyika et al., 2000). Evidence that these aspects of diet have become incorporated into the general public's conceptions of what constitutes healthy eating has also been reported (Povey, Conner, Sparks, James, & Shepherd, 1998).

The evidence relating dietary fat to health is well established and has been incorporated into consensus recommendations (e.g., American Cancer Society, 1996; COMA, 1991; U.S. Department of Agriculture/U.S. Department of Health and Human Services [USDA/USDHHS], 1995) to consume no more than 35% of daily energy from fat (and less than 11% calories from saturated fat) to reduce the risk of CVD and cancer. Research has also indicated the health benefits of increased dietary fiber consumption on lipid and glucose metabolism and prevention of colon cancer (Anderson, Smith, & Gustafson, 1994; Brown, Rosner, Willett, & Sacks, 1999, Wolk et al., 1999). Again, this has been translated into recommendations (e.g., American Cancer Society, 1996; Krauss et al., 1996), namely, to increase dietary fiber consumption (to 20–30 grams per day). Finally, there is epidemiological evidence to indicate that increased levels of fruit and vegetable consumption are protective against cancer and CVD (Appel et al., 1997; Deckelbaum et al., 1999; Giovanucci, Willett, & Stubbs, 1999; Ness & Powles, 1997). Recommendations (e.g., USDA/USDHHS, 1995) have focused on increasing the portions of fruit and vegetables consumed to at least five per day (e.g., the five-a-day campaign; Heimendinger, Van Ryn, Chapelsky, Forester, & Stables, 1996; U.K. Department of Health, 2007).

Taken together, these findings suggest that stress can contribute to both CVD and cancer risk to the extent that it produces deleterious changes in diet and/or helps maintain unhealthy eating behaviors, such as high fat intake or low fiber or fruit/vegetable intake. Over the last 25 years, a large volume of research has been concerned with understanding the precise nature of the relationship between stress and eating behavior. This work has been conducted using animal models of stress-induced eating as well as eating-disordered and noneating-disordered populations. However, the focus of this chapter is to provide an overview of research findings from noneating-disordered populations. Interested readers are also directed towards more comprehensive reviews of this area by Greeno and Wing (1994), Adam and Epel (2007), and Nieuwenhuizen and Rutters (2008). This chapter provides a summary of research that has explored

(1) nature of changes in eating behavior in response to stress;
(2) types of stress affecting eating behavior;
(3) moderators of the stress–eating relationship;
(4) influence of stress on cognitive processes relating to eating;
(5) biological mechanisms associated with stress-related eating.

NATURE OF CHANGES IN EATING BEHAVIOR IN RESPONSE TO STRESS

In examining the impact of stress on eating, it is important to be specific not only about the type of the stress (as discussed later) but also about the nature of the expected changes in eating behavior. The major focus of early research on stress and eating was on whether stress increased, decreased, or produced no change in overall eating behavior. For example, early animal work, in particular, focused on how stress might lead to eating more food (i.e., hyperphagia) or eating less food (i.e., hypophagia). Such a focus was particularly apparent in early theoretical accounts of the stress–eating relationship and its impact on obesity provided by researchers such as Kaplan and Kaplan (1957) and Schachter, Goldman, and Gordon (1968). For example, Kaplan and Kaplan (1957) argued that certain (obese) individuals did not learn to distinguish between hunger and anxiety and thus responded to stress as if it were hunger (i.e., an increase in eating under stress). An alternative view, put forward by Schachter et al. (1968), was that some (obese) individuals had not learned to label various physiological cues (e.g., gastric contractions) as hunger. It was suggested that these cues are reduced under stress leading to a reduction in eating (i.e., a decrease in eating under stress) except among those who have failed to learn to label these cues appropriately (see later section on stress–eating moderators). More recent accounts have suggested that rather than having a general impact on overall eating, the effect of stress on eating might be specific to particular types of foods (with increases in the consumption of some foods and decreases in the consumption of others). This might include effects on more palatable or easily consumed foods (e.g., fast foods), foods with particular sensory or health characteristics (e.g., high-fat foods), or foods generally consumed between meals (e.g., snack foods) or at meals (cf., Gibson, 2006). The focus of this more recent work has been less about understanding the role of stress in obesity or weight control and more about how stress could have damaging effects on health through leading to the consumption of a less healthy diet. This section overviews the types of eating behaviors that have been considered in different research designs addressing the stress–eating relationship.

Much work on the stress–eating relationship in humans over the last 25 years has focused not only on overall amount eaten but also on changes to the types of food consumed. For example, a study by Bellisle et al. (1990) looked at men in hospital on days they were or were not due to undergo surgery and recorded both the amount and types of food eaten in the morning. Similarly, Michaud et al. (1990) examined both the overall calorie intake and calorie intake from fatty foods, such as snacks, in a sample of school children on days they were or were not due to take an examination. Although Bellisle et al. found no significant effects, Michaud et al. found that stress was associated with increases in overall calorie and calorie from fat intake, at least among the girls in the sample. This latter finding was confirmed in a laboratory study by Grunberg and Straub (1992), where women were found to be more likely to select foods high in calories (and fat) when under stress. Relatedly, Steptoe et al. (1998) reported that "fast food" was eaten more frequently when respondents reported experiencing greater number of hassles. Comparable results were obtained by Oliver and Wardle (1999) in a study of the effects of perceived stress on food choice. Oliver et al. (2000) also reported increased consumption of sweet high-fat foods and more energy-dense foods in response to stress. Finally, O'Connor et al. (2008) reported increased consumption of both high fat and high-sugar snacks in response to stress as assessed by number of hassles. Stress being associated with an increased consumption of palatable foods that are higher in calories and/or fat appears to be one of the more consistent findings in this area and certainly more consistent than any effect on overall calories consumed. This is potentially important because of the established relationship between excessive fat consumption and CVD and cancer (e.g., Kumanyika et al., 2000; Van Horn & Kavey, 1997; Wong & Lam, 1999).

Another aspect of eating behavior that has been a focus of research on effects of stress has been examination of effects on between-meal food consumption as opposed to food consumed at meals. A justification for this focus has been that between-meal snacks may be more responsive to the effects of stress because they are more within the control of the individual than the typical meal (Conner et al., 1999). Indeed several studies do show that the number of snacks consumed is responsive to stress. For example, using a daily diary design, Conner et al. (1999) showed a linear relationship between the number of hassles experienced on a day and the number of snacks consumed the same day. Similar results were reported by O'Connor et al. (2008) using a similar design in relation to overall number of snacks, number of high-fat snacks, and number of high-sugar snacks (see also Oliver et al., 2000). Oliver and Wardle (1999) also reported a study of the perceived effects of stress on snacking. Snacking was generally perceived to increase under stress. In contrast, the consumption of foods usually eaten as meals was reported to decrease under stress (see also Weinstein, Shide, & Rolls, 1997). This contrasting effect of stress on main meals was also reported by O'Connor et al. (2008), who additionally reported hassles to be associated with a reduction in the amount of vegetables consumed. Together, this research suggests that stress may be associated with a disruption to normal eating patterns by increasing the amount of food consumed between meals (as snacks) but decreasing the amount of food consumed at meals. This disruption of normal eating patterns may have manifold effects on health. Not only might overall calories consumed increase, but, more importantly, the overall nutritional quality of the diet might decrease

(e.g., higher percentage of calories from fat; reduction of calories from fruit and vegetables).

As this brief review shows, research on stress and eating has gradually moved from a focus on overall amounts consumed to a focus on changes in eating patterns in response to stress. This partly reflects the growing understanding of the impact of diet on health and how not only does the overall number of calories matter but also the balance of macronutrients in the diet and, in particular, the percentage of calories derived from fat. As we noted, the consumption of high-fat foods appears to be influenced by stress and is one pathway by which stress may influence health outcomes. Between-meal snacks may represent one aspect of diet that is both sensitive to stress and can lead to increased fat consumption (because of the preponderance of high-fat snack foods). The extent to which it is the palatability or the calorie density of such foods that mediates such effects may be a key issue in relation to developing healthy alternative "stress-snack" foods (cf., Gibson, 2006). However, this finding should not lead us to ignore the impact that stress may have on unhealthy choices within meals. For example, Steptoe et al.'s (1998) finding that stress was associated with increased fast food consumption is important given that such foods also tend to be higher in fat and sugar. Again, the extent to which such effects are mediated by palatability, energy density, or some other factor (e.g., speed of consumption) is an important issue for future research in relation to understanding the effects of stress on eating. Finally, by increasing between-meal snacking, stress may have an impact on health simply through increasing the frequency of energy intake, which is beginning to be considered a risk factor for health (Mattson, 2005).

TYPES OF STRESS AFFECTING EATING BEHAVIOR

Less is known about the importance of the type of stress experienced and whether some stressors serve as key moderators of eating behavior, whereas others have little or no effect (Conner & Armitage, 2002). Several researchers have found stressors of an ego-threatening nature (e.g., where there is a fear of failure) to have distinct effects from those that elicit physical fear (e.g., fear of an electric shock). Heatherton, Herman, and Polivy (1991, 1992) suggested that situations involving potential negative evaluation or task failure (ego-threatening) will lead to disinhibition (overeating) in restrained eaters or current dieters, whereas physically threatening situations will not. In contrast, these authors found that fear of an electric shock led to a reduction in food intake in unrestrained participants. The impact of "interpersonal stress" has also been investigated (e.g., Oliver, Huon, Zadro, & Williams, 2001; Tanofsky-Kraff, Wilfley, & Spurrell, 2000). Tanofsky-Kraff et al. (2000) compared the effects of interpersonal stress (i.e., stress associated with feeling a sense of social alienation and being interpersonally ill-equipped) with ego- and physically threatening stress and found that in the interpersonal stress group, individuals with high levels of restraint consumed the most food.

More recently, Lattimore and Caswell (2004) and Wallis and Hetherington (2004), using laboratory methods, have also highlighted the importance of taking into account different types of stressors together with eating style variables (e.g., restraint and emotional eating). In particular, Wallis and Hetherington (2004) showed that cognitively demanding stressors (such as the incongruent Stroop task), as well as ego-threats, have the capacity to enhance food intake. The incongruent Stroop task was found to increase chocolate intake by 15% relative to control. Moreover, dietary restraint was associated with greater intake after the cognitively demanding stressor as well as an ego-threatening stressor compared with the control condition. In contrast, emotional eating was related to greater intake only after the ego threat, relative to control. These authors argued that their findings demonstrated differential effects of ego threat and cognitive demand on stress-related eating in restrained and emotional eaters. Lattimore and Caswell (2004) also demonstrated the importance of distinguishing between psychological (e.g., reaction time tasks and delivering a speech) and physical stressors (e.g., the cold pressor task) when considering stress–eating relations. They argued that reaction time-type tasks require active coping, whereas cold pressor-type tasks require passive coping. Within this framework, active coping involves a behavioral response whereby an individual is able to influence the outcome of a task. Passive coping involves passive sensory intake with no opportunity to influence the outcome of a task. In their study, Lattimore and Caswell (2004) found that restrained eaters consumed more than unrestrained eaters following the active coping stressor compared with the passive coping stressor and to a relaxation condition. Moreover, consistent with Wallis and Hetherington (2004), these results showed that stressors that are cognitively demanding, but do not have an ego-threatening or social evaluation element, still have the capacity to induce increases in food intake.

Other types of stressors, such as work-related stress, have received less attention. Relatively few studies have examined the impact of work-related stress as a distinct type of stressor or investigated whether ego-threatening or interpersonal-related work stressors have similar effects in the workplace as they do more generally. This is a significant oversight given that the psychosocial work environment is a major source of stress (Abraham, Conner, Jones, & O'Connor, 2008; Karasek & Theorell, 1990; O'Connor, O'Connor, White, & Bundred, 2000a, 2000b; Willis, O'Connor, & Smith, 2008). In addition, stressors that disrupt time (and work) schedules have received relatively less attention but may be important determinants of changes in eating behavior. A notable exception is a study by Wardle et al. (2000) of staff at a large department store. They found that periods of high

work stress were associated with greater calorific energy, saturated fat, and sugar intake compared with periods of low stress. More recently, Jones, O'Connor, Conner, McMillan, and Ferguson (2007), using hours worked as an index for work stress (as well as measures of the psychosocial work environment such as demands and control), found that long work hours were associated with greater consumption of high fat and sugar between-meal snacks in women only, whereas higher levels of negative mood were linked with snack intake in men. These differential findings for men and women are likely to be explained by the fact that women often have greater family responsibilities, which leaves less capacity for self-care on long work days. In addition, these results highlight the need for researchers to consider the fact that the impact of stress on eating behavior operates differently for men and women (an issue we return to later). Moreover, this study is also noteworthy in indicating that proximal, dynamic factors—daily variations in work hours and mood—were the main predictors of daily between-meal snack consumption, as opposed to the more distal and stable aspects of the psychosocial work environment as detailed by prominent models such as the job demands-control model (Karasek & Theorell, 1990).

A large amount of the previous research into the effects of stress on eating behavior has been overly reliant on laboratory-based, cross-sectional methodologies. As a result, it is difficult to discern the extent to which the influence of different types of stressors is generalizable to everyday stress–eating relationships. Much of the existing research has ignored the growing body of evidence showing that fluctuations in within-person stressful daily hassles are important in understanding stress-outcome processes (e.g., Affleck, Tennen, Urrows, & Higgins, 1994; Affleck, Zautra, Tennen, & Armeli, 1999; Dancey, Taghavi, & Fox, 1998; Delongis, Folkman, & Lazarus, 1988; Fifield et al., 2004; O'Connor & Ferguson, 2008). The latter work has prompted investigators to consider alternative research designs. For example, the use of open-ended diaries allows respondents to record day-to-day minor life events or hassles that are part of everyday life and have the advantage of not constraining respondents to a limited number of events. A recent study using this approach found strong evidence for the moderating effects of different types of daily hassles on the stress–snacking relationship (O'Connor et al., 2008). Ego-threatening, interpersonal, and work-related hassles were found to elicit a hyperphagic response, whereas physical hassles were found to elicit a hypophagic response. The latter findings confirm the work by Heatherton et al. (1991) and demonstrate that the differential effects of stressors observed in the laboratory are generalizable to naturalistic settings. In addition, contrary to previous investigations, this research identified work-related hassles, and not ego-threatening or interpersonal, as the type of hassles that exerted the strongest effects on between-meal snacking (cf. Heatherton et al., 1991, 1992; Oliver et al., 2001; Tanofsky-Kraff et al., 2000). It is also particularly noteworthy that these effects were not restricted to vulnerable individuals who were inhibiting their food intake per se (e.g., restrained eaters), as they have been in other studies (Heatherton et al., 1991; Wardle et al., 2000). Instead, these findings clearly demonstrate that daily hassles can directly influence snack food intake.

MODERATORS OF THE STRESS–EATING RELATIONSHIP

Previous research has examined either the "general effects hypothesis" that stress changes consumption of food generally or the "individual differences hypothesis" that stress leads to changes in eating in particular groups (e.g., the obese, restrained eaters, and women; Greeno & Wing, 1994; O'Connor et al., 2008). The individual differences model of stress–eating relationships (Greeno & Wing, 1994) suggests that differences in learning history, attitudes toward eating, or biology produce variations in vulnerability to the effects of stress. Those exhibiting vulnerability are assumed to respond to stress with an environmental or psychological change that has a secondary effect on eating behavior. In contrast, those with low vulnerability exhibit a different environmental or psychological change that does not promote changes in eating. Several vulnerable groups have been proposed, and the relevant research is reviewed in this section. The groups that have been compared are the obese and nonobese, restrained and unrestrained eaters, women and men, and emotional and nonemotional eaters.

OBESE VERSUS NONOBESE

Interest in the effect of stress on eating in humans began as an attempt to understand obesity. As noted earlier, it was suggested that overweight individuals were more likely to respond to stressful or emotional stimuli by eating (Stunkard, 1959). This view arose from psychosomatic views of obesity that suggested that obese individuals did not learn to distinguish between hunger and anxiety (Kaplan & Kaplan, 1957). Such individuals were assumed to respond to stress as if it was hunger (i.e., by eating) rather than anxiety. An alternative view was put forward by Schachter et al. (1968). These researchers suggested that unlike normal-weight individuals, obese individuals had not learned to label various physiological cues (e.g., gastric contractions) as hunger and that these cues are reduced under stress. Therefore, the prediction was that stress should produce a reduction in hunger and eating in normal-weight individuals but have no impact on the feelings of hunger and eating behavior in the obese. Thus, both the views predict differences in eating behavior of obese and nonobese in response to stress. However, the

direction of change is different across views. In Schachter et al.'s view, it was predicted that stress would decrease eating in normal-weight individuals and have no effect on obese individuals. From the psychosomatic view, stress would be expected to increase eating in obese individuals and have no effect on normal-weight individuals. The evidence in support of both these different predictions is disappointing.

Greeno and Wing (1994) reviewed 11 studies that addressed the effect of stress on eating in obese and nonobese groups. Schachter et al. (1968) produced the first laboratory test of this effect: Anticipating a painful compared with a mild shock (high vs low stress) produced a decrease in eating in normal-weight participants, but had no effect on obese participants. This finding is consistent with the Schachter et al. model outlined above. However, only one of the other 10 tests of this hypothesis reviewed by Greeno and Wing (1994) produced a similar decrease in consumption in normal-weight individuals, who in the other studies generally showed no change in consumption in response to stress. This represents very weak support for the Schachter et al. account of the impact of stress on eating in nonobese groups. Support for the psychosomatic account has also been mixed. Of the 11 studies reviewed by Greeno and Wing (1994), three demonstrated an increase in eating in obese individuals when stressed, three studies found that only some obese individuals eat more when stressed, and five studies failed to find any relationship between stress and eating in obese individuals. Taken together, this is the only relatively modest support for the psychosomatic account. In addition, those studies only finding partial support for the psychosomatic view suggest an alternative interpretation. For example, Baumcom and Aiken (1981) demonstrated that rather than obesity it was dieting that was the key predictor of stress-related eating in their study. For both obese and nonobese groups, stress only produced increases in eating in the dieting group. Given the fact that many obese individuals are dieting in an attempt to control their weight, the failure to control for dieting may explain the contradictory findings across studies in the impact of stress on eating in the obese. In effect, it may be the fact that dieting is more prevalent in the obese than the nonobese that explains why stress appears to lead to greater eating in the obese compared with the nonobese group. This perhaps accounts for the relatively limited attention that has been given in recent years to the possible role of obesity as a moderator of stress–eating relationships compared with that focusing on dieting status.

RESTRAINED VERSUS UNRESTRAINED

The concept of restrained eating developed from the "set point" theory of obesity (Herman & Polivy, 1975). Restrained eaters are assumed to restrict their food intake through self-control processes. When these self-control processes are undermined, disinhibition of eating occurs, and excessive food intake takes place. For example, restrained eaters appear not to adjust their food intake for previous food intake (Herman & Mack, 1975). Unrestrained eaters adjust for consuming a "preload" of food by eating less in a subsequent eating test, whereas restrained eaters eat just as much as if they had not eaten the preload. It is believed that the preload disinhibits the restraint they normally show over eating. Stress is also expected to affect restrained eaters by disrupting the control normally exerted over eating. Thus, individuals with high restraint scores should be more likely to respond to stress by eating, whereas those low in restraint should show no change. Heatherton et al. (1991) and Schotte et al. (1990) both compared high and low restrained eaters and found that not only did restrained women eat more than unrestrained women, but restrained women who were stressed ate more than restrained women who were not stressed. Cools et al. (1992) used restraint as a continuous variable, rather than dividing subjects into high and low restraint groups, and showed that the stressed group consumed progressively more food as restraint scores increased. A number of other studies have also produced consistent results indicating that stress produces greater increases in eating in restrained compared with unrestrained eaters (see Greeno & Wing, 1994; see also Adam & Epel, 2007, for a useful recent review). Nevertheless, it must be conceded that the vast majority of studies to date have only demonstrated this effect in college-aged women. Future research needs to confirm these effects in other samples. In one study partly addressing these issues, Wardle et al. (2000) showed that work stress leads to increased eating in both restrained women and restrained men. However, in a recent review article, Lowe and Kral (2006) have argued that the moderating effect of restraint is not caused by restrained eating or by stress per se. These authors state that "restraint is primarily a result of, rather than a cause of, the behavioral patterns with which it has consistently been associated" (Lowe & Kral, 2006, p. 18). Instead, they contend that existing behavioral and physiological data indicate that restrained eating may be a proxy risk factor for vulnerability to weight gain.

Some other recent research has suggested that disinhibition rather than restraint may be a better predictor of food consumption under stress (see Ouwens, van Strien, & van der Staak, 2003). Disinhibition is one of the three subscales measured by the three-factor eating questionnaire (Stunkard & Messick, 1985) that assesses the tendency to overeat. O'Connor et al. (2008) have reported that both restraint and disinhibition moderated the stress–eating relationship, although there was a stronger effect for disinhibition. In both cases, the daily relationship between number of hassles and number of snacks consumed was stronger for higher levels of restraint or disinhibition. The effects of restraint in men, the impact of disinhibition in general, and the exploration of the precise mediating mechanisms are issues particularly worthy of further study in this area.

WOMEN VERSUS MEN

Several studies have looked at differences between female and male eating in response to stress. For example, Grunberg and Straub (1992) sought to determine whether there are differences between women and men in vulnerability to stress-induced eating. Sweet, salty, and bland foods were provided for participants while they were watching a video, and for half the subjects the video was unpleasant (i.e., stress-inducing). Results showed that unstressed men consumed significantly more food than any other group. However, stressed women did consume twice as much sweet food as unstressed women, suggesting the importance of food type, at least in women. Although stress generally reduced eating in men, this effect was not significant. Pine (1985) compared obese and nonobese men and women and found that stress-induced eating was more pronounced among women than men. Stone and Brownell (1994) examined the relationship between stress and eating for married couples who completed daily records of stress and eating. Results showed both men and women were likely to eat less than usual in response to stress, and the tendency to eat less with an increasing severity of stress was particularly pronounced in women. It is not clear why increased levels of stress were associated with decreased rather than increased eating in this sample. Using a similar design, O'Connor et al. (2008) reported that stress was more strongly associated with between-meal snacking in women compared with men. Interestingly, stress was associated with a reduction in consumption of food at meals in this study, suggesting that the nature of the eating behavior examined may be key in determining whether stress decreases, increases, or has no effect on amount eaten. As outlined earlier, Jones et al. (2007) also found that the impact of work stress (indexed by work hours) on eating behavior was statistically significant only in women.

Thus, the evidence for gender differences in stress-induced eating is somewhat contradictory. The effects appear to be generally greater in women than men, but in some studies stress appears to increase eating, in others it appears to decrease eating, and in still others it has no effect on eating. Some of the effects also appear to be specific to particular types of food (e.g., sweet foods). Interpretation of these findings is further complicated by the fact that gender is found to be correlated with restrained eating (i.e., women generally show higher levels of restraint). In addition, comparatively few studies have examined the effect of restraint on stress–eating relationships in men.

EMOTIONAL VERSUS NONEMOTIONAL EATERS

Emotional eating refers to a tendency for some individuals to eat more when anxious or emotionally aroused compared with nonemotional eaters who do not show such reactivity to emotion in their eating habits. Emotional eating is found to be generally higher in women than men (Van Strien, Frijters, Bergers, & Defares, 1986). Stress is assumed to lead to increased eating in emotional eaters because they fail to distinguish between anxiety and hunger (i.e., they respond to stress as if it were hunger), whereas it does not affect those low in emotional eating. The origins in psychosomatic approaches to understanding stress–eating relationships discussed earlier in relation to understanding obesity should be clear. Psychometric measures of emotional eating have been developed (e.g., Van Strien et al., 1986). Van Strien et al. (1986) found that stressful life events predicted weight gain in men over a period of 18 months, but only amongst those who were emotional eaters. In women, stress led to weight gain irrespective of their level of emotional eating. Other studies have reported a limited (Schlundt et al., 1991) or lack of impact (e.g., Conner et al., 1999) of emotional eating on stress–eating relationships. More recently O'Connor et al. (2008) reported a strong impact of emotional eating on stress–eating behavior relationships. However, given the limited number of published studies of emotional eating, its impact on stress–eating relationships remains an issue for further study.

OTHER MODERATORS

A number of other factors have received more limited attention as moderators of the stress–eating relationship. These include external eating and personality traits. The concept of external eating derives from "externality theory" (Schachter et al., 1968). It suggests that external eaters eat in response to food-related stimuli, regardless of the internal state of hunger and satiety, whereas internal eaters are more responsive to internal cues such as hunger in deciding to eat. Van Strien et al. (1986) have developed a measure of external eating that uses items such as "If food tastes good to you, do you eat more than usual?" Only a few studies have examined external eating as a moderator of stress–eating relationships. In one that was conducted in a student sample, Conner et al. (1999) found that hassles were more strongly related to number of between-meal snacks consumed in individuals high in external eating than they were in those low in external eating. Although O'Connor et al. (2008) reported the same effect using a similar design in a sample of working adults, further studies are required to confirm the generality of these findings.

In addition to the aforementioned eating-specific moderators, some recent studies have begun to examine personality traits as moderators of the stress–eating relationship. Two personality traits in particular have drawn attention: conscientiousness and perfectionism. Conscientiousness is one of the Big Five personality traits (Costa, McCrae, & Dye, 1991). It refers to the ability to control one's behavior and to complete tasks. Those with high conscientiousness scores are seen to be more organized, careful, dependable, self-disciplined, and

achievement-oriented than those low in conscientiousness. Conscientiousness has been found to be related to longevity (Friedman et al., 1993), and some of this effect is attributable to health behaviors such as eating (Hampson, Goldberg, Vogt, & Dubanoski, 2007). The possibility that conscientiousness might moderate the stress–eating relationship was explored by O'Connor, Conner, Jones, McMillan, & Ferguson (2009). They found that stress significantly reduced the consumption of vegetables only among individuals with lower levels of facets of conscientiousness. Those with higher levels of conscientiousness were able to maintain their levels of vegetable consumption on both low- and high-stress days. O'Connor and O'Connor (2004) also reported that a manipulation of stress was associated with an increase in between-meal snacking in low-conscientiousness individuals, but only for those who were dieting.

Perfectionism is another personality trait that has been explored in relation to the stress–eating relationship. Perfectionism refers to the tendency to experience distress when events and situations are perceived to be imperfect. Ruggiero et al. (2003) have reported that stress promotes behaviors related to eating disorders in individuals high on perfectionism. O'Connor and O'Connor (2004) reported that exam stress was associated with an increase in consumption of between-meal snacks among those high in one facet of perfectionism, although this difference was only significant among those low in conscientiousness. These are interesting findings that await further confirmation from future studies.

MULTIPLE MODERATORS

As this review makes clear, the individual differences approach to studying stress–eating relationships while answering some questions has raised many others. A key issue is the integration of the effects of the different moderators. This is particularly important given their known interrelationships. For example, restrained eaters are reported to be more likely also to be emotional eaters (Weissenberger, Rush, Giles, & Stunkard, 1986) and external eaters (Heatherton & Baumeister 1991), and we have noted the relationship of gender to emotional and restrained eating and of obesity to restraint. Research examining such moderators simultaneously would appear to be an obvious avenue for research but is one that has been little explored. Two studies have particularly focused on testing a number of the above moderators simultaneously.

Conner et al. (1999) used a daily diary study to compare eating behavior on high- and low-stress days in a sample of 60 students over 7 consecutive days. Stress was assessed in terms of number of hassles reported, and the eating behavior was assessed in terms of the number of between-meal snacks consumed. The moderator variables examined were external eating, emotional eating, restrained eating, gender, and severity of stress. Number of snacks was significantly positively correlated with number of hassles. Thus, on days that respondents reported greater numbers of hassles, they also reported consuming more snacks, compared with days on which they reported fewer hassles. When considered independently, external eating and gender were significant moderators of the stress–eating relationship, whereas severity of hassles, restraint, and emotional eating were not. More importantly, when these moderators were considered simultaneously, only external eating emerged as a significant moderator. O'Connor et al. (2008) used a similar design to consider the simultaneous effects of various moderators in a sample of 422 workers over 28 consecutive days. In addition to a larger sample size, O'Connor et al. also used more sophisticated statistical techniques (multilevel modeling) to control for multiple responses from each individual and considered a greater range of moderators. In their data, consistent with previous findings, restraint, emotional eating, external eating, disinhibition, gender, and obesity all individually moderated the relationship between daily hassles and number of between-meal snacks in a direction consistent with previous research. However, when considered simultaneously, only emotional eating emerged as a significant moderator of the stress–eating relationship. These findings suggest the need for further studies to examine the simultaneous effects of multiple moderators on the stress–eating relationship using more sophisticated research designs.

INFLUENCE OF STRESS ON COGNITIVE PROCESSES RELATING TO EATING

A number of studies have employed more cognitive approaches to explore the mechanisms that may transmit the effects of stress on eating behavior in relation to the various moderating variables. Much of this work has been influenced by Heatherton and Baumeister (1991), who have argued that stress causes increased awareness of the immediate environment and decreased awareness of the self. More specifically, it is hypothesized that for particular individuals, stress narrows the level of attention to the current and immediate stimulus environment (i.e., accessible food such as snacks), thereby shifting attention away from negative self-appraisals and/or from feeling distressed. It is argued that such low levels of attention reduce self-awareness to a point where meaningful thought, evaluations of self, and the implications of one's activities are avoided. In the context of stress-induced eating, vulnerable individuals may experience greater distress and negative self-appraisals when they encounter daily hassles and therefore shift their attention toward high-fat/sugar, energy-dense snack foods to escape from this negative emotional state. Moreover, this shift toward snack-type foods may also be driven by the learned outcomes from dietary-induced changes in

neurohormonal mechanisms. Future research ought to investigate further the effects of high-fat and high-sugar snack foods on the stress response within the context of the escape from self theory.

EXTERNAL EATING

One possible explanation for stress-induced eating in external eaters is a change in attention toward environmental cues during stress. Since external eaters are driven to eat by environmental cues, an attentional shift toward the immediate environment might be expected to increase food intake in these individuals. To date, only two studies have investigated attentional biases for food stimuli in external eaters (Johansson, Ghaderi, & Andersson, 2004; Newman, O'Connor, & Conner, 2008). Interestingly, Johansson et al. (2004) showed that external eaters showed a bias away from, rather than toward, food words presented in a dot probe task. However, this study did not manipulate or measure participants' stress levels. Since external eaters have been found to increase snack intake during periods of stress (Conner et al., 1999), an attentional bias toward food stimuli may emerge when stressed rather than under normal conditions. Newman et al. (2008), using an emotional Stroop task, found partial support for this notion when they observed a significant interaction between external eating and stress for snack food words. Further exploration of the interaction showed two marginal effects: High external eaters tended to have a greater bias in the stress condition than did low external eaters, and low external eaters tended to have a greater bias in the control condition than in the stress condition. That a difference between high and low external eaters only emerged in the stress condition may indicate a difference in processing of snack-related information between high and low external eaters only under conditions of stress. This is consistent with the finding that high external eaters increase snack food intake when stressed (Conner et al., 1999). The construct of external eating and its relationship to stress-induced eating has not as yet been well validated or greatly researched. It might be speculated that the greatest bias scores for snack foods would appear only in high external eaters who are also high-emotional eaters and may be especially prone to stress-induced eating, a possibility that future studies could test.

DIETARY RESTRAINT AND EMOTIONAL EATING

Food-related processing biases have been frequently observed in restrained eaters, emotional eaters, and obese individuals (e.g., Long, Hinton, & Gillespie, 1994; Overduin, Jansen, & Louwerse, 2006; Stewart & Samoluk, 1997; Tapper, Pothos, Fadardi, & Ziori, 2008). In a recent crosscultural study, Tapper et al. (2008) showed that high restraint was associated with a processing bias toward food words using an adapted version of the emotional Stroop. This is consistent with cognitive theories of emotional disorders (e.g., Williams, Mathews, & MacLeod, 1996) that contend that attentional processes, such as schema elaboration, may promote selective bias toward negative stimuli. For example, Waller, Watkins, Shuck, and McManus (1996) showed that bulimic attitudes were associated with an attentional bias toward ego threats that were self-directed. These authors suggested that this finding was accounted for by schema elaboration for those particular forms of threat. Nevertheless, because relatively little research has examined attentional processes in restrained or emotional eaters in response to stress, it is difficult to discern the importance of this line of inquiry. Researchers ought to endeavor to utilize more cognitive techniques, such as the emotional Stroop and the dot probe task, to fully understand the role played by attentional processing biases in stress-induced eating.

BIOLOGICAL MECHANISMS ASSOCIATED WITH STRESS-RELATED EATING

Several plausible psychological and biological mechanisms have been proposed to explain why stress promotes increased food intake in vulnerable individuals. Psychosomatic theory (outlined earlier) contends that the normal response to stress/arousal is loss of appetite (Bruch, 1973; Kaplan & Kaplan, 1957). However, some individuals have an inability to differentiate between hunger and other unpleasant sensations/feelings and as a result react to stress by overeating, a response that is thought to originate in early learning experiences.

Neurohormonal factors have also been investigated. Markus et al. (1998) found that carbohydrate-rich, protein-poor food intake can prevent stress-related deterioration of mood and cortisol elevations in stress-prone individuals via serotonergic mechanisms. These authors argued that carbohydrate-rich, protein-poor diets allow greater uptake in the brain of the precursor amino-acid tryptophan, thus facilitating reduced negative mood and better coping. Moreover, as suggested by Oliver et al. (2000), vulnerable individuals may learn to "self-medicate" by shifting their preferences to low-protein foods such as sweet and high-fat snacks to experience reduced general dysphoria. These findings suggest that important neurohormonal pathways are likely associated with stress-related eating, although further confirmatory studies are required.

Another potential mechanism for stress-induced eating involves the activity of the hypothalamic–pituitary–adrenal (HPA) axis during stress, particularly the release of glucocorticoids from the adrenal cortex. Sapolsky (1998) proposed that corticotropic releasing hormone (CRH) and glucocorticoids (GCs) have opposing effects on appetite such that food intake is inhibited by CRH

and promoted by GC production. Direct manipulations of GC levels support the association of GCs with appetite and food intake. Adrenalectomized rats unable to secrete GC have been shown to consume smaller amounts of carbohydrate relative to other macronutrients (Laugero, 2001), and GC appears to protect against the hypophagic effects of leptin (Zakrzewska, Cusin, Sainsbury, Rohner-Jeanrenaud, & Jeanrenaud, 1997). In humans, the administration of glucocorticoids has been shown to increase energy consumption, especially from carbohydrates and proteins (Tataranni et al., 1996).

Surprisingly, less work has explored the link between cortisol, stress, and eating. However, two recent studies have investigated the role of changes in cortisol levels (i.e., cortisol reactivity) in understanding individual differences in stress-related eating behavior. The first, a laboratory study by Epel, Lapidus, McEwen, and Brownell (2001), found that participants who exhibited a high cortisol response to stress consumed more calories afterwards compared with those who exhibited a low cortisol response. The second, using a naturalistic diary research design (Newman, O'Connor, & Conner, 2007), found a significant positive relationship between daily hassles and between-meal snacking in a sample of high cortisol reactors but not in a sample of low cortisol reactors. The latter study also found that the relationships between the eating style variables (including emotional eating, restraint, external eating, and disinhibition) and snack intake were significantly stronger in the high cortisol reactivity group compared with the low reactivity group. These findings provide strong evidence that the stress-induced release of cortisol may underpin the effects of stress on eating behavior. More alarmingly, the release of GC also appears to promote the release of insulin (Dallman et al., 1994). This combination of insulin release and food consumption increases the likelihood that consumed energy will be stored as fat, particularly around the abdominal region where GC receptors are abundant (Laugero, 2001; Strack, Sebastian, Schwartz, & Dallman, 1995). Therefore, the appetite-stimulating effects of GC may have adverse consequences for obesity and health. Broadly speaking, these findings are consistent with a recently proposed theoretical model of reward-based stress eating, which highlights the role of cortisol and brain reward circuitry in motivating calorically dense food intake (Adam & Epel, 2007; see also Nieuwenhuizen & Rutters, 2008). Adam and Epel (2007) argue that stress, as well as palatable food, can stimulate the release of endogenous opioids and that the latter may protect individuals from the deleterious effects of stress by reducing the activity of the HPA axis. These authors go on to suggest that "repeated stimulation of the reward pathways through either stress induced HPA stimulation, intake of highly palatable food, or both, may lead to neurobiological adaptations that promote compulsive overeating. Cortisol may influence the reward value of food via neuroendocrine/peptide mediators such as leptin, insulin, and neuropeptide Y" (Adam & Epel, 2007, p. 449). Further studies are required to explore the robustness of this new theoretical model.

In addition to the links with obesity, it has also been suggested that the effects of stress on food intake may contribute to increased risk of metabolic syndrome (Brooks, McCabe, & Schneiderman, chapter 29; Epel et al., 2004). The characteristics of metabolic syndrome include obesity, insulin resistance (or type II diabetes), high blood pressure, high blood triglyceride levels, and low *high-density lipoprotein* cholesterol levels. Recently, Epel et al. (2004) examined the effects of self-reported stress–eating tendencies (more eaters vs. less eaters) in a longitudinal study. They assessed changes in cortisol, insulin, adiposity, lipid levels, and food intake from baseline to exam-stress periods in a sample of medical students. These authors found that increases in weight, cortisol, insulin, and lipid profile in response to stress were only observed in those who respond to stress by eating more and not in those who respond to stress by eating less. Taken together, these findings indicate that stress-related changes in food intake, if maintained overtime, may be a risk factor for the development of metabolic syndrome as well as obesity, CVD, and cancer. Larger and more comprehensive longitudinal investigations are required to determine more precisely the causal pathways.

CONCLUSION AND FUTURE DIRECTIONS

This review of research on the effects of stress on eating behavior indicates both the range of knowledge we have acquired and the important remaining gaps for future research to address. Considerable evidence now indicates that the impact of stress on eating behavior is an important pathway through which stress influences health outcomes. Stress can be associated with overall increases or decreases to the amount eaten as well as changes in the patterns of eating. However, the nature of the eating behavior, as well as the type of stressor, is key in determining what the effect of stress will be. Much recent research has shown how stress is associated with increases in the consumption of high-fat and high-sugar foods, particularly when consumed as fast food or between-meal snacks (e.g., O'Connor et al., 2008; Steptoe et al., 1998). Future research could fruitfully explore the effects of stress on a broader range of eating behaviors (e.g., meals and snacks) and use more precise measurements of food intake (e.g., 24-hour recall). In relation to the stressor, ego-threatening, work, and interpersonal stressors appear to be particularly likely to show associations with increased eating (e.g., Wallis & Hetherington, 2004), whereas physically threatening stressors are generally associated with decreased eating (e.g., O'Connor et al., 2008). More detailed research is required to further elucidate the exact impacts of different types of stressors on eating and how these might interact. Understanding of the stress–eating behavior relationship is further

complicated by the presence of various important moderating effects. Here, evidence specifically suggests that stress–eating relationships are strongest among individuals high in restraint, disinhibition, external eating, or emotional eating, with one study having identified emotional eating as the preeminent moderating variable (O'Connor et al., 2008). Future research could usefully follow the suggestion from some authors (e.g., Conner et al., 1999) to simultaneously assess the effects of various moderators.

In addition to pursuing carefully designed studies in the laboratory, future research should also consider using innovative multilevel, daily diary methods in naturalistic settings. Daily diaries allow researchers to identify more closely "real-time" occurrences or moments of change in study variables, reduce recall bias, decrease potential confounding by using participants as their own controls, and provide stronger tests of causality in naturalistic settings (Affleck et al., 1999). Previous research has given insufficient attention to evidence indicating that assessment of fluctuations in within-person daily events is important (cf., Affleck et al., 1999; O'Connor & Ferguson, 2008). Using daily diary techniques, interval-contingent (i.e., assessments completed at the end of each day), event-contingent (i.e., assessments completed in response to an event), or signal-contingent methods (i.e., assessments completed in response to random alarms or beeps from a palmtop computer) can be employed. In such designs, participants complete diaries each night at a fixed time period, during each day triggered by stressful encounters, or in response to random signals. This methodology facilitates the use of the powerful multilevel random coefficient modeling techniques. This approach provides accurate analyses of multilevel data structures and allows the modeling of day-to-day within-person effects together with the impact of between-person factors such as potential vulnerability variables (emotional eating, restraint, etc.; see O'Connor et al., 2008, for an example in the stress–eating area).

A further important area for development is in relation to exploration of the psychological and biological mechanisms underlying the stress–eating relationship. As our review makes clear, these mechanisms are likely to be complex if they are to account for the complexity of findings reported. Interesting research has focused on various attentional biases that might explain some of these effects (e.g., Tapper et al., 2008), although further research using more sophisticated techniques (e.g., dot probe task) is required to clarify the consistency of these effects. Advances are also being made in relation to understanding biological mechanisms. For example, differences in cortisol reactivity appear to offer one explanation of some moderating effects on the stress–eating relationship (Newman et al., 2008). However, further careful assessment of daily fluctuations in cortisol levels in relation to changing stress levels is required to clarify the importance of this pathway. Moreover, several of the studies reviewed here also point to diathesis–stress mechanisms that suggest that psychological vulnerabilities, when activated by stress, may result in negative outcomes. For example, coping styles (the behavioral and cognitive responses individuals consistently use when they encounter stress), in particular, have been shown to have well-established moderating effects on an individual's response to a stressful encounter (cf., O'Connor & O'Connor, 2003). It would therefore be beneficial for future research to assess the psychological factors (e.g., coping) associated with the cortisol response to stress and to test whether this differs according to stressor type (e.g., ego-threatening, interpersonal, work-related).

In addition, work on Adam and Epel's (2007) brain reward system notion offers the promise of a fuller explanation of the impacts of stress on eating. Studies that include detailed exploration of stressors and eating behavior and measurement of relevant biological markers may be a useful model for studies hoping to significantly contribute to this area.

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22 Stress and Drug Use

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INTRODUCTION

Stress clearly has profound psychological and biological effects, as revealed by the many and diverse chapters in this *Handbook*. Of these many effects, the association between stress and recreational drug use is fascinating and particularly complex because it involves the interplay of behaviors, cognitions, and motivations with biochemical, physiological, and molecular biological responses to stress and to drug actions. The fact that stress is positively correlated with the self-administration of various recreational drugs suggests that there are common, underlying mechanisms to explain this association. Yet the fact that recreational drugs have markedly different biological actions stalls the rush to a single principle or overarching explanation for the stress–drug use relationship. The fact that drug self-administration involves biologically active substances that affect the brain, autonomic nervous system (ANS), and viscera in ways that mimic, offset, or interact with stress responses further complicates understanding of the stress–drug use relationship. This chapter is focused on particular drugs that are commonly self-administered, legal (nicotine, alcohol, caffeine) or illegal (cocaine, heroin), central nervous stimulants (caffeine, cocaine), central nervous depressants (alcohol, heroin), or both (nicotine; see Table 22.1). The chapter begins with separate, brief discussions of stress, substance use, and each of the five substances to provide background information relevant to the stress–drug relationship. Next, the relationship between stress and each substance is reviewed. Then, many of the explanations that have been offered to account for the stress–drug use relationship are catalogued into four separate groups: (1) drug use decreases stress ("self-medication hypotheses"), (2) abstinence from drug use is altered by or resembles stress ("withdrawal hypotheses"), (3) stress alters drug actions ("pharmacodynamic hypotheses"), and (4) drug use increases stress ("positive feedback loop hypotheses").

WHAT IS STRESS?

Stress is the process by which environmental demands tax or exceed the adaptive capacity of the organism (Baum, Gatchel, & Krantz, 1997). The stress response may constitute eustress (stress resulting from positive stimuli) or distress (stress resulting from negative stimuli; Selye, 1976). Stress causes physiological responses in the body that help an organism to maintain homeostasis during the demands of the stressor, including activation of the ANS. Sympathetic nervous system (SNS) arousal (including release of the catecholamines epinephrine, norepinephrine, and dopamine; increased heart rate, blood pressure, and respiration; dilation of the pupils; increased blood flow to the skeletal muscles; and an increase in blood glucose) is part of the stress response and also occurs in response to some drugs (e.g., caffeine, cocaine, amphetamines, nicotine) that sometimes are called sympathomimetics, central nervous system (CNS) stimulants, or just stimulants. Interestingly, catecholamines (especially dopamine) are involved in drug reward in the ventral tegmental area (VTA) of the brain, an area that has been implicated as central to drug addiction.

The ANS response also includes alterations in activity of the parasympathetic nervous system, which acts to calm the body by decreasing heart rate, blood pressure, and respiration, constricting the pupils, and dilating the blood vessels. Drugs known as CNS depressants (e.g., alcohol, opiates [such as heroin], benzodiazepines, and barbiturates) mimic the actions of the parasympathetic system. Nicotine, a sympathomimetic, has CNS depressant as well as CNS stimulant actions that make it unique among recreational drugs. In addition to the ANS response during stress, there also is activation of the hypothalamus-pituitary-adrenal (HPA) axis. Activation of the HPA axis causes corticotropin-releasing factor (CRF) to be released from the hypothalamus in the brain, adrenocorticotropin (ACTH) from the pituitary in the brain, and cortisol from the adrenal cortex of the adrenal glands

Table 22.1 ■ Drugs of Emphasis in This Chapter

	Legal substances	Illegal Substances	
Stimulants	Caffeine	Cocaine	Nicotine
Depressants	Alcohol	Heroin	("paradoxical drug")

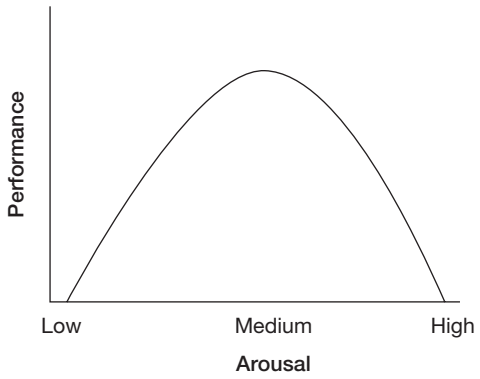

Figure 22.1 ■ Yerkes-Dodson curve.

that sit atop the kidneys. This hormonal system operates as a negative feedback system with the SNS to maintain homeostasis in the body when a stressor occurs. These systems underlie protective psychological and biological responses to acute stress, but can become deleterious and life-threatening when prolonged or severe. The fact that recreational drugs also alter ANS activation is relevant to the stress–drug use relationship. The effect on the ANS can be the mechanism for detrimental effects, but it also is often the reason the drug is used in the first place. For example, individuals use caffeine, a stimulant, to wake up; it increases heart rate and blood pressure, but too much caffeine can lead to heart arrhythmias.

The endogenous opioid peptide (EOP) system also is involved in the body's stress response and actions of many recreational drugs, including opioid and nonopioid drugs. EOPs are responsible for analgesic actions by blunting distress (the affective component of pain) without dulling the sensation. Opioids diminish stress-induced neuroendocrine and autonomic responses and stimulate EOP effector systems in the nonstressed state. Moreover, opioids play a role in the stress response by attenuating the emotion and affect associated with stress and by causing mild euphoria and a sense of well-being (see Drolet et al., 2001, for a complete review).

It also is relevant to the stress–drug use relationship to consider the effects of stress on performance and on emotional reactions. Yerkes and Dodson (1908) proposed that there is an inverse-U shaped relationship between arousal and performance, such that low levels of arousal are associated with low levels of performance, moderate levels of arousal produce high levels of performance, and high levels of arousal produce low performance. This function was based on studies in mice examining effects of electric shock (to manipulate arousal) on performance (i.e., movement to a white box to avoid further electric shock) similar to a passive avoidance task. Yerkes and Dodson found that the number of trials to choose the white box was related to the amount of electrical stimulation by an inverted-U function (see Figure 22.1).

Although Yerkes and Dodson are credited with this "law" of psychology, it actually is remarkably similar to Wundt's inverted-U hedonic curve (Berlyne, 1971) that relates arousal and hedonic tone (or perceived pleasure). Hebb (1955) interpreted the Yerkes-Dodson curve as a relationship between arousal and "cue function." In other words, as arousal increases, stimulus–response (S-R) connections are strengthened and then gradually weaken. Whether arousal (including arousal caused by stress) results in an inverted-U in S-R connection, hedonic response, performance, or a combination of these effects remains unclear, but the so-called Yerkes-Dodson Law may help to account for the stress–substance use relationship and may help to resolve the puzzle of why self-administration of CNS stimulants and depressants increases under stress. More specifically, stimulants may be used under mild arousal to push us up the ascending limb of the Yerkes-Dodson curve, whereas depressants may be used under high arousal conditions to push us back from the descending limb of this function. Nicotine self-administration may be especially common during stress because it seems to jazz people up when they are down but calm them down when they are overaroused.

There also appear to be individual differences in the stress response. There are correlational reports that females show a predisposition toward emotion-based disease (e.g., depression; Becker et al., 2007). Women also self-report that they experience more stress (e.g., Greenglass & Noguchi, 1996). In addition to these reports, Taylor and colleagues (2000) argue that women may differ from men in stress responses with more oxytocin release in females rather than testosterone or other androgen release in males (see Taylor et al., 2000, and chapter 8). The authors contend that there is more of a social affiliation response in females to stressors ("tend and befriend"), rather than the classic "fight or flight" identified by W. B. Cannon (1935), which may be a more common stress response in males. These possible sex differences in stress responses also should be considered along with sex differences in drug use and drug effects. For example, alcohol dependence is more common among males (*DSM-IV-TR*, 2001). There also are sex differences in other drugs of abuse, including nicotine. In the United States, men are more likely to smoke cigarettes (23.9%) than women (18.0%), and men smoke more cigarettes than do women. In developing countries, men smoke dramatically more than do women (Centers for Disease Control [CDC], 2007). If we can better understand individual differences in the stress response, then this knowledge may have clinical utility in treating substance abuse and other mental health disorders.

WHAT IS SUBSTANCE USE?

This chapter is focused on specific recreational drug use, which also may involve drugs acting as reinforcers, addictive substances, and abused substances. Drug use refers to the self-administration of at least one nonprescribed drug. Drug reinforcement is the capacity of the drug to maintain self-administration (O'Brien, 2006). Drug addiction or drug dependence occurs when there is highly controlled or compulsive drug use. Addictive behaviors often involve stereotypic patterns of use, use despite harmful effects, relapse following abstinence, and recurrent drug cravings. Furthermore, dependence-producing drugs often produce tolerance (i.e., drugs have weakening effects with repeated administration or greater amounts of drug are required to have similar effects), physical dependence, pleasant or euphoric affect, and withdrawal effects after cessation (United States Department of Health and Human Services [USDHHS], 1998). Drugs vary in their addiction potential based on properties of the drug itself, individual biological and psychological differences, and interactions with environmental variables. Drugs with potent reinforcing properties are more likely to lead to substance abuse or dependence. Withdrawal refers to the development of a substance-specific syndrome that interferes with functioning and is the result of cessation or reduction in substance use that has been heavy and prolonged. Substance abuse is commonly based on the definition in the *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition ([*DSM-IV*]; American Psychiatric Association, 1994), which includes symptoms such as recurrent use in situations where it presents a physical danger, failure to meet obligations at work or school, or recurrent social or interpersonal problems caused by effects of the drug. According to the National Institute on Drug Abuse's (NIDA, 2007) Web site:

> Addiction is a chronic, often relapsing brain disease that causes compulsive drug seeking and use despite harmful consequences to the individual that is addicted and to those around them. Drug addiction is a brain disease because the abuse of drugs leads to changes in the structure and function of the brain.

Many variables affect drug onset, continued use, abuse, or addiction. Relevant drug variables include availability, cost, potency, mode or route of administration, and speed of onset. Relevant person variables include hereditary tolerance, drug metabolism, psychiatric symptoms, prior experiences/expectations, and propensity for risk-taking behavior. Environmental variables include the social setting (e.g., a bar vs. the office), community attitudes, availability of other reinforcers, employment or educational opportunities, and conditioned stimuli (environmental cues become associated with drugs after repeated use in the same environment; O'Brien, 2006).

SUBSTANCES OF FOCUS

Drugs of abuse and recreational drugs are often categorized by pharmacological groups: CNS stimulants; CNS depressants; psychedelics (e.g., marijuana, peyote, lysergic acid diethylamide [LSD], phencyclidine [PCP]); and inhalants. Drugs of abuse also can be categorized as licit (e.g., nicotine, caffeine, alcohol, and over-the-counter drugs) or illicit (e.g., cocaine, heroin). Each of these categories is large and the effects of stress on each of them could be a chapter in itself. Therefore, this chapter focuses on the most widely used licit stimulant (caffeine), illicit stimulant (cocaine), licit depressant (alcohol), illicit depressant (heroin), and a paradoxical drug that has stimulant and depressant actions (nicotine).

Nicotine

Nicotine is a tertiary amine made up of pyridine and pyrrolidine rings and is the pharmacologic agent of addiction in tobacco. Nicotine is an oily liquid that forms salts with acids. It occurs naturally in the tobacco plant, with a high concentration in the leaves. In humans, nicotine is administered most often via smoking (through cigarettes, cigars, pipes, or hookah). Nicotine also can be administered orally through chewing and smokeless tobacco, transdermally via nicotine patch, or by aerosol inhalation. It has a relatively short half-life (about 2 hours in humans), which helps to explain why addicted smokers self-administer nicotine so often (USDHHS, 1998).

Nicotine acts at nicotinic acetylcholine receptors (nAChRs) in the brain and nervous system to stimulate dopaminergic, glutamatergic, and cholinergic nerve terminals. Stimulation of nAchRs in the VTA of the brain enhances dopamine release in the nucleus accumbens (NAcc), which is thought to play a key role in the reinforcing effects of many drugs (Feldman et al., 1997).

Approximately 20% of adults in the United States smoke tobacco cigarettes (CDC, 2007). Smoking rates have decreased in recent years in the United States but are increasing in developing nations. In the United States, it is estimated that roughly 4,000 youth try smoking every day and that about 2,000 become regular smokers (World Health Organization, 2006). The health hazards associated with tobacco smoking are well documented and profound. Worldwide, someone dies every 8 s from tobacco use and it is the single most preventable cause of death. Health hazards include cardiovascular diseases, pulmonary damage, and a variety of cancers (CDC, 2006). Potential cardiovascular outcomes include myocardial infarction, sudden cardiac death, peripheral vascular disease, atherosclerosis, and hypertension. Pulmonary changes include lung damage, decreased pulmonary function, histologic abnormalities, and chronic obstructive pulmonary disease. Cancers occur everywhere that carcinogens in tobacco reach in the body, including the lung, larynx, oral cavity, esophagus, urinary bladder,

kidney, and pancreas. Despite these well-publicized health hazards, people continue to use tobacco products largely because of the highly addictive actions of nicotine and other psychobiological effects that people enjoy.

Nicotine stimulates the SNS and, therefore, increases heart rate and respiration. In small to moderate doses it causes release of catecholamines from isolated organs; large doses prevent catecholamine release from the adrenal medulla. Nicotine also can induce vomiting by stimulating emetic chemoreceptors and cause an alert EEG pattern (low voltage, fast activity), decrease skeletal muscle tone, decrease amplitude in EMG, decrease deep-tendon reflexes, and increase plasma levels of growth hormone, cortisol, and glycerol (Jaffe, 1980). Nicotine increases plasma glucose levels and circulation levels of endogenous opioids, and acts to decrease body weight (Glauser, Glauser, Reidenberg, Rusy, & Tallarida, 1970; Grunberg, 1982; Pomerleau, 1981; Wack & Rodin, 1982; USDHHS, 1998).

Repeated administration of nicotine is accompanied by tolerance, dependence, and withdrawal following abstinence. Withdrawal from nicotine includes nausea, headache, constipation, irritability, insomnia, inability to concentrate, decrease heart rate and blood pressure, and weight gain. These effects can last for weeks with the most intense symptoms occurring in the first few days after cessation.

Alcohol

Ethanol, more commonly known as alcohol, is a two-carbon alcohol (CH_3CH_2OH) and a CNS depressant. More than 90% of American adults report experience with alcohol and approximately 70% report some level of current use. The lifetime prevalence of alcohol abuse and dependence (alcoholism) in the United States is 5% to 10% for men and 3% to 5% for women (O'Brien, 2006). Alcohol is administered orally through beverages such as beer, wine, or liquor. The alcohol content of beverages typically ranges from 4% to 6% for beer, 10% to 15% for wine, and 40% or higher for distilled spirits.

Alcohol is a general CNS depressant and causes decreased heart rate and blood pressure and vasodilation. It enhances cutaneous and gastric blood flow, which results in a feeling of warmth. Alcohol also can stimulate the release of adrenocortical hormones and lead to an increase in the urinary excretion of epinephrine and norepinephrine.

Prolonged alcohol use can result in the disruption of sleep patterns including EEG and evoked cortical responses, increases in hepatic microsomal enzyme activity, fatty liver, cirrhosis of the liver, damage to the cardiac and skeletal muscle, and cerebral atrophy. Repeated administration can result in tolerance and/or dependence. Withdrawal symptoms of prolonged alcohol use include tremulousness, nausea, weakness, anxiety, sweating, cramps, vomiting, hyperreflexia, hallucinations, and possibly grand mal seizures. Attention and motor reflex disruptions caused by moderate to high levels of alcohol intake contribute to alcohol-related traffic and other accidents.

Amphetamines, Cocaine, and Caffeine

Amphetamines are racemic β-phenylisopropylamines. Examples of amphetamines include methamphetamine, dextroamphetamine (Dexedrine), and methylenedioxymethamphetamine (also known as Ecstasy). Depending on the specific amphetamine, methods of administration can include oral, intravenous, or intranasal (snorting/sniffing). Amphetamines stimulate the CNS and increase synaptic levels of norepinephrine and dopamine. They increase blood pressure, cause a reflexive decrease in heart rate, relax bronchial smooth muscle, and decrease gastrointestinal motility. Amphetamines have a host of behavioral effects including sleeplessness, decreased appetite, elevated mood, and increased alertness. Some amphetamine use can result in a sense of physical strength, energy, and mental capacity.

There are additional effects associated with excessive amphetamine use including anxiety, irritability, loquaciousness, and drowsiness. Acute intoxication may result in dizziness, tremor, irritability, confusion, tachycardia, headache, hallucination, chest pain, heart palpitations, hypertension, sweating, cardiac arrhythmias, and even death. Toxic symptoms may include bruxism, touching and picking at the face and extremities, and paranoia.

Cocaine also stimulates the CNS. It occurs in an alkaloid form that lends itself to smoking and a hydrochloride potassium form that is used for nasal or intravenous use. Cocaine has a shorter half-life than many other stimulants.

It is estimated that more than 23 million Americans have used cocaine at some point, but the number of current users has declined markedly since the 1980s. The breakdown in numbers and type of use is estimated to be 8.6 million occasional users, 5.8 million regular users, and 3.6 million chronic cocaine users. Cocaine stimulates the CNS, blocks the initiation or conduction of nerve impulses, and potentiates the response of sympathetically innervated organs to norepinephrine. Cocaine leads to increased dopamine concentrations in the brain by blocking dopamine reuptake at presynaptic sites.

Health hazards of cocaine include irritability, loss of appetite, paranoia, and lethal effects. Tolerance develops to repeated cocaine administration. Withdrawal symptoms include craving for the drug, prolonged sleep, general fatigue, lassitude, hyperphagia, and possibly depression (Jaffe, 1980; Johanson, 1986).

Caffeine is the most commonly used CNS stimulant. It is a plant alkaloid closely related to the methylated xanthines, theophylline, and theobromine. Caffeine usually

is self-administered orally in beverages, such as coffee and soft drinks, or in foods including chocolate.

It is estimated that 80% of Americans are coffee drinkers (64% daily drinkers). Caffeine is a direct stimulant of the CNS that increases respiration, stimulates voluntary muscles, decreases fatigue, increases alertness, and serves as a mild diuretic. Caffeine is not generally considered by the public to be a dangerous drug, but that is because doses usually are quite low. In extremely high doses, caffeine's effects can be similar to amphetamines and cocaine. Like other stimulants, it can be addictive. Yet estimates of caffeine addiction prevalence are not well researched. One telephone survey did find that 30% of individual who used caffeine met *DSM-IV-TR* criteria for caffeine dependence (Griffiths, Juliano, & Chausmer, 2003). Of individuals who meet *DSM-IV* criteria for caffeine dependence, 10% to 55% of them show clinically significant impairments during withdrawal (Juliano & Griffiths, 2004). In large doses, caffeine also can lead to arrhythmias or mental changes (e.g., irritability). Withdrawal symptoms include headaches, fatigue, lethargy, and depression (*DSM-IV-TR*, 2001).

Opioids and Heroin

"Opioid" refers to all compounds related to opium (exogenous and endogenous). Opiates refer to drugs that affect opioid systems in the body. Opium is a drug derived from the juice of the opium poppy that contains more than 20 distinct alkaloids. Opioid drugs (or opiates) act on the endogenous opioid system, which is made up of three classes of opioids: enkephalins, endorphins, and dynorphins. Each opioid class has a different role but they share the common amino-terminal sequence of Tyr-Gly-Gly-Phe-(Met or Leu). Opioid drugs also are called narcotics (based on the word "narcosis" or sleep). They are commonly used to treat pain (e.g., morphine) but also are common drugs of abuse (e.g., heroin, which is diacetylmorphine). Routes of administration are oral or via intravenous administration. Approximately 1% to 2% of individuals in the United States have used heroin (Gutstein & Akil, 2001). Opiates prescribed for pain are the most commonly abused prescription drugs.

Opiates have significant effects on the CNS and the bowel. They also have analgesic, euphoric, sedative, and addictive effects. Respiratory depression and decreased blood pressure, emesis, warm flushing of the skin, and sensation in the lower abdomen may occur. Other effects include decreased intestinal contractions, delayed gastric emptying, decreased gastric contractile activity, restriction of the pupils, changes in temperature, and inhibition of norepinephrine release from sympathetic neurons.

Chronic administration of opiates results in an eventual decrease in glucocorticoid secretion. Morphine also increases levels of ACTH and decreases hypothalamic levels of norepinephrine. Tolerance develops to the analgesic, sedative, emetic, and euphoric effects of opiates. There appears to be little tolerance for the gastrointestinal effects that cause constipation. Acute administration of heroin can be dangerous because of its depressant effect on respiration and blood pressure.

Withdrawal occurs after cessation from chronic use and can include CNS hyperexcitability, nausea, cramps, lacrimation, rhinorrhea, yawning, sweating, tremors, and increased respiration, dilated pupils, anorexia, gooseflesh, restlessness, irritability, insomnia, tremor, weakness, increased heart rate, increased blood pressure, and diarrhea.

THE RELATIONSHIP BETWEEN STRESS AND DRUG USE

Now that stress and several recreational drugs have been briefly discussed, we turn to the relationship between stress and each of the drugs highlighted above. The relevant information is summarized and, where available, specific explanations for the individual drug relationships with stress are provided.

Stress and Nicotine

Stress is associated with the initiation and maintenance of tobacco use (Kassel, Stroud, & Patronis, 2003). Cigarette smokers report that they smoke more when they are stressed, angry, anxious, or sad (McKennell, 1970; Russell, Peto, & Patel, 1974; Shiffman, 1993). Smoking increases after adverse childhood experiences (Anda et al., 1999), negative life events (Koval & Pederson, 1999), acute and chronic stressors (Koval, Pederson, Mills, McGrady, & Carvajal, 2000), and perceived stress (Dugan, Lloyd, & Lucas, 1999). Some research suggests that this relationship may be more pronounced in cases of social stress based on gender (Byrne & Mazanov, 1999) or race (Biafora, Warheit, Vega, & Gil, 1994). Smokers commonly report that smoking reduces anxiety (Frith, 1971; Leventhal & Cleary, 1980) and alleviates negative moods (Brandon & Baker, 1991; Copeland, Brandon, & Quinn, 1995). Many smokers report that they lapsed or relapsed to smoking while experiencing stress or negative affect (Borland, 1990; Cummings, Jaen, & Giovino, 1985; Shiffman, 1982; Swan et al., 1988). Yet smokers also report more stress than nonsmokers (e.g., Jorm et al., 1999; Naquin & Gilbert, 1996; Vollrath, 1998).

Nicotine (in tobacco) is usually classified as a stimulant because it often increases CNS arousal and acts to stimulate the SNS. So, the relationship between stress and smoking/nicotine is a bit more difficult to understand and nicotine is, therefore, considered to be a paradoxical drug (because it acts as a stimulant, yet it also is reported to induce a calming effect). In the laboratory, stress increases smoking intensity (e.g., Pomerleau & Pomerleau, 1987), amount smoked (Epstein & Collins,

1977; Rose, Behm, & Levin, 1993; Schachter, Silverstein, et al., 1977; Schachter, Kozlowski, & Silverstein, 1977), and desire to smoke (Perkins & Grobe, 1992). Whether smoking actually reduces stress or whether abstinence from smoking increases stress (so that smoking only reduces stress by contrast) is not clear (Grunberg & Kozlowski, 1986; Schachter, Kozlowski, et al., 1977; Schachter, Silverstein, et al., 1977).

Stress and Alcohol

Many people report that they drink alcohol in response to stress (Pohorecky, 1991). Alcohol use has been associated with a wide range of stressors, including exposure to traumatic stress (e.g., Donovan, Padin-Rivera, & Koaliw, 2001), unhappy marriages, and dissatisfaction with employment (Jose, van Oers, van de Mheen, Garretsen, & Mackenbach, 2000). Alcohol also is used to cope with tension associated with stress in the environment (Tyseen, Vaglum, Aasland, Gronvold, & Ekeberg, 1998) or to relieve symptoms of anxiety, irritability, and depression in individuals with posttraumatic stress disorder (PTSD; Volpicelli, Balaraman, Hahn, Wallace, & Bux, 1999). Furthermore, stress may exert its greatest influence in precipitating the initial consumption of alcohol after a period of abstinence (Brown, Vik, Patterson, Grant, & Schuckit, 1995). Rats exposed to stress increase alcohol self-administration (Higley, Hasert, Suomi, & Linnoila, 1991; Hilakivi-Clarke & Lister, 1992; Volpicelli, 1987). The fact that alcohol is a CNS depressant makes sense as an account for the stress–alcohol relationship. Yet there also is evidence that drinking alcohol produces physiological stress (Meaney et al., 1995; Rivier, Imaki, & Vale, 1990; Tsigos & Chrousos, 1995; Waltman, Blevins, Boyd, & Wand, 1993), which clouds an otherwise clear picture. There also may be individual differences underlying whether one drinks in response to stress. Some factors that potentially mediate the stress–alcohol use relationship are genetic determinants of drinking in response to stress, expectations regarding the effect of alcohol on stress, type of stressor, sense of control over the stress, and the range of available responses for coping with stress (e.g., Clarke et al., 2008; Jennison, 1992; Pohorecky, 1991; Sadava & Pak, 1993; Volpicelli, 1987).

Stress and Cocaine

Cocaine use increases during stress in humans and animals (e.g., Goeders, 1997; Kreek & Koob, 1998) even though cocaine, a sympathomimetic, clearly stimulates many of the same neurochemical and hormonal systems activated by stress exposure (e.g., CRF, ACTH). Cocaine can even produce anxiety and panic in humans and anxiogenic responses in animals through its effects on CRF release (Goeders, 1997, 2002). Cocaine stimulates parts of the mesolimbic area of the brain (the area involved in feeling pleasure), which may help to explain the stress–cocaine relationship (Kreek & Koob, 1998). In humans, individuals with a history of cocaine use reported more cocaine craving and negative affect in response to stress and drug cue imagery but not with neutral-relaxing imagery (Sinha, Fuse, Aubin, & O'Malley, 2000). In a sample of individuals who were dependent on cocaine, individuals who were more sensitive to daily hassles used more cocaine (Waldrop et al., 2007). Stress and cocaine also interact to affect reward during various phases of cocaine self-administration and withdrawal. During acquisition of cocaine self-administration, rats exposed to physical or social stress increase cocaine intake (Goeders, 2002). During reinstatement (a preclinical method that is widely regarded as an animal model for the propensity to relapse drug use) and relapse, stress also is associated with cocaine intake.

Stress and Caffeine

There is little empirical research directly relevant to effects of stress on caffeine consumption. One study did find that 41% of habitual coffee drinkers self-reported that they increase consumption under stress and faced with a lab test in which stress was perceived they did increase their coffee consumption (Ratliff-Crain, 1991). There is a wealth of literature on how caffeine affects the stress response (e.g., Goldstein, Kaizer, & Whitby, 1969). If caffeine use is altered during times of stress, then there would be at least two possible explanations. First, caffeine use may increase because caffeine is a mild CNS stimulant that decreases feelings of fatigue (Patat et al., 2000). Given that stress can result in less sleep, caffeine may alleviate this negative effect of stress. A second, alternative explanation is that caffeine use decreases in response to stress because caffeine consumption also can result in increased anxiety ratings in nonclinical populations (Chait, 1992; Goldstein et al., 1969) and individuals with high baseline measures of anxiety are less likely to choose caffeine over placebo in a blind choice procedure (Evans & Griffiths, 1992; Griffiths & Woodson, 1988). The stress–caffeine use/effect relationship appears to be more complex than a simple, linear function or a single underlying mechanism of action.

Stress and Opiates (e.g., Heroin)

There is a strong relationship between stress and heroin use, particularly with regard to heroin reinstatement (e.g., Bossert, Ghitza, Lu, Epstein, & Shaham, 2005; Shaham, Shalev, Lu, De Wit, & Stewart, 2003; Shalev, Grimm, & Shaham, 2002). Stress is one of the best predictors of relapse in individuals addicted to opiates (Brewer, Catalano, Haggerty, Gainey, & Fleming, 1998). Also, stress increases rat self-administration of morphine (Shaham, Alvares, Nespor, & Grunberg, 1992; Shaham, Klein, Alvares, & Grunberg, 1993; Shaham & Stewart,

1994). Because endogenous opioids and exogenous opiates inhibit the stress cycle and produce feelings of well-being and euphoria, it could be that heroin and other opiates (e.g., morphine) blunt the stress response and experience of stress (Kreek & Koob, 1998).

EXPLANATIONS FOR THE RELATIONSHIP BETWEEN STRESS AND DRUG USE

It is clear that stress and recreational drug use are related, but why? This section describes explanations that have been offered and also proposes new ones. We categorize these explanations into four broad groups that we believe are most likely to help explain the stress–drug use relationship: (1) self-medication hypotheses, (2) withdrawal hypotheses, (3) pharmacodynamic hypotheses, and (4) positive feedback loop hypotheses.

SELF-MEDICATION HYPOTHESES

Self-medication is a popular explanation for why there is a stress–drug use relationship. Simply put, individuals use a given drug under stress to reduce stress. Actually, even this "simple" explanation is a large bin with several different possible mechanisms. For example, the drug may actually decrease the body's stress response; the drug may maintain performance (either behavioral or cognitive performance) during stress but not actually decrease stress; or the drug may distract the user from a stressor or stress response. The drug also may act indirectly to help buffer stress. Each of these self-medication hypotheses is discussed below.

Drugs Decrease Stress

Self-administration of CNS depressants, especially under stress, is consistent with this particular self-medication hypothesis. Stress is arousing. CNS depressants reduce arousal. Therefore, CNS depressants are taken during stress to reduce it and the more stress, the more CNS depressants are taken. With regard to the recreational drugs discussed in this chapter, this explanation works for alcohol, opiates, and possibly nicotine (because of its "paradoxical" actions).

Another source of evidence for this hypothesis comes from the relationship between drug use and depression. It has been suggested that recreational drug use and dependence involve self-medication to reverse neurotransmitter abnormalities associated with depression (e.g., Khantzian, 1997; Koob & LeMoal, 2008; Markou, Kosten, & Koob, 1998). To the extent that depression is a stressful state, this hypothesis about depression and drug use might be generalized to stress and drug use. Even if the depression argument cannot be generalized to stress in the broad sense, it does offer the possibility that drugs other than CNS depressants per se may act to medicate a stressful state (via normalization of neurotransmitter levels).

Drugs Help to Maintain Performance

Drug use might increase as a method of self-medication to help maintain performance while stressed (e.g., increase attention, decrease distraction, and maintain energy level). Many students and professionals use stimulants (including caffeine, cocaine, amphetamines, and the paradoxical nicotine) during stressful periods that demand long hours of work in order to stay awake and to perform (University of Michigan Health System, 2008). This particular explanation, therefore, can account for the stress–CNS stimulant relationship, but not for the stress–CNS depressant relationship.

Drugs Affect Attention

Another variant of self-medication emphasizes cognitive mechanisms (rather than cognitive performance). People may use drugs under stress to increase attention, to focus or "narrow" attention, or to reduce the interference of distracters (e.g., Kassel, 1997; Kassel & Shiffman, 1997). These attention effects can then serve indirectly to reduce anxiety or negative affect that is associated with the stressor. This particular explanation is consistent with that fact that shifts in attention for drug-related stimuli are implicated in drug addiction (e.g., Field, 2005). Attentional bias for drug-related stimuli (defined a phenomenon whereby attentional channeling is directed toward a drug despite an individual's efforts to ignore them it; Williams, Mathews, & MacLeod, 1996) predicts relapse to cigarette smoking (Waters et al., 2003) and to alcohol use (Cox, Hogan, Kristian, & Race, 2002) in individuals attempting to quit. Manipulating attentional bias for alcohol-related stimuli causes participants trained to attend to alcohol-related stimuli to experience increased craving for alcohol and to consume more alcohol than participants trained to attend away from alcohol-related stimuli (Field & Eastwood, 2005).

Also relevant to this discussion is Franken's (2003) hypothesis that dopamine mediates attentional bias and Oswald et al.'s (2005) report regarding interrelationships among cortisol levels, subjective responses to amphetamines, and dopamine (DA) release. Attentional bias for drug-related stimuli increases motivation to consume drugs. Drug use may increase under stress because stress-induced dopamine release increases attentional bias for drug-related stimuli, which increases craving and leads to increased consumption. This version of the self-medication hypothesis is relevant to any drug that alters dopamine release, which includes most, if not all, recreational drugs and even some prescription drugs.

Drug Use Increases Social Support

A different explanation that can be viewed as a self-medication hypothesis is that stress increases drug use because drug use increases social interactions that act to buffer stress. For example, smoking is frequently used as a social tool (e.g., Russell et al., 1974). Kassel et al. (2003) suggested that cigarette smoking decreases negative affect by promoting social interactions. Social support decreases stress responses in humans (Kirschbaum, Klauer, Filipp, & Hellhammer, 1995) and animals (e.g., Westenbroek et al., 2003) and thereby acts to "buffer" stress (Cohen & Wills, 1985). Therefore, to the extent that drug use involves increased social interaction, the drug use may act indirectly to buffer stress. This explanation could be applied to any of the drugs, regardless of pharmacological class, if their use involves increased social interaction.

Drugs Might Alter Extinction Learning

Another variation of the self-medication explanation is that drug use decreases stress by enhancing extinction learning which in turn diminishes memories for negative events. Davis, Walker, and Myers (2003) have suggested that extinction learning is disrupted in PTSD, thereby enhancing memories associated with traumatic events (or decreasing the naturally protective process of extinguishing unpleasant memories). Furthermore, they suggest that receptor activation of the neurotransmitter N-methyl-D-aspartate (NMDA) in the amygdala is critical for the extinction of fear and other negative emotions. Extinction is a conditioning phenomenon that occurs when presentation of a conditioned stimulus ceases to elicit the conditioned response and is a component of treatment for conditioned fear disorders, such as phobias and PTSD. It appears that NMDA is critical for learning new associations in extinction. So if drugs augment the release of NMDA, then drug use may serve to reduce stress by increasing the learning of new stimulus-response contingencies. This novel idea fits under the self-medication category but involves neurobiological and cognitive mechanisms. If, indeed, drugs discussed in this chapter act on NMDA (as many do), then they may act via this extinction learning mechanism.

WITHDRAWAL HYPOTHESES

Another, quite different set of explanations for the stress–drug use relationship focuses on withdrawal symptoms associated with abstinence from previously self-administered drugs. This set of explanations is not as straightforward as the self-medication hypotheses, and it too has several variations.

Pharmacokinetic Explanations

Stress may alter the pharmacokinetics (i.e., the distribution, absorption, metabolism, or elimination) of drugs in the body in ways that increase the self-administration of the drugs. For example, Schachter, Kozlowski, et al. (1977) argued that stress acidifies the urine, thereby increasing the elimination of unmetabolized nicotine from the body, resulting in increased cigarette smoking to replenish the lost nicotine to avoid the unpleasant state of nicotine withdrawal. According to this stress-drug use explanation, cigarette smoking does not relieve stress in general. Instead, stress precipitates increased smoking withdrawal and smoking increases to offset this exacerbated unpleasant state. Smokers perceive that smoking relieved stress but, instead, stress exaggerated and hastened nicotine withdrawal. Although increased smoking alleviates the stress-potentiated withdrawal, it does not reduce stress compared with a "baseline stress" state. This negative reinforcement explanation for why smoking increases under stress was based on the physical chemistry and pharmacokinetics of nicotine (Beckett, Rowland, & Triggs, 1965; Beckett & Triggs, 1966; Grunberg, Morse, & Barrett, 1983). It also could be applied to opiates, cocaine, and perhaps caffeine (based on physical chemistry and responses to pH alterations) but is unlikely to explain the alcohol–stress relationship.

Psychological Explanations

Alternatively, stress may precipitate drug self-administration because the experience of stress resembles the unpleasant state of withdrawal that accompanies abstinence from dependence-producing drugs. As a result, individuals misinterpret the experience of withdrawal as the experience of stress. This Cognitive Misattribution Model (Grunberg & Baum, 1985) suggests that drugs are taken to offset stress because the same drugs offset withdrawal. So, over time, the cognitive misattribution becomes a strongly learned response. This explanation is consistent with Pham's (2007) report that individuals misattribute the valence of their incidental affective states, their arousal, and cognitive appraisal components. Incidental emotional arousal can be misinterpreted as an integral affective response to a target stimulus (e.g., Dutton & Aron, 1974). Classical and operant learning processes are likely to be involved in and reinforce the misattribution.

Another related psychological explanation based primarily on nicotine withdrawal research also might explain stress and drug use. When an individual addicted to nicotine abstains from drug use, a withdrawal syndrome of negative psychological symptoms results, including irritability and negative affect (Hughes, Higgins, & Hatsukami, 1990; Shiffman, 1979). Nicotine self-administration to offset this unpleasant withdrawal is an example of negative reinforcement. Parrott (1995) termed this phenomenon "nicotine withdrawal escape" and emphasized the reduction of negative affect. The notion of escape can be extended and applied to any drug that involves withdrawal states after cessation of repeated administration. People increase drug use to reduce negative psychological symptoms associated with withdrawal

from a drug. When stress increases negative affect, drug use would increase to "escape" the negative affect. This explanation, therefore, overlaps with the cognitive misattribution model and the self-medication hypotheses.

Neurobiological Explanations

Kreek and Koob (1998) offered a neurobiological explanation for the stress–drug use relationship that drew primarily from studies with cocaine and hypothesized a key role for the HPA axis and withdrawal. Recently, Koob's research group has built upon this early explanation based on empirical work with nicotine. More specifically, George et al. (2007) reported that nicotine withdrawal recruits the CRF system and activates CRF(1) receptors, resulting in anxiety-like behaviors. This response is part of the HPA axis activity that is central to the stress response. Additional stressors during withdrawal may augment the CRF-CRF(1) system and exacerbate withdrawal. There also is evidence that brain stress/emotional systems are activated and provide an additional source of negative hedonic valence (i.e., unpleasant feeling) during withdrawal (Koob & LeMoal, 2006). Therefore, increased drug use under stress may modulate the HPA axis via the same mechanisms that are involved during withdrawal. This neurobiological explanation has some overlap with the self-medication hypotheses but the emphasis is on withdrawal. There also is some overlap with the psychological withdrawal hypotheses because of the hedonic component of this explanation. It would apply to any drug that involves the HPA-axis in withdrawal.

PHARMACODYNAMIC HYPOTHESES

There is some compelling evidence that stress itself may alter drug actions and thereby explain why drug use increases during stress. Pharmacodynamic explanations for the stress–drug use relationship hold that increased stress leads to increased drug response and increased reward, which in turn leads to increased drug taking. Either increases or decreases in sensitivity to drug actions during stress could lead to increased drug use during stress. There is evidence, for example, that corticosteroids increase actions of nicotine. Specifically, corticosteroid administration increases the development of sensitization to the locomotor-activating effects of nicotine (Caggiula et al., 1998). Such an effect could result in increased drug use under stress, but this mechanism has received little research attention. Conversely, it has been reported that adrenalectomy increases, and corticosterone administration decreases, some of the physiological and behavioral effects of nicotine (Caggiula et al., 1998).

Incentive Sensitization Theory

Incentive Sensitization focuses on how drug cues trigger excessive incentive motivation for drugs, leading to compulsive drug seeking, drug taking, and relapse (Robinson & Berridge, 1993, 2000, 2003). Addictive drugs affect NAccs-related brain systems that mediate incentive salience. These neural circuits become sensitized to specific drug effects and drug-related stimuli with repeated exposure to the drugs. Perhaps, stress interacts with incentive sensitization. That is, stress associated with drug use may come to act as a conditioned stimulus for drug use. Over time, the stress cues may serve to increase sensitivity to the drug action and thereby increase the stress–drug use relationship. This mechanism might apply to all drugs that result in dopamine release because dopamine is a key neurotransmitter that often signals reward and is released in response to pleasurable activities (Bratcher, Farmer-Dougan, Dougan, Heidenreich, & Garris, 2005). Dopamine also may mediate a signal for reward opportunity (Schultz, 1998), or it may mediate activation of an organism toward a potential reward (Dommett et al. 2005; Horvitz, 2002; Robbins & Everitt, 1992; Salamone, Cousins, & Bucher, 1994; Salamone, Cousins, & Snyder, 1997; Stricker & Zigmond 1986). Dopamine might also mediate hedonia, pleasure, or reinforcement (Small, Jones-Gotman, & Dagher, 2003; Volkow et al., 1999; Wise, 1980;). Finally, dopamine might mediate incentive salience or desire for the drug (Berridge, 2007). Research by Pecina, Berridge, Aldridge, and Zhuang (2003) suggests that dopamine mediates drug "wanting." Because stress also increases dopamine release, stress might increase wanting and craving for drugs that also release dopamine.

Cross-Sensitization of Stress and Drugs

There also may be cross-sensitization of stress and drugs. Sensitization is the progressive augmentation of behavioral hyperactivity and neurobiological responses elicited by repeated intermittent administration of psychostimulant drugs (Kalivas & Stewart, 1991). Repeated intermittent administration of amphetamine, cocaine, morphine, and nicotine to rats augments the motor stimulant effects of these drugs (DiFranza & Wellman, 2007; Kalivas & Stewart, 1991). Because stress and drugs target similar pathways (i.e., dopaminergic pathways and the HPA axis), it is possible that prior exposure to stress may cross-sensitize pathways underlying reinforcement from nicotine (Kassel et al., 2003) and other drugs. Cross-sensitization between stress and the reinforcing actions of drugs may help to explain the relations between stress and drug use. Kassel et al. (2003) speculate that cross-sensitization might explain the role of stress in initiation, maintenance, and withdrawal from nicotine. Stress may act through cross-sensitization to increase the reinforcing effects of other drugs of abuse during the initiation, maintenance, and withdrawal stages of drug use and addiction, which would increase an individual's vulnerability to use drugs during times of stress. This explanation may be applied to any drug use but it has not received empirical attention.

DRUG USE INCREASES STRESS

An entirely different type of explanation for the stress–drug use relationship is that drug use acts to increase stress, which serves as a positive feedback loop that then links with one or more of the mechanisms discussed above to increase drug use under stress. In other words, stress increases drug use (by one or more of the mechanisms discussed above), which increases stress, which increases drug use, and so on. There are at least two explanations that can be categorized under this broad interpretation.

Stress and Opponent Processes

Solomon and Corbit's (1973) Opponent Process Theory provided a two-process explanation for drug use. Initially, drug administration activates a "pleasant" dose-dependent A-process shortly after presentation of the drug, which correlates closely with the stimulus intensity, quality, and duration of the reinforcer, and involves tolerance. Activation of the A-process triggers the opponent B-process, which serves to bring the body back to homeostasis. Temporally, the B-process lags behind the A-process, especially upon first use, and lasts longer. The sum of the A and B processes creates the final subjective state experienced by the drug user. The B-process gets larger with repeated exposure and can become a conditioned response (Siegel, 1975). Over time, therefore, the drug response involves less drug "excitement" and increasing drug "withdrawal." The drug use, therefore, may be conceptualized as increasing a dysphoric, stress-like effect. So the drug use would come to induce stress even when it is a response to stress. Koob and Kreek (2007) provide a more detailed neurobiological explanation that applies the opponent process conceptualization to stress and drug use.

Allostasis Explanation

McEwen (1998) has proposed that allostasis, a change in homeostatic set point or ranges in response to stress, is the process of adaptation to acute stress and involves the output of stress hormones to restore homeostasis in the face of challenge. Allostasis comprises actions in the brain and throughout the body. The allostatic load is the detrimental toll taken on the body when it is forced to adapt to repeated adverse psychosocial or physical situations. Over time with continuous demand, the body's ability to make allostatic adaptations decreases, leading to breakdown and illness. Koob and LeMoal (2001) hypothesized that drug addiction is similar to the allostatic process. They suggested that repeated exposure to an addictive drug alters drug reward set point and reflects an allostasis. In addiction, the stability to be maintained is reward function. Change in the mobilization of multiple neurotransmitters and hormonal systems (including dopamine and EOPs) is needed to maintain normal reward function. Molecular or cellular changes occur within a given reward-circuit to accommodate overactivity of hedonic processing associated with addiction, resulting in a decrease in reward function. Neural circuitry changes act as opposing actions to limit reward function. Perhaps, stress further alters the drug reward set point through the effects of stress on dopamine release. Additional stressors during withdrawal may augment the CRF-CRF(1) system and exacerbate withdrawal. Koob and LeMoal (2001) address stress that originates from the drug cycle. But the effect of additional stressors could be to augment the "antireward system," causing the release of more CRF (and downstream, cortisol), which would in turn promote more drug administration, just as in the proposed stress application of the Opponent Process Theory. Koob and LeMoal (2001) apply and extend the Opponent Process Theory, arguing that the A process also involves incentive sensitization and that the B process acts as an antireward system. Stress may potentiate both arms of the opponent process. This explanation has not received direct empirical examination.

Stress Hypersensitivity

Another variation on the theme that drug use may increase stress suggests that drug users may be hypersensitive to stress. This hypersensitivity may occur because of drug use or because these hypersensitive individuals may have a genetic predisposition toward stress sensitivity (Kreek, 1984; Kreek & Koob, 1998; Schluger et al., 1998; Stocker, 1999).

SUMMARY AND AREAS FOR FUTURE RESEARCH

It is clear that there is a bidirectional relationship between stress and drug use. It also is clear that the stress–drug use relationship occurs for recreational (and likely for some prescription) drugs of different pharmacological classes. Therefore, considering traditional psychopharmacological mechanisms alone (e.g., CNS stimulation vs. CNS depression), it is unlikely that a single biological or psychobiological mechanism can explain the stress–drug use relationship. Several interesting explanations have been offered to explain the stress–drug use relationship. Each has tended to ignore alternatives. As a result, with each new explanation or variation on an old explanation, the list just gets longer and longer with little attempt to achieve some conceptual order or parsimony.

In this chapter, we offer a conceptual framework to classify various explanations into four major groups: (1) drug use decreases stress ("self-medication hypotheses"), (2) abstinence from drug use is altered by or resembles stress ("withdrawal hypotheses"), (3) stress alters drug actions ("pharmacodynamic hypotheses"), and (4) drug

use increases stress ("positive feedback loop hypotheses"). The self-medication hypotheses are more varied than may appear from the category label. They include direct and indirect, biological, psychological, and social mechanisms. The withdrawal hypotheses also are quite different from each other even though they all involve drug-induced withdrawal effects. The pharmacodynamic and positive-feedback loop hypotheses draw from ideas that were offered decades ago but do so in novel psychobiological ways.

Our own view is that several or all of these mechanisms are operating with regard to stress and drug use. Each explanation seems logical and has some theoretical or empirical support. However, most lack convincing, empirical examination and no research has pit one explanation against another in a "head-to-head" comparison. We hope that these stress–drug use explanations receive more research attention to determine which are most useful. We also hope that individual differences (including sex, age, genetic variations) are thoughtfully incorporated into these investigations. Furthermore, we believe that identification of the operating mechanisms will lead to novel treatments for drug abuse, including biological/pharmacological and psychological/social interventions. Better mechanism identification may even lead to novel stress management strategies. We began this chapter with the position that this topic is complex. We end this chapter with the conclusion that the explanations for the stress–drug use relationship are indeed complex but with the belief that conceptual progress is being made. No doubt this topic, and the advances in biotechnology that allow us to examine this topic, will keep many of us engaged for years to come.

NOTE

The opinions expressed in this chapter are the sole ones of the authors and are not to be construed as official or reflecting the views of the Uniformed Services University or the Department of Defense.

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23 Exercise and Stress Reduction

Teresa M. Edenfield and James A. Blumenthal

The physical benefits of exercise are widely recognized, and an abundance of epidemiological evidence exists to support an association linking exercise to physical health and overall quality of life (Lee, Hsieh, & Paffenbarger, 1995; Leon, Connett, Jacobs, & Rauramaa, 1987; Paffenbarger, Hyde, Wing, & Steinmetz, 1984; Paffenbarger et al., 1993; Warburton, Nicol, & Bredin, 2006). Exercise is believed to play a role in the prevention of various medical conditions such as hypertension, diabetes, cardiovascular disease (CVD), cancer, and osteoporosis (Fentem, 1994; Warburton et al., 2006), and physical activity has been shown to reduce premature mortality (Paffenbarger & Hyde, 1988; Paffenbarger et al., 1993). As a result, initiation and maintenance of a regular exercise program have become topics of research and clinical practice for a wide range of health professionals, including physicians, exercise physiologists, nurses, and clinical and health psychologists. The concept of stress runs through much of this work.

In addition to the physical benefits associated with exercise, research has documented the psychological benefits of exercise participation (Camacho, Roberts, Lazarus, Kaplan, & Cohen, 1991; Lawlor & Hopker, 2001; Martinsen, 1995; McAuley, 1995; Mutrie & Biddle, 1995; Scully, Kremer, Meade, Graham, & Dudgeon, 1998). Anecdotal reports regarding the positive effects of exercise (e.g., "feel good effect" or "runner's high") have been made for decades. These claims were originally rooted in philosophical ideas dating back more than 2,500 years. For example, Socrates and Plato argued that physical activity and training were essential in the search for virtue, and Hippocrates and Galen advised that inappropriate levels of exercise participation (i.e., too much or too little) would be detrimental to an individual's health (Berryman, 1989; Eaton & Shostak, 1988; Galen, 1951). There is growing empirical support regarding the beneficial effect of physical activity on psychological and emotional well-being (for reviews see Salmon, 2001; Scully et al., 1998). Researchers have also begun to investigate whether a dose-response relationship exists between exercise participation and positive health changes and whether improvements in physical fitness are necessary to effect changes in psychological status (Dunn, Trivedi, Kampert, Clark, & Chambliss, 2002, 2005; Hamer, Stamatakis, & Steptoe, 2008; Hamer, Taylor, Steptoe, 2006; Lawlor & Hopker, 2001). As with work on physical health outcomes, the stress concept has been a useful focus in research on the mental health effects of exercise.

This chapter will first define "stress" and "exercise." Next, we will review the relationship of exercise to stress and discuss possible mechanisms by which exercise can affect stress responses and stress-related health outcomes. Recommendations will be offered regarding directions for future research on the relationships between exercise, stress reactivity, and their physical and emotional health consequences.

EXERCISE

Exercise training involves participation in a program of regular, structured, physical exertion of varying degrees of intensity designed to increase heart rate and/or muscle strength. A related concept, physical activity, involves physical exertion but without the necessary intent to increase heart rate. It encompasses a variety of unstructured forms of exertion such as those required by many occupational and domestic tasks. Exercise may be broken into two classifications, aerobic (literally "with oxygen") and anaerobic ("without oxygen") activities. Aerobic exercise involves sustained activity for which the body requires larger amounts of oxygen (e.g., jogging, walking, and cycling). Oxygen is used by muscles to burn fat and glucose to produce adenosine triphosphate, which supplies energy to the body cells. By contrast, during anaerobic exercise, the muscles depend on the metabolism of muscle glycogen to produce power, instead of relying on large amounts of oxygen. Anaerobic exercise, therefore, involves short bouts of high-intensity exertion (e.g., weight lifting, sprinting, and jumping) for which the body does not rely on oxygen to derive its energy.

Although aerobic exercise has been established as optimal for cardiovascular health, there is evidence that both aerobic and anaerobic exercises (strength training) can improve mental health. Clearly, aerobic exercise has been more widely studied, but including both forms of exercise as part of a healthy lifestyle is essential to

maximizing health benefits. In 1995, both the American College of Sport Medicine and the Centers for Disease Control and Prevention (CDC) recommended that adults engage in at least 30 minutes of moderate physical activity most days of the week (preferably all days of the week) to improve overall health and well-being (Pate et al., 1995). A statement on health and physical activity came from the U.S. Surgeon General's Office in 1996, indicating that inclusion of regular physical activity is essential in maintaining physical and mental well-being, and the Healthy People 2010 objectives (U.S. Department of Health and Human Services, 2000) include increasing the proportion of adults who engage regularly in moderate or vigorous exercise to ≥50%. Physical inactivity has been shown to increase the risk for all-cause mortality (Paffenbarger & Hyde, 1988), and adoption and/or maintenance of exercise has been shown to reduce the risk for mortality (Hakim et al., 1998; Leon & Connett, 1991; Leon, Myers, & Connett, 1997; Paffenbarger, Kampart et al, 1994; Yusuf et al., 2004). In general, exercise participation has consistently been shown to demonstrate an inverse dose-response relationship with various medical illnesses such as coronary heart disease (Blair, Goodyear, Gibbons, & Cooper, 1984; Martin, Dubbert, & Cushman, 1990; Yusuf et al., 2004) and may have potential for preventing or decreasing risk for other conditions such as colon cancer, diabetes mellitus (Helmrich, Ragland, Leung, & Paffenbarger, 1991), and osteoporosis (for review see Dubbert, 1992; Warburton et al., 2006).

The cardiovascular benefits of exercise participation are well-established and have guided the development of research investigating psychological benefits of exercise. For example, the typical duration of a training program included in psychological research incorporating a program of exercise training is 8–12 weeks, reflective of the usual period of participation required to produce cardiopulmonary conditioning effects (i.e., increased physical fitness). Similarly, many researchers emphasize aerobic exercise, because the most commonly used measure of fitness in research is aerobic fitness, or the body's capacity for aerobic work (i.e., oxygen uptake measured by maximal exertion [VO_2 max] assessments). Although alternative programs of exercise training have been developed (e.g., nonstrenuous flexibility and relaxation programs), in research such interventions are often used as "control conditions" for aerobic exercise studies because they do not produce significant improvements in cardiovascular functioning (Desharnais, Jobin, Cote, Levesque, & Godin, 1993; Heaps, 1978; Hilyer & Mitchell, 1979; Ransford & Palisi, 1996).

Although exercise is widely considered an essential component of a healthy lifestyle, and recent consensus statements have begun to address the importance of including a healthy regimen of physical activity across the lifespan, surprisingly few people engage in significant levels of regular exercise. Approximately 60% of adults in the United States are minimally active, and 22% engage in no leisure time activity at all (National Health and Nutrition Examination Survey-III; CDC, 1996). The CDC (2005) have reported that ~25% of the U.S. population is mostly sedentary and, therefore, do not achieve the recommended levels of physical activity (i.e., at least 30 minutes of moderate physical activity most days; Pate et al., 1995; U.S. Department of Health and Human Services, 1996). Brawley and Rodgers (1993) reported that only ~30% of western populations engage in significant levels of exercise on a weekly basis, and if a program is initiated, attrition is high with ~50% of exercisers becoming sedentary at 3–6 months follow-up. Levels of activity are believed to be even lower in individuals suffering from psychiatric disorders (Goldberg & Huxley, 1992; Martinsen, Hoffart, & Solberg, 1989), raising a question of causality relative to the relationship between exercise and mental health.

STRESS

"Stress" has been conceptualized in different ways, but definitions have commonly referred to: (1) a stimulus, that is, an acute and time-limited event (e.g., earthquake or other natural disaster, death of a spouse, or a laboratory challenge such as mental arithmetic) or chronic condition (e.g., marital conflict, job pressure, and poverty) that results in a stress response; (2) a response, that is, an emotional reaction such as anxiety, or a physiological change such as increased heart rate, blood pressure, or adrenal activity (Selye, 1974); or (3) an interaction between an individual and his/her environment (e.g., a heart attack is induced in an extremely competitive person during an intense soccer match (Lazarus & Folkman, 1984). The concept of "stress" has also been viewed more broadly as a general rubric for a complex and interacting set of processes that involve mental state, emotional experiences, and physiological and biochemical adaptations that occur when environmental demands tax or exceed an individual's adaptive capabilities (Cohen, 2000; Cooper, 1996; Hubbard & Workman, 1998).

Although more negative challenges (e.g., loss, work-related stress, and financial problems) are often highlighted when individuals describe stressors, because they are generally considered more harmful, stressors may range from negative to more positive in nature. For example, new challenges (e.g., a job promotion and having a child) that may not be described as strictly negative in nature can also trigger the stress response and demand significant energy and attention from the individual experiencing the life change. Stress has been identified as one of the most common patient complaints across medical settings and has been linked to various health consequences (Dimsdale, 2008; Hamer et al., 2006; Kamarck & Jennings, 1991; Manuck, 1994; Manuck, Kamarck, Kasprowicz, & Waldstein, 1993), including coronary heart disease and essential hypertension (Carroll, 1992; Eliot, Buell, & Dembroski, 1982; Frank & Smith, 1990; Goldstein &

Niaura, 1992; Manuck, 1994; Niaura & Goldstein, 1992; Pickering, 1991; Treiber et al., 2003). Measures of the stress response range from self-report questionnaires asking individuals to report on the nature, severity, and chronicity of stressors they have experienced to physiological and behavioral reactivity that may manifest itself in terms of heart rate, blood pressure, respiratory rate, and/or neuroendocrine responses (Cohen, 2000; Krantz & Manuck, 1984; Kuhn, 1989; Manuck et al., 1993).

PHYSIOLOGICAL ASSESSMENT OF THE STRESS RESPONSE IN EXERCISE RESEARCH

Studies of cardiovascular risk factors often involve the assessment of physiological reactivity to stressors, with an underlying assumption that physiological reactivity in response to real-world or laboratory stressors is related to disease-promoting mechanisms and therefore provides useful information regarding how to more reliably predict who may be at risk for developing various clinical conditions (e.g., heart disease) in the future. Although the mechanisms by which exercise training exerts its beneficial effects on mortality relative to CVD are not fully understood, the available data suggest a beneficial effect on various aspects of functioning, including blood pressure, lipids inflammation and platelet function, and autonomic nervous system, including measures of heart rate variability (HRV). Measures of hemodynamic effects of stress (e.g., increased heart rate or blood pressure) are commonly used in stress exercise research conducted in laboratory settings because they are practical, noninvasive, and reliable methods of assessing physiological reactivity (Georgiades, de Faire, & Lemne, 2004). Biochemical and neuroendocrine changes also have been shown to accompany hyperreactivity to stressors, including increased circulating catecholamines and cortisol levels (Eliot, 1987; Frankenhauser, 1983), and may be measured through blood, urine, or salivary modalities. Hemodynamic response patterns have been shown to differ in the presence of different kinds of stressors (Sherwood, Allen, Obrist, & Langer, 1986). Accordingly, more subtle measurement techniques have been brought to bear to determine, for example, whether sympathetic adrenomedullary activity may underlie the observed cardiovascular effects (de Geus, van Doornen, de Visser, & Orlebeke, 1990; Shulhan, Scher, & Furedy, 1986; van Doornen & de Geus, 1989). Cardiac vagal tone is an (inverse) index of stress vulnerability and reactivity and is frequently used in exercise-stress research because it can be improved by exercise training. HRV, that is, beat-to-beat variations in heart rate determined by the magnitude of respiratory sinus arrhythmia, and heart rate recovery after exercise, can reflect cardiac vagal activity and have been shown to be improved by exercise training. Low resting heart rate is generally believed to be a good indicator of physical fitness and is positively correlated with improved prognosis in individuals with heart disease (Buch, Coote, & Townend, 2002).

To gather information about the stress reactivity in a "real-world" environment, ambulatory monitoring devices are often used in exercise-stress research. Ambulatory monitoring allows for assessment of the stress response to acute and chronic stressors in an individual's free-living environment, through continuous data collection relative to an individual's physiological responses to "real-life" stressors. Devices such as heart rate monitors and accelerometers are frequently used to collect objective data relative to physiological variables. Accelerometers are attached to one or more body areas (e.g., trunk, thigh, and shank) as a relatively noninvasive method of collecting continuous data relevant to exercise activity and cardiac functioning. Accelerometers recognize a person's body postures (e.g., sitting, lying, and standing) and distance moved based on motion detections. Ambulatory monitors (heart rate and blood pressure) and electrocardiographic recorders worn on the chest allow for collecting data regarding cardiac activity. Calculations such as total energy expenditure, which provides a measure of an individual's activity level and metabolic expenditure over a period of time, are often used to translate these continuous data into clinically meaningful information relative to functional capacity/changes.

MEASUREMENT OF EXPOSURE TO PSYCHOSOCIAL STRESSORS

Measures that focus on identifying environmental contributors to the stress response attempt to identify events and conditions that require adaptive adjustments, including the use of coping responses. There are various self-report measures for assessing the presence and/or effect of particular life stressors, including instruments such as the Survey of Recent Life Experiences (Kohn & Macdonald, 1992a, 1992b), the daily hassles scale (Kanner, Coyne, Schaefer, & Lazarus, 1981), and the perceived stress scale (Cohen, Kamarck, & Mermelstein, 1983). Stress diaries, including methods such as ecological momentary assessment (Shiffman & Stone, 1998; Shiffman, Stone, Shiffman, & Hufford, 2008; Stone & Shiffman, 1994, 2002) and experience sampling (Myin-Germeys, van Os, Schwartz, Stone, & Delespaul, 2001; Simons, Gaher, Oliver, Bush, & Palmer, 2005) are used by many researchers to assess stress levels of participants during daily activities and reduce retrospective recall bias (Cruise, Broderick, Porter, Kaell, & Stone, 1996; Shiffman et al., 2002; Shiffman, Paty, Gnys, Kassel, Hickcox, 1996; Shiffman & Waters, 2004; Stone et al., 2003). The use of stress diaries allows for the investigation of important problems, including the nature of chronic stressors, mechanisms by which important stressors exert their effects on individuals, and the role that personality and social or environmental factors play in the stress process. In addition, stress diaries provide a means of learning about what an individual perceives as stressful on a daily basis, common sources of stress and patterns in reoccurring stressors, details regarding

a given stressor, including patterns of response to, and occurrence or perception of, stressors. These methods may be particularly useful in exercise-stress studies because more timely observation of the effect of exercise on psychological reactivity may be possible by comparison with the use of standard retrospective inventories completed in the laboratory.

RELATIONSHIP BETWEEN STRESS, EXERCISE, AND HEALTH

CVD is the leading cause of mortality and disability in the United States (Murray & Lopez, 1996; World Health Organization, 2003), and a vast literature exists linking CVD to stress (Dimsdale, 2008; Hamer, Taylor, & Steptoe, 2006). Exercise training has been studied extensively in relation to decreasing CVD risk and has been associated with reduced morbidity and mortality. Specific questions that have received a large amount of attention concern the effect of exercise training on decreasing the negative effects of overweight and obesity and on reducing cardiovascular responses to stressors in individuals characterized by coronary-prone behaviors and other psychosocial risk factors.

In the INTERHEART study, Yusuf et al. (2004) performed a case-control study of acute myocardial infarction (MI) in 52 countries relative to a variety of known, potentially modifiable correlates of heart disease (e.g., diabetes, waist/hip ratio, dietary patterns, activity levels, alcohol and tobacco use, and psychosocial factors). The investigators found that 90% of risk for an acute MI was predicted by the nine risk factors assessed in the study (i.e., smoking, hypertension, diabetes, central adiposity, psychosocial factors, daily consumption of fruits and vegetables, regular alcohol use, and regular physical activity). This relationship was consistent across all geographic regions of the world, for individuals of all ethnic groups, and for all age groups and gender. Psychosocial variables, as well as central obesity, diabetes, and history of hypertension, were second only to smoking and abnormal lipid levels in relation to occurrence of first MI. The investigators concluded that prevention efforts regarding cardiovascular and coronary artery disease may be based on a similar set of principles worldwide and that these principles, if applied globally and effectively, may aid in the prevention of premature acute MI. These findings are consistent with previous data supporting the role of exercise and improved physical fitness in reducing the risk for morbidity and mortality, particular as it relates to weight and stress management.

Regarding other psychosocial and psychological variables relative to CVD, individuals demonstrating an exaggerated behavioral response (e.g., coronary-prone or "Type A" behavior pattern) to stressors may be at an increased risk for developing heart disease and associated risk factors (e.g., hypertension). Aerobic exercise training has been shown to reduce coronary-prone behaviors (e.g., hostility and anger) and may also serve to lower cardiovascular reactivity to stressors. In addition, exercise may help reduce blood pressure, at rest as well as subsequent to stress induction procedures, in hypertensive individuals. Furthermore, exercise may reduce hemodynamic activity to a level targeted by antihypertensive pharmacotherapies, and this effect may be most evident when paired with a behavioral weight loss program (Georgiades et al., 2000). Such findings suggest that exercise participation may be important in the management of cardiovascular response (e.g., blood pressure) to psychological stressors and offer support for the importance of including exercise as an adjunct treatment in the long-term management of CVD.

EXERCISE-RELATED STRESS REDUCTION

A variety of observational and interventional studies have examined the effects of exercise on stress reactivity and other aspects of emotional well-being. Generally, cross-sectional studies compare fit versus unfit persons or active versus inactive ones. On the other hand, interventional studies compare people who exercise with nonexercising controls before and after exercise training over a specific time period. The results provide somewhat different findings, which we summarize below. Meta-analytic reviews conducted to examine the relationship between aerobic fitness and reactivity to psychosocial stress are also summarized.

CROSS-SECTIONAL STUDIES

Cross-sectional research generally has provided support for the notion that exercise can decrease stress reactivity for individuals who may be classified as physically fit (Collier et al., 2008; Holmes & Roth, 1985; Light, Obrist, James, & Strogatz, 1987). Some researchers have suggested that higher levels of physical fitness may allow individuals to recover more quickly after exposure to stress compared with less fit individuals (Cox, Evans, & Jamieson, 1979; Holmes & Cappo, 1987). It has been suggested, however, that if baseline differences in anxiety and cardiovascular reactivity are consistently controlled, no differences will exist between individuals of varying fitness levels (Plante & Karpowitz, 1987).

In a study of aerobic fitness in 72 women, Holmes and Roth (1985) found that the 10 most physically fit participants demonstrated a smaller increase in heart rate while performing a memory stress task compared with the 10 least fit participants included in the study. Interestingly, however, fitness level (based on submaximal cycle ergometer test) had no effect on participants' subjective response to the mental stress task. In subsequent studies (Hull et al., 1984; Light et al., 1987; van

Doornen & de Geus, 1989), smaller increases in heart rate, diastolic blood pressure, total peripheral resistance, and other cardiovascular measures have been found in more physically fit individuals in response to laboratory stressors (e.g., cognitive tasks, emotionally unpleasant stimuli, and reaction time tasks).

Steptoe et al. (1993) compared cardiovascular reactivity in 36 trained male athletes versus 36 inactive (male) control counterparts. The investigators measured cardiovascular response in relation to a mental stressor (i.e., public speaking task) after 20 minutes of exercise at varying levels of intensity (i.e., high intensity at 70% VO_2 max, moderate intensity at 50% VO_2 max, or light exercise control). They reported that the trained athletes demonstrated a hypotensive response after exercise at moderate to high intensity. In addition, they reported that systolic and diastolic blood pressure measurements were lower for the high-intensity exercisers relative to controls during performance of the stress task. They also reported that systolic blood pressure was lower for high-intensity exercisers during recovery from the mental stressor. Interestingly, although significant differences in body mass index (BMI) were found between groups (i.e., trained athletes had lower BMI compared with inactive controls), consistent with earlier studies comparing extremely sedentary versus active individuals (Roth, 1989), the baseline difference in BMI did not moderate the postexercise hypotensive effect observed in this study.

Individuals with borderline increases in blood pressure with higher levels of fitness have shown improvements in cardiovascular functioning in response to a mental stress task. Perkins, Dubbert, Martin, Faulstich, and Harris (1986) found that borderline hypertensives classified as aerobically fit demonstrated smaller increases in both systolic and diastolic blood pressure compared with their unfit counterparts. Sothmann, Horn, Hart, and Gustafson (1987) found that physically fit participants showed a decrease in plasma norepinephrine after exposure to a stressor; however, no change in subjective report of mood status was observed.

Some researchers have attributed changes in cardiovascular reactivity to stressors to significant differences in anger/hostility between physically fit versus unfit individuals (Czajkowski et al., 1990). Dorheim et al. (1984) studied cardiovascular responses to mild mental stress (i.e., video game, reaction time test, and 90-second cold pressor test) in a sample of competitive marathoners and their unfit, but otherwise healthy, counterparts. Interestingly, the researchers reported that distance running did not seem to mitigate cardiovascular reactivity to behavioral stressors, because the highly fit marathoners actually experienced greater increase in blood pressure responses to mental challenges relative to their unfit counterparts. The authors assessed for differences in achievement motivation that may have explained these unexpected findings but reported no between-group differences in performance during mental challenges (e.g., work speed or accuracy). It is possible that differences in reactivity were due to differences in how engaged participants were during the task or to differences in physiological adaptations (e.g., upregulation of β receptors) associated with exercise. In summary, it remains unclear to what degree fitness is associated cross-sectionally with cardiovascular reactivity.

INTERVENTION STUDIES

There have been relatively few longitudinal studies of exercise training and cardiovascular reactivity to stress. In a study of healthy, but coronary-prone (Type A) men, Blumenthal et al. (1988) found that aerobic exercise training resulted in more rapid recovery of heart rate, blood pressure, and myocardial oxygen consumption after a mental arithmetic stress task. By using a similar methodology in a new sample of coronary-prone men, Blumenthal et al. (1990) found that aerobic versus strength training exercise resulted in greater reductions in heart rate, diastolic blood pressure, and myocardial oxygen consumption. In addition, levels of circulating epinephrine during recovery were lower for the aerobically trained group. Interestingly, modality of exercise did not produce important differences in cardiovascular reactivity to the stress task. The researchers concluded that aerobic exercise produced overall changes in levels of blood pressure and HRV instead of a reduction of stress reactivity. In a follow-up study of participants from the initial cohort, similar results were seen but only in those Type A men who were also identified as borderline hypertensive (Sherwood, Light, & Blumenthal, 1989). Seraganian et al. (1987), however, found no effect of exercise training in a longitudinal study of Type A men, although they excluded participants who were initially identified as demonstrating exaggerated psychophysiological activity, which may have limited the generalizability of their findings.

Other research has yielded findings indicating reduced cardiovascular reactivity in response to laboratory stressors after aerobic exercise training, although these studies have used less rigorous methodologies. Studies of borderline hypertensive participants have shown that low- to moderate-intensity exercise training may reduce blood pressure in response to the Stroop color-work conflict task (Rogers, Probst, Gruber, Berger, & Boone, 1996) or a videogame (Cleroux, Peronnet, & de Champlain, 1985). Holmes and McGilley (1987) reported that aerobically trained participants who had lacked physical fitness before enrollment in the study demonstrated a decrease in heart rate during a memory task. Although fitness level increased significantly for both groups, participants who had been physically fit before enrollment in the study did not show decreased cardiovascular reactivity. Holmes and Roth (1987) also used a memory task to compare aerobic versus anaerobic exercise training and reported that absolute heart rate during task performance was lower for aerobically trained

participants, although the groups did not differ regarding reactivity to stress induction procedures.

Still other investigators have found no significant differences in cardiovascular reactivity when comparing aerobic and anaerobic exercise training programs. For example, Sinyor, Golden, Steinert, and Seraganian (1986) reported that aerobic training, compared with strength training, resulted in no difference in heart rate or subjective stress ratings in response to a series of mental stressors. In a longitudinal study of healthy "Type A" men, Roskies et al. (1986) compared a 10-week cognitive behavioral stress management program (cognitive behavioral therapy [CBT]), an anaerobic strength training program, and an aerobic training program. The CBT stress management group demonstrated significant changes in behavioral reactivity to laboratory stressors (i.e., 13–23% below baseline levels) compared with the exercise conditions, in which smaller reductions were observed. The authors reported that changes in physiological reactivity were minimal for all treatment groups and concluded that more research is needed to explore the relevance of physiological reactivity as an outcome measure for interventions with Type A populations.

In general, more recent findings have provided somewhat mixed results regarding the effects of exercise on cardiovascular reactivity to stressors as compared with its effect on resting/baseline measures of cardiovascular activity. For example, King et al. (2002) reported that participants demonstrated significant reductions in blood pressure responses to a mental stressor (i.e., a speech task) after a 12-month exercise training intervention in caregivers. Georgiades et al. (2000), however, reported no changes in stress-related blood pressure responses after a 6-month exercise intervention in hypertensive individuals, despite finding reductions in exercise-induced blood pressure levels. Steffen et al. (2001) also demonstrated reductions in absolute blood pressure levels measured during exposure to daily life stressors after a 6-month exercise program but did not report findings for stress-related blood pressure responsiveness. In a study of the benefits of a 4-week aerobic versus strength training intervention on arterial stiffness, blood flow, and blood pressure in unmedicated prehypertensive and stage-1 hypertensive men (N = 20) and women (N = 10), Collier et al. (2008) found that resting systolic blood pressure decreased to a similar degree for both interventions. However, increases in arterial stiffness (i.e., central and peripheral pulse wave velocity and vasodilatory capacity) were found after resistance training. These findings suggested that reliance on resistance training alone may not be optimal for improving cardiovascular functioning.

META-ANALYTIC STUDIES OF EXERCISE, FITNESS, AND STRESS REACTIVITY

Researchers have obtained results suggesting that initial level of fitness may be effective in attenuating physiological reactivity to mental stress (de Geus et al., 1990), whereas participation in an exercise regimen more intense than one's habitual regimen may be less likely to reduce stress reactivity and might even worsen subjective emotional experience (depressive symptoms; for a review see Yeung, 1996). Moreover, de Geus, van Doornen, and Orlebenke (1993) found that cardiovascular reactivity was actually greater in more physically fit subjects compared with their similarly active but less fit counterparts. It also has been reported that low-intensity training that did not result in increases in VO_2 max performance was more effective in decreasing cardiovascular reactivity to stressors than was high-intensity exercise that produced fitness improvements (Rogers et al., 1996). In general, the role of fitness in mediating stress response in these studies remains unclear, and more interventional studies are needed to clarify this relationship.

Given the large volume of studies investigating the association between aerobic fitness and reactivity to psychological stress, several meta-analytic reviews have been conducted in an effort to summarize this relationship. In a review of 34 studies investigating the effect of aerobic training on reactivity to psychosocial stressors, Crews and Landers (1987) reported that aerobically trained individuals who demonstrated improvements in aerobic fitness showed reduced reactivity to psychosocial stressors (average effect size estimate of 0.48, $p < 0.01$). In a more recent meta-analysis, Hamer et al. (2006) reviewed 15 randomized controlled trials (RCTs) examining the effect of acute aerobic exercise (single session) on blood pressure in response to psychosocial laboratory tasks. Exercise interventions included in the studies reviewed varied from mild to moderate (i.e., exercise intensity less than 60% VO_2 max or 75% heart rate reserve) to vigorous (i.e., exercise intensity ≥60% VO_2 max or 75% heart rate reserve), and stress tasks included the Stroop test, mental arithmetic, cold pressor task, and public speaking. The authors reported that an acute bout of aerobic exercise of moderate to high intensity attenuated stress-related blood pressure responses comparable with the exercise training effects found in the meta-analysis by Crews and Landers (1987). The authors therefore concluded that the primary benefits of habitual exercise promoted by training may reflect a tendency for habitual exercisers to more frequently encounter daily stressors during their postexercise window and therefore more frequently experience and benefit from an attenuated stress response. Further research is needed to improve our understanding of the relationship between exercise, physical fitness, and stress reactivity.

PSYCHOLOGIC BENEFITS OF EXERCISE

Individuals with psychological disorders have been found to be mostly sedentary (for a review see Richardson et al., 2005), although the directionality of this relationship remains unclear. Given the close relationship between

depression and stress (see Gutman and Nemeroff, chapter 25), it is of particular interest that exercise seems to represent a form of behavioral activation that is capable of producing decreases in depressive symptomatology (including cognitive dysfunctions), similar to what has been found in studies of behavioral activation as a treatment for clinical depression (for reviews see Barbour, Edenfield, & Blumenthal, 2007; Carlson, 1991; Craft & Landers, 1998; North, McCullagh, & Vu Tran, 1990). The inclusion of exercise in the treatment of depression has been recommended as an adjunct to other empirically supported interventions (Pate et al., 1995), and some researchers assert that exercise alone may be an effective intervention for some individuals (Craft & Landers, 1998; Netz, Wu, Becker, & Tenenbaum, 2005; Nicoloff & Schwenk, 1995). Exercise training has consistently been shown to result in a reduction of symptoms of depression and anxiety (Biddle & Mutrie, 2001; Craft & Landers, 1998; Landers & Petruzzello, 1994; Long & Stavel, 1995; Martinsen, 1995; North et al., 1990; Petruzzello, Landers, Hatfield, Kubitz, & Salazar, 1991), and although there have been discrepant reports, the preponderance of the evidence supports the mood enhancement properties of exercise (Steptoe, Kimbell, & Basford, 1998; Yeung, 1996). The role that exercise may play in treating and preventing mental illness (e.g., depression), as well as the potential for increasing functional capacity in the presence of an existing mental illness, has been subject to many investigations in recent years.

ANTIDEPRESSANT EFFECTS OF EXERCISE

Prospective studies have consistently demonstrated that sedentary individuals are more likely to endorse symptoms of depression during follow-up assessments relative to their more active counterparts (Camacho, Roberts, Lazarus, Kaplan, & Cohen, 1991; Hassmen, Koivula, & Uutela, 2000; Ruuskanen & Ruoppila, 1995; Stephens, 1988). Interestingly, when individuals increased physical activity from baseline, their risk for depression at follow-up was comparable with those who were active throughout the study protocol. However, those who became more sedentary were found to endorse more depressive symptoms compared with participants who maintained participation in higher levels of physical activity (Camacho et al., 1991). Although these findings are important and provide further evidence regarding the general relationship between exercise and depression, correlational methodologies cannot address the issue of causality. The question regarding whether sedentary lifestyle causes depression, or whether more significant depression results in lower activity levels, cannot be addressed in the absence of RCTs designed to investigate the direction and independence of the relationship between exercise and changes in mental well-being.

Exercise training has consistently resulted in lower levels of depressive symptoms in individuals, ranging from nonclinical (i.e., normal, not depressed) to subclinical and clinical samples meeting criteria for diagnosing depressive disorders contained within the *Diagnostic and Statistical Manual—IV* (*DSM-IV-TR*; American Psychiatric Association, 2000). In a number of rigorous RCTs investigating exercise as a treatment for depressed mood, individuals who received exercise training demonstrated more significant declines in depressive symptoms relative to controls, regardless of age, race, or gender (for review see Scully et al., 1998). However, discrepant findings exist, suggesting that exercise may not always result in significant mood improvements, which is likely a result of a floor effect within these studies (King, Taylor, Haskell, & DeBusk, 1989; Moses, Steptoe, Mathews, & Edwards, 1989), because it may be extremely difficult to observe significant improvements in mood in a sample of individuals who are not suffering form significant symptoms of depression on initiation of training. Studies of clinically depressed individuals (i.e., individuals meeting *DSM-IV* criteria for major depressive disorder [MDD]) offer a more viable opportunity to observe changes in depressive symptomatology that may occur after exercise training.

Blumenthal et al. (1999) at the Duke University conducted an RCT evaluating the efficacy of exercise as a treatment for depression relative to antidepressant medication, a selective serotonin reuptake inhibitor (SSRI), or combination treatment (SSRI and exercise). Individuals identified as meeting criteria for MDD were enrolled and assigned to either a 16-week aerobic exercise treatment, a standard SSRI regimen (i.e., sertraline), or a combination treatment (exercise plus SSRI). The exercise training intervention involved three sessions of monitored aerobic activity per week for 16 weeks. Participants in each of the treatment arms experienced significant reductions in depressive symptoms, with no significant differences between treatment groups. The investigators concluded that exercise may represent a viable treatment alternative for some individuals relative to antidepressant medication. In a 10-month follow-up of the study cohort of Blumenthal et al. (1999), Babyak et al. (2000) observed significantly lower rates of relapse in the exercise-only condition compared with antidepressant medication alone or the combination treatment. Interestingly, the combined program of exercise and medication did not produce greater benefits than either treatment alone.

Aside from the 1999 Duke study (Blumenthal et al., 1999; Babyak et al., 2000), few RCTs have compared exercise with medication. However, some researchers have reported that individuals suffering from mental illness who participate in exercise as a component of treatment describe exercise as the "most effective" aspect of treatment (Martinsen et al., 1989; Porter, Spates, & Smitham, 2003; Sexton, Maere, & Dahl, 1989). In a recent placebo-control study by Blumenthal et al. (2007), 202 adults (153 women and 49 men) diagnosed with MDD were randomly assigned to 16 weeks of either supervised group exercise, home-based unsupervised exercise, antidepressant

medication (SSRI), or placebo pill. After the 16-week intervention, 41% of participants achieved remission of depression (i.e., Hamilton Rating Scale for Depression [HAM-D] score <8), with active treatment groups demonstrating the largest remission rates. Participants who completed 16 weeks of supervised exercise or SSRI demonstrated the highest rates of remission (45% and 47% respectively), followed by home-based exercise (40%) and placebo (31%). Although no statistically significant differences between treatments were demonstrated, these findings provide further evidence regarding the efficacy of exercise as a treatment for depression. The comparable antidepressant effects demonstrated for exercise relative to SSRI are particularly important, because exercise may represent a more cost-effective, accessible, and acceptable treatment for some individuals compared with more traditional treatments for depression.

Although few RCTs have examined the relative benefits of exercise in the treatment of psychiatric conditions such as depression, various studies have demonstrated support for exercise used as an adjunctive treatment (Morgan & Goldston, 1987). Farmer et al. (1988) found that women who were minimally active were twice as likely as women engaging in higher levels of exercise to meet criteria for clinical depression over the course of an 8-year follow-up investigation. Similarly, men who were inactive were more likely to maintain a state of depression. Comparable results have been obtained in a study of initially depressed men and women examined using a 10- and 20-year follow-up protocol (Camacho et al., 1991). In this study, minimally active men and women were at significantly higher risk for developing depression than those engaging in a regular program of moderately strenuous exercise (i.e., three 30-minute sessions per week of jogging or cycling at 75–80% heart rate reserve). In an epidemiological survey of college-aged men, Paffenbarger, Lee, and Leung (1994) found that depression rates were lower among those who were physically active (including involvement in competitive sports) compared with their minimally active counterparts.

Exercise may have a more prominent mood enhancement effect on individuals reporting a higher level of depression (Gauvin, Rejeski, & Norris, 1996), an assertion that is consistent with findings suggesting that behavioral activation may represent an adequate treatment for clinical depression (Jacobson et al., 1996; Lejuez, Hopko, & Hopko, 2001; Martell, Addis, & Jacobson, 2001). The results of these studies also accord with evidence that the benefits of cognitive-behavioral psychotherapy, which pairs behavioral activation with cognitive restructuring activities, are most evident during the early phase of treatment, when behavioral foci are more prominent (Beckham & Leber, 1995; Hollon, Shelton, & Davis, 1993; Otto, Pava, & Sprich-Buckminster, 1996). In a meta-analysis of 14 RCTs investigating the efficacy of exercise as a treatment for MDD, Lawlor and Hopker (2001) noted that exercise consistently produces greater improvements in depression (i.e., larger decreases in depressive symptoms) compared with no treatment and that exercise produces antidepressant effects similar to cognitive therapy for depression. However, the authors concluded that the full extent of the effectiveness of exercise in the treatment of depression could not be determined because of a variety of methodological shortcomings in virtually all of the studies included in the meta-analysis. In a more recent meta-analysis, Mead, et al., (2009) examined data from 23 studies and 907 participants and came to essentially the same conclusions. They reported a pooled standardized mean difference of 0.82, indicating a large effect size, which was reduced to 0.42 when only three better quality studies were included, and noted that "outstanding uncertainties remain about how effective exercise is for depression." Despite the methodological limitations of research in this area, however, Mead et al. suggested that exercise should be recommended to people with clinical depression. In a subsequent editorial, Blumenthal and Ong (2009) noted that because all studies included research volunteers, who may not be representative of patients seeking psychiatric treatment, such recommendations may be premature. Generally, research participants are less severely depressed compared to patients seeking treatment and may be more highly motivated to exercise, which may not be the case in patients seeking psychiatric treatment for depression.

EFFECTS OF EXERCISE ON OTHER STRESS-RELATED PSYCHIATRIC DISORDERS

Although most studies of mental health and physical activity have focused on the impact regarding depressive symptoms, some data support exercise as an effective intervention for anxiety, as well as for some forms of possibly stress-related severe mental illness (SMI; e.g., bipolar disorder [BD] and schizophrenia). Early, uncontrolled reports suggest that individuals with phobias may be treated successfully through exposure to a phobic stimulus subsequent to exhaustive exercise (Driscoll, 1976; Muller & Armstrong, 1975; Orwin, 1973). In addition, acute bouts of exercise have been found to reduce self-reported symptoms of state anxiety (for review see Petruzzello et al., 1991) as well as panic symptoms (Rejeski, Hardy, & Shaw, 1991). Moreover, although subjective anxiety may be increased for panic patients relative to healthy controls (Cameron & Hudson, 1986), it has been found that individuals with panic disorder symptoms tolerate aerobic exercise as well as healthy controls (i.e., demonstrate physiological responses no greater than those produced by healthy controls; Rief & Hermanutz, 1996; Stein et al, 1992). Although more research is needed, these data suggest that exercise may be beneficial for the treatment of anxiety disorders, with relatively little risk for adverse consequences.

Other researchers have investigated the effect of exercise on anxiety sensitivity, or a fear of physical sensations that are subjectively interpreted as anxiety (e.g., increased heart rate and shallow or rapid breathing) and

may precipitate panic attacks (Ehlers, 1995). In a study of exercise-induced physiological arousal, Broman-Fulks, Berman, Rabian, and Webster (2004) found that both low-intensity (i.e., walking at 1 mph on a treadmill) and high-intensity (i.e., walking or jogging on treadmill at a pace sufficient to achieve a heart rate of 60–90% of the age-adjusted predicted maximum heart rate) exercise reduced anxiety sensitivity. A more rapid decrease in anxiety sensitivity scores was produced by high-intensity exercise.

Cognitive theories regarding the beneficial effect of exercise training on anxiety symptoms and anxiety sensitivity suggest that exercise may facilitate a benign attribution of the arousal produced by a phobic stimulus, thereby preventing the maladaptive, fear of bodily sensations experienced in panic (Clark, 1986). It is also theorized that exercise training serves as an exposure technique, a common component of cognitive behavioral therapies for anxiety disorders that involve intentionally inducing a feared bodily sensation in the absence of severe negative consequences (e.g., panic attack). Therefore, it is possible that exercise training may represent a viable treatment option for individuals prone to panic attacks by reducing the levels of anxiety sensitivity (Broman-Fulks et al., 2004). Additional research is needed to evaluate these suggestions. In addition, research addressing issues of the dose-response relative to the anxiolytic benefits of exercise is needed, and investigations of the physiological adaptations seen in healthy and depressed individuals should be replicated in samples of anxiety-disordered individuals to determine whether exercise produces similar benefits across a spectrum of common psychiatric conditions.

Although research investigating the efficacy of exercise as an adjunctive treatment for severe forms of mental illness is lacking, exercise has been found to decrease psychotic hallucinations (Falloon & Talbot, 1981) and depression in the context of SMI (Faulkner & Biddle, 1999; Pelham, Campagna, Ritvo, & Birnie, 1993). Kilbourne et al. (2007) conducted a cross-sectional analysis of exercise and nutrition behaviors for patients enrolled in the *Veterans Affairs (*VA) National Psychosis Registry (Blow, McCarthy, & Valenstein, 2000). Participants included 6,710 VA patients who were either free of SMI (46%) or met criteria for BD (29%) or schizophrenia (26%) during fiscal year 1999, who also completed the VA's Large Health Survey of Veteran Enrollees subsection on health and nutrition behaviors. The investigators reported that individuals with BD or schizophrenia were more likely to report poorer nutritional habits (e.g., eating only one meal per day and more difficulty obtaining or preparing food) compared with their counterparts in the non-SMI group. Interestingly, relative to those diagnosed with schizophrenia or the non-SMI group, patients with BD were more likely to report suboptimal exercise habits (e.g., walking less than 3 days per week) and that they experienced a weight gain of more than 10 pounds during the previous 6 months. Unfortunately, patients with BD also reported that their physician discussed exercise habits with them in the recent past, which clouds interpretation of these results. Overall, the findings suggest that it would be worth examining whether individuals with BD may be more vulnerable to adverse consequences associated with poor nutrition and exercise habits than patients with SMI.

Pharmacological treatments remain the standard of care for most chronic and severe forms of mental illness, including BD (e.g., lithium and depakote). As a result, most research on the etiology and treatment of such conditions has emphasized biological mechanisms and pharmacological interventions. Preliminary data regarding the efficacy of exercise as a treatment for individuals with BD suggest that compliance with a prescription of low-intensity exercise (i.e., walking 30 minutes, four times per week, for 4 weeks), followed by subsequent independent maintenance of this program, resulted in an increase in the use of adaptive coping strategies at posttest assessment. Longer-term follow-up data suggested that decreased frequency of exercise participation over the ensuing 6 months resulted in a greater level of depressive symptoms reporting, particularly for those who initially had participated in 4 weeks of prescribed (vs elective initiation) exercise during the treatment phase (Edenfield, 2007). These findings suggest that including a prescription for mild- to moderate-intensity exercise may have an important effect on an individual's perception of, and response to, stressful life events. In addition, self-maintained exercise subsequent to participation in a 4-week program of prescribed exercise may serve to prevent a worsening of depressive symptoms over time.

Ng, Dodd, and Berk (2007) completed a retrospective cohort investigation of patients diagnosed with BD who were admitted to a private psychiatric hospital over a 2-year period. All admitted patients were invited to participate in a voluntary exercise program (i.e., walking group) during their admission, and the investigators stratified patients into two groups (exercise vs nonexercise) based on participant activity selection (e.g., exercise, art therapy, relaxation, music therapy, psychoeducation, or group discussions) after admission. The researchers reported that the individuals who participated in the walking program (N = 24) had significantly lower scores on a self-report measure of illness severity (the depression anxiety stress scale; Lovibond & Lovibond, 1995) at discharge. However, clinician-rated symptom severity did not differ between groups. Although the authors described several limitations to the study (e.g., small sample, no randomization or control for confounding variables, and no control for BD subtype), findings suggest that for some patients exercise participation may assist in reducing perceived levels of symptom severity.

In summary, psychotropic medication, in conjunction with empirically supported psychotherapeutic interventions (e.g., CBT and family focused therapy), remains the standard treatment for SMIs. However, a more fully integrated approach pairing empirically validated treatments with regular exercise may offer a more effective

intervention. Further research, including RCTs, is warranted to further investigate the relationship between exercise and symptom improvement in BD. In addition, interventions targeting improved nutrition and exercise behaviors, which also account for the unique challenges faced by patients with SMI (e.g., social support issues, financial considerations, and medication side effects), should be investigated. Finally, more explicit attention to the role of stress and coping factors, for example, as potential moderators and mediators of treatment effects is clearly warranted.

CONSIDERATIONS REGARDING EXERCISE DOSE, MODALITY, AND INTENSITY

In the exercise literature it is often implicitly assumed that, because exercise is known to be beneficial, it is also enjoyable. In fact, there is evidence to support immediate mood improvements associated with strenuous exercise (Steptoe, Kimbell, & Basford, 1998; Yeung, 1996) for regular exercisers. If exercise is performed in a competitive setting, success seems to mediate the mood-enhancing effects of participation (Clingman & Hilliard, 1994). Overall, mood-enhancing effects of exercise (for regular exercisers) are most evident when mood is poor before exercise induction (Gauvin, Rejeski, & Norris, 1996).

In the relatively small number of sedentary samples studied in the exercise literature, mood enhancement seems most likely to have resulted when the prescribed exercise program was of mild- to moderate-intensity and performed on a voluntary basis (McIntyre, Watson, & Cunningham, 1990; Raglin & Wilson, 1996; Steptoe, Kearsley, & Walters, 1993). Exercise prescribed at a level that is of greater intensity than an individual's habitual exercise level may be less likely to positively impact mood. In fact, strenuous exercise in nonhabitual exercisers has consistently demonstrated unpleasant effects (i.e., increased negative mood or decreased positive mood; Petruzzello, Jones, & Tate, 1997; Raglin & Wilson, 1996; Steptoe & Bolton, 1988; Steptoe & Cox, 1988). Similarly, when comparisons are made between sedentary/unfit and more active/fit individuals, mood improvements after strenuous exercise are most commonly observed in the more physically fit participants (Dishman, Farquhar, & Cureton, 1994; Petruzzello et al., 1997) or for those who tend to be more confident regarding their exercise capacity (Bozoian, Rejeski, & McAuley, 1994). Overall, aerobic exercise may provide a positive experience when performed at a habitual level, and strenuous exercise, in particular, may have a differential effect on mood depending on fitness level (i.e., positive impact for habitual exercisers and negative impact in sedentary samples).

Moreover, there is significant uncertainty regarding the frequency, duration, and intensity of exercise necessary to promote mental health benefits (e.g., antidepressant effects). In the Depression Outcomes Study of Exercise study (Dunn et al., 2002), 80 initially sedentary adults meeting criteria for MDD were randomized to one of five possible 12-week exercise training conditions (low energy expenditure/3 days per week, high energy expenditure/3 days per week, low energy expenditure/5 days per week, high energy expenditure/5 days per week, or stretching/flexibility control). Findings from this study suggest that exercise involving high energy expenditure, as recommended in the CDC's public health guidelines, may be most effective in reducing depressive symptoms in clinical samples. Although participants randomized to the low energy expenditure exercise demonstrated a reduction in depressive symptoms, the response was not significantly greater than that in controls. Regarding frequency of exercise, no significant difference in treatment response was found (i.e., 3 days of exercise produced similar effects compared with 5 days of exercise). The authors concluded that total energy expenditure may be the most crucial factor in the antidepressant effect of exercise participation/training.

In a more recent study of the dose-response relationship between exercise and mental well-being, Hamer et al. (2008) examined the risk reduction benefits of self-reported exercise and lifestyle activity on overall psychological distress in the periodically performed (i.e., every 3–5 years) Scottish Health Survey. The investigators used interviews to collect self-report data from a representative sample of households regarding exercise and lifestyle activity participation and health history. Height and weight measurements were also taken at each of two visits. During the second household visit, nurses collected a detailed medical history. The investigators reported that participation in any form of daily activity was associated with lowered risk for psychological distress, even when factors such as age, gender, socioeconomic status, marital status, BMI, chronic illness, and smoking were controlled. Although they reported that moderate reductions in distress were found with minimal activity (i.e., 20 minutes or more per week), the investigators concluded that greater risk reduction was found for individuals engaging in higher levels of activity (i.e., higher frequency and intensity). These findings are consistent with findings from the Depression Outcomes Study of Exercise trial (Dunn et al., 2002) regarding the importance of energy expenditure in producing psychological improvements.

Another issue that remains open to empirical investigation is effect of exercise modality, that is, whether varying forms of exercise produce differing reductions in depressive symptoms or psychological distress. As reviewed above, most studies have emphasized aerobic exercise training, although data exist to support the potential stress and mood improvement benefits of anaerobic (strength) training. In an RCT investigating this issue, a sample of older adults reporting depressive symptoms underwent either a 20-week program of progressive resistance training or a health education control intervention (Singh, Clements, & Fiatarone-Singh,

2001). Individuals who completed the resistance training program showed a significantly greater reduction of depressive symptoms at the end of treatment relative to the control group. Similar to other studies showing the long-term benefits of aerobic training (Babyak et al., 2000; Blumenthal et al., 1999), Singh et al. (2001) found that the antidepressant effect for those who completed the exercise training intervention remained at follow-up assessment 26 months later. In fact, many participants (33%) who completed the exercise intervention continued to participate in regular resistance training (i.e., weight lifting). Given the results of this investigation, resistance training may be a viable option for those not motivated or capable of participating in a regular aerobic program (Stathopoulou et al., 2006). Another interesting conclusion suggested by findings such as those from the Singh et al. (2001) investigation is that the antidepressant effect associated with exercise participation may not be dependent on improvements in cardiovascular fitness (Stathopoulou et al., 2006).

MECHANISMS OF CHANGE REGARDING THE PSYCHOLOGICAL BENEFITS OF EXERCISE

Despite continuing research that demonstrates the positive effects of exercise on depressed mood, no single theory adequately explains how exercise leads to a reduction in depressive symptoms. However, a plethora of physiological and psychological theories have been proposed to explain the interaction between mood state and exercise. Many theories focus on physiological factors such as an increase in core body temperature (Thermogenic Model; Petruzzello et al., 1991) and differential neocortical activation after exercise (Kubitz & Landers, 1993). Other models focus on biochemical mechanisms such as increased secretion of amine metabolites and enhanced synthesis and metabolism of serotonin (e.g., Monoamine Hypothesis; Dey, Singh, & Dey, 1992; Dishman et al., 1997; Dunn & Dishman, 1991; Esler et al., 1990; Morgan, 1996). The central premise of these biochemical theories is that exercise acts on the same pathway that antidepressant medications target in the treatment of clinical depression (Ransford, 1982).

Additional biochemical theories focus on specific areas of the brain (i.e., hypothalamic–pituitary–adrenal (HPA axis; Peronnet & Szabo, 1993) or specific endogenous chemicals (e.g., endorphins and enkephalins) or systems (e.g., endocannabinoid system) to explain the antidepressant properties of exercise. Theories such as the HPA axis model propose that stress hormones are released in response to physical (e.g., exercise) and psychological stress experiences. Accordingly, habitual levels of exercise are believed to decrease the amounts of stress hormones secreted from the HPA axis, resulting in lower levels of depression and stress reactivity (Peronnet & Szabo, 1993; Salmon, 2001).

According to the endorphin hypothesis, endogenous opioids (e.g., endorphins and enkephalins) are released during and after exercise and result in a euphoric state frequently reported by individuals who are physically fit (Christie & Chesher, 1982). In a recent investigation, Sparling, Giuffrida, Piomelli, Rosskopf, and Dietrich (2003) confirmed the existence of an endogenous cannabinoid system by identifying two cannabinoid receptors (CB1 and CB2) and their naturally occurring ligands (anandamide and 2-AG). These chemicals are located predominantly in regions of the brain responsible for motor function, emotion regulation, and cognitive functioning (Glass, Faull, & Dragunow, 1997). The endocannabinoid system hypothesis addresses various weaknesses of former theories, but further research is needed to determine its adequacy in explaining the antidepressant effect of exercise.

Still other researchers focus on interactions between neurotransmitters and their specific receptors (Meeusen & DeMeirleir, 1995). Russo-Neustadt, Beard, and Cotman (1999), Russo-Neustadt, Beard, Huang, and Cotman (2000), and Russo-Neustadt, Ha, Ramirez, and Kesslak (2001) point to evidence that exercise rapidly increases brain-derived neurotrophic factor messenger RNA in the hippocampus, which is important for behavioral regulation. In addition, the role of phenylethylamine has been highlighted. Concentrations of this endogenous neuroamine, which has been linked to the regulation of physical energy, mood, and attention (Sabelli, Fink, Fawcett, & Tom, 1996), seem to be increased by moderate- to high-intensity exercise (Szabo, Billett, & Turner, 2001).

In addition to the aforementioned physiological models, several psychological theories have been proposed to explain the effect that exercise has on depressed mood (Gauvin et al., 1996; Martinsen, 1990; Peterson & Stunkard, 1992; Salmon, 2001; Steptoe et al., 1998). Psychological theories of exercise focus on constructs such as intrinsic motivation (cognitive evaluation theory; Deci, 1975), self-determination (self-determination theory; Deci & Ryan, 1985, 1991), and self-efficacy (self-efficacy theory; Bandura, 1977). Several social-cognitive and expectancy-value theories (e.g., theory of reasoned action; Ajzen & Fishbein, 1980, theory of planned behavior; Ajzen, 1988, 1991, 2002) address issues of intention, perception of control, and actual engagement in behavioral activity and therefore may be relevant to exercise. In general, these models focus on a variety of mechanisms that might explain the link between exercise and reduced depressed mood (e.g., improved accomplishments and confidence, positive distraction, greater self-esteem, environmental reinforcement, and enhanced skills for coping with stressful situations).

In an attempt to bridge these various psychological models regarding exercise and mood, Salmon (2001) has proposed an integrative model called the stress adaptation model. In the stress adaptation model, an increase in life structure occurs as a result of including exercise in

one's daily routine. In addition, individuals who exercise on a daily basis may experience a simultaneous decrease in stress reactivity (Salmon, 2001). Support for this theory can be obtained from previous research that found reductions in the perceived experience of stress in daily living in individuals who exercise on a regular basis (Steptoe et al., 1998). According to the stress adaptation model, regular exercise protects individuals from the effects of stress and ultimately prolongs euthymic periods or prevents depressive relapse. In this model, exercise is also conceptualized as a stressor, albeit one with potential positive benefits. In addition, Salmon (2001) proposes that the controllability of the exercise stressor may provide a substantial benefit. This controllability may decrease reactivity to stressful life events, promote quicker adaptation to stressors, reduce the likelihood of relapse, and lead to the development of more effective coping responses (Salmon, 2001).

EXERCISE ADHERENCE

Long-term adherence to an exercise regimen is often low, as evidenced by the CDC's 2005 report that 25% of the U.S. population is mostly sedentary, with few people meeting the recommended guidelines for exercise participation. Although sedentary lifestyles are prevalent in western cultures, individuals suffering from medical or psychiatric illness may have even greater difficulty adhering to an exercise routine. Previous research has shown that 50% of cardiac patients who initiate a program of exercise in the context of cardiac rehabilitation will discontinue exercise within 6 months of initiation (Carmody, Senner, Manilow, & Matarazzo, 1980). Data from the National Exercise and Heart Disease Project (Shaw, 1981) suggest that, although exercise participation resulted in somewhat lower mortality rates, the differences between exercisers and nonexercise controls were not significant. In studies reporting higher adherence rates, however, researchers have found significant differences in relative risk for mortality and other relevant endpoints (e.g., rate of hospitalization) for those participating in an exercise training program (Belardinelli, Georgiou, Cianci, & Purcaro, 1999).

Rates of nonadherence to exercise may be even higher for individuals suffering from depression, as some symptoms of depression (e.g., fatigue, anhedonia, and social withdrawal) may act as an additional impediment to exercise initiation and/or maintenance. Glazer, Emery, Frid, and Banyasz (2002) found that individuals reporting a higher level of depression on entry into a program of cardiac rehabilitation participated in fewer exercise sessions and dropped out of the program at higher rates relative to their counterparts endorsing fewer depressive symptoms. The relationship between exercise nonadherence and depression is not surprising, in that depressive symptoms themselves (e.g., fatigue and anhedonia) may result in greater difficulty initiating or maintaining exercise participation.

Assessing motivation to exercise before enrollment in a program of exercise training may be a useful way to improve adherence (Marcus & Forsyth, 2003) because motivation is a critical aspect of behavior change and maintenance. Research has shown that brief counseling interventions that are tailored to match an individual's motivation level may assist individuals in achieving stated exercise goals (Bock, Marcus, Pinto, & Forsyth, 2001). From this perspective, counselors would assist individuals in reviewing lapses in exercise participation to identify unique barriers to adherence. The process of identifying unique barriers to exercise adherence would allow treatment to be individualized and would address challenges specific to an individual's needs and experiences. Additional research is needed to explore the relationship between various psychological variables and exercise adherence rates, as some individual differences in anxiety and life satisfaction are believed to be associated with dropout from exercise participation in some populations (Herman et al., 2002).

PSYCHOPATHOLOGY IN EXERCISERS AND RELATED CONSIDERATIONS

It is important to consider the less desirable aspects of prescribed exercise, including psychiatric predisposition to the misuse of this "treatment" that may result in significant harm to the exerciser (e.g., nutritional depletion and orthopedic injury). Some clinical research suggests that, in addition to providing a means of coping with psychiatric symptoms, exercise may also cause symptoms in some populations. Weight preoccupation and excessive exercise tendencies often occur in separate subgroups (Davis & Fox, 1993). Clinical samples (e.g., individuals suffering from anorexia nervosa) and competitive athletes (e.g., runners) have been shown to demonstrate different physiological and psychological profiles (Powers, Schocken, & Boyd, 1998). More specifically, preoccupation with diet and weight, pathological beliefs regarding exercise participation, and the presence of obsessive–compulsive tendencies tend to be more prevalent in individuals with anorexia than in competitive athletes (Davis et al., 1995). Moreover, no clear evidence exists to suggest that excessive exercise leads to a preoccupation with dieting and/or weight (Davis, Fox, Cowles, Hastings, & Schwass, 1990). Important considerations remain, however, regarding the possibility of sustaining injuries as a result of exercising at a level above that with which an individual is habituated. A conservative approach, providing thorough and continued education, may be advisable when participant safety and health are at risk. There is little research regarding the benefits of education to prepare for and guide an appropriate exercise program based on age, weight, and overall health status.

EXERCISE AND EATING DISORDERS

Elite athletes may be at an increased risk for engaging in disordered eating patterns, including bingeing, followed by compensatory behaviors (e.g., fasting and self-induced vomiting; Borgen & Corbin, 1987; Walberg and Johnston, 1991), as weight and/or body size/shape is often associated with performance (e.g., weight class for wrestling, weight associated with speed resistance for swimmers, and size and shape concerns for gymnasts). However, eating disorders (e.g., anorexia nervosa) have not been consistently shown to occur more frequently in competitive athletes relative to their nonathletic counterparts. Although findings are mixed, there is limited data available to support the relationship between exercise and eating disorders, despite theories that suggest connections between exercise, obsessive–compulsive characteristics, and eating disorders (Yates, Leehey, & Shisslak, 1983).

COMPULSIVE EXERCISE AND EXERCISE ADDICTION

Although habitual exercisers are often referred to as "exercise addicts" (Chalmers, Catalan, Day, & Fairburn, 1985; Glasser, 1976; Morgan, 1979; Sachs & Pargman, 1984; Yates et al., 1983), habitual exercise must be distinguished from exercise habits that represent abusive or addictive behavior (DeCoverley-Veale, 1987; Dishman, 1985). Differences between these two descriptors include sustained positive effects on quality of life (e.g., mood, stress reactivity, and physical health) observed in habitual versus compulsive exercisers or exercise "addicts." Some individuals, however, may experience a "negative addiction" process (Morgan, 1979), during which exercise participation is rigidly maintained despite negative medical (e.g., injury) and/or psychosocial (e.g., strained interpersonal relationships) consequences. Exercise dependence is likely to manifest as persistent injury at a medical sports or orthopedic clinic, and exercise-dependent individuals may also experience withdrawal symptoms such as anxiety, depression, and increased irritability when access to exercise is restricted (Morris, Steinberg, Sykes, & Salmon, 1990; Sachs & Pargman, 1984).

Blumenthal, O'Toole, and Chang (1984) compared personality profiles (i.e., Minnesota multiphasic personality inventory [MMPI] responses) of so-called compulsive or obligatory runners with individuals meeting criteria for anorexia nervosa and found that although the anorexics demonstrated increases in depression, anxiety, and hostility, the runners scored in the normal range on the MMPI. Following a critique of these results (Dresser, 1985) that suggested a sampling bias existed in the selection of runners making them less likely to demonstrate significant pathology (i.e., a significant difference in baseline psychiatric functioning), Blumenthal et al. reanalyzed the data (Blumenthal, Rose, & Chang, 1985) and reported that even those runners who indicated the highest likelihood of exercising despite significant physical impediments (e.g., illness or injury) did not exhibit significant pathology on the MMPI profile. On the basis of a small, qualitative study of a subset of exercise-dependent women, Bamber, Cockerill, Rodgers, and Carroll (2000) concluded that the presence of a comorbid eating disorder and exercise dependence (i.e., secondary exercise dependence) was associated with psychological distress but found no evidence for a primary exercise dependence (e.g., in the absence of an eating disorder). Furthermore, they reported that individuals identified as primary exercise dependent demonstrated healthy exercise attitudes and behaviors consistent with previous findings (Bamber et al., 2000). Additional research using rigorous methodology is needed to accurately measure and classify exercise "addiction" versus more healthful forms of habitual exercise.

SUMMARY AND FUTURE DIRECTIONS

Claims regarding the psychological and emotional benefits of exercise participation began to be made centuries ago, and only recently has the empirical evidence existed to support these anecdotal reports. Nonetheless, exercise now has consistently been shown to produce various physiological (e.g., improved glucose metabolism, decreased risk for CVD, and osteoporosis) and psychological benefits (e.g., improved mood and self-efficacy and social integration). In addition, growing evidence supports the role of exercise in reducing psychophysiological responses to stress (Crews & Landers, 1987; Hamer, Taylor, & Steptoe, 2006). However, the findings are mixed regarding the effect of exercise on well-being, especially when issues of dose (e.g., frequency, intensity, and duration) of exercise relative to effects are considered. More recent studies (Dunn et al., 2002) suggest that physical exertion may play the most important role regarding the stress attenuation, antidepressant, and anxiolytic effects associated with exercise.

It remains unclear whether fitness changes are necessary for an individual to experience optimal stress-reducing benefits of exercise. Larger-scale studies that control for methodological weaknesses may help to clarify these issues. It will be important for future research to continue addressing factors such as individual differences (e.g., fitness level, medical status, age, gender, and personality) to produce a clearer understanding of the relationship between fitness, stress response, and overall health and well-being.

Another issue that requires further attention is the mechanism(s) of change that may explain the various benefits of exercise participation. Physiological adaptations in response to exercise, relative to the stress response, have been attributed to a variety of mechanisms such as reduced sympathetic activity and

improved vagal tone. However, more direct evidence to support any of the proposed hypotheses is needed. Similarly, a plethora of mechanisms of change (e.g., biochemical, psychological, and social) have been proposed to explain the psychological benefits of exercise, but no single mechanism of change has been established. More research is needed to clarify the psychobiological nature of the various health benefits associated with exercise. Moreover, there is a need for more research addressing ways of adapting the exercise prescription to various cultural and environmental differences (e.g., access to safe forms of exercise, environmental factors that limit exercise participation, and acceptability of varying modalities of exercise) to advance the literature and make exercise an increasingly viable alternative in the general population.

Ongoing research investigating issues surrounding the relationship between exercise, stress reactivity, and mood, is essential to inform and improve public health initiatives, given the high cost associated with sedentary lifestyles, including healthcare costs and loss of healthy years of life. Exercise may represent a clinical intervention strategy important in the treatment and prevention of various disease processes, including the onset or relapse of psychological conditions (e.g., depression and anxiety). Exercise may also offer a method of ameliorating the effects of stressors that occur in an individual's life (Salmon, 2001), which is particularly relevant for individuals who are already suffering functional impairments associated with psychopathology. Overall, exercise may represent a more accessible and acceptable treatment option for some populations, particularly for individual's who are resistant to more traditional therapies or for whom traditional therapies are not available because of cultural, financial, or other personal factors. Further research is needed to investigate differential benefits of various forms of stress management treatments (e.g., exercise, relaxation training, meditation, and psychotherapy), including investigations of the efficacy of these interventions in various subgroups of the population for whom exercise may represent a more viable treatment option (e.g., coronary-prone individuals). In addition, further investigation of the dose-response relationship relative to the psychological benefits of exercise is warranted. This line of research would provide greater insight regarding the effectiveness of exercise as a treatment for stress-related disorders and would also provide information necessary to improve the identification of individuals who may experience the greatest benefits of exercise as an adjunctive intervention for particular health concerns.

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24 Stress in Pregnancy: Empirical Evidence and Theoretical Issues to Guide Interdisciplinary Research

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> The most important nine months of our lives are probably the nine months we know the least about.
>
> *Christopher Coe, May 3, 2008, Invited address, American Psychological Society meetings, Chicago, IL*

Distinguished professor, Christopher Coe, "hit the nail right on the head" with the words above, delivered in a plenary lecture at a 2008 scientific conference. We know relatively little about biopsychosocial processes in pregnancy, yet we are learning that this short period of the life span as a fetus has profound consequences for the rest of our lives. We focus here on only one aspect of this topic, the role of stress in pregnancy and its effects on preterm birth. As with the study of the prenatal period in general, the study of the effects of stress in pregnancy has changed dramatically in the past decade from a small amount of inconclusive research conducted mainly in medicine to a sizable body of multidisciplinary studies evolving at lightning speed. As a 1990 review pointed out (Lobel & Dunkel-Schetter, 1990), investigations until then had been largely retrospective with weak conceptualizations and measures of stress, and many other methodological problems limiting conclusions (cf. Paarlberg, Vingerhoets, Passchier, Dekker, & Can Geijn, 1995). In the intervening 20 years, research scientists from many disciplines have contributed to a significant body of stronger research demonstrating that stress in one form or another during pregnancy is associated with preterm birth, low birth weight, maternal postpartum depression, infant complications, and developmental effects lasting long after infancy and even into adulthood (Beydoun & Saftlas, 2008). Furthermore, research on mechanisms has suggested that stress operates through neuroendocrine, immune, and behavioral pathways during pregnancy to influence specific outcomes in complex ways (e.g., Coussons-Read, Okun, & Simms, 2003; Hobel, Goldstein, & Barrett, 2008).

Before we explore the state of knowledge on this issue in detail, we note that progress in the investigation of stress in pregnancy has been challenging. Although research scientists in diverse disciplines agree that they must collaborate to study complex biopsychosocial processes in pregnancy, their goals remain different as do their areas of expertise.[1] Finding effective interventions and policies are pressing public health needs in the United States (IOM, 2006) dictating research approaches that differ from basic scientific discovery, yet both are needed. As with most multidisciplinary work, progress can be slow and the process is cumbersome. Halbreich (2005) stated, "Currently the multiple clinical and research disciplines that are concerned with the various aspects of pregnancy, delivery and postpartum period are not conceptually and practically integrated" (p. 1312). This remains the context within which this body of research is now growing.

THE DILEMMA OF DEFINING STRESS

There is no consensus on the definition of stress for studying its contribution to adverse outcomes of pregnancy. In fact, many pregnancy researchers have treated major life events as a proxy and de facto definition of stress. Others view stress as any physiological threat, including physical strain, exercise, fasting, or sleep deprivation. Still others conceptualize stress as appraisals of threat, consistent with the psychological literature (Cohen, Kessler, & Gordon, 1995; Lazarus & Folkman, 1984). In keeping with a lack of consensus on definitions, measures of stress vary considerably and are inconsistently evaluated for the quality of measurement. Relatively few researchers use a multidimensional approach to compare measures, despite evidence of the value of this approach in prenatal stress research (e.g., Dole et al., 2003; Lobel, Dunkel-Schetter, & Scrimshaw, 1992; Roesch, Dunkel-Schetter, Woo, & Hobel, 2004).

In our work, we use the term *stress* as a rubric or umbrella concept, following the work of Richard Lazarus (Lazarus, 1966, 1968). The overarching concept may then be divided into *stressors* (environmental exposures) and

[1] The relevant experts are physicians from obstetrics and pediatrics, health and developmental psychologists, social scientists, endocrinologists and immunologists, community health researchers, and epidemiologists.

responses (including biological, emotional, cognitive, and behavioral reactions). A further theoretical component is *cognitive appraisals* of stress, which operate as a critical mediator between stressors and responses in human research (Lazarus & Folkman, 1984). It is not easy to study the unfolding of dynamic stress processes (stressors, appraisals, responses) in pregnancy because a multitude of stressors and responses unique to each woman occur over the course of 9 months. Therefore, researchers have had to conduct observational investigations in which stressors and responses are assessed using self report and aggregated over specific time periods within pregnancy at various standard intervals. Measures of life events (stressors) and of anxious and depressed mood (i.e., presumed responses to stressful conditions) have been the most common. Only recently have experimental studies of stress reactivity in pregnant women begun to appear (e.g., Hatch et al., 2006), which add to the larger body of evidence from observational research. Intervention research on pregnancy has generally not been designed to pinpoint the role of stress in reducing rates of preterm birth, although such approaches are very valuable (cf. Bastani, Hidarnia, Montgomery, Aguilar-Vafael, & Kazemnejad, 2006).

We have been working individually and together on stress in pregnancy for many years endeavoring to make inroads. We share a commitment to bringing strong psychological theory and methods to the endeavor. In our multiple collaborations with health and biological scientists, we have tackled the challenges inherent in this research. In this chapter, we limit our attention to the effects of stress on preterm labor and delivery. Related findings on low birth weight are sometimes noted, although that is not the main focus. Our goals here are to review current evidence on stress and preterm birth, discuss primary hypothesized and known mechanisms of these effects (HPA, immune, behavioral), describe models of stress and preterm birth, and note larger theories of stress as they might enrich this body of work. In closing, we highlight promising directions for further inquiry.

PREVALENCE AND CONSEQUENCES OF PRETERM BIRTH

Preterm birth is the birth of a baby by any means (vaginal or Caesarian section) before 37 weeks' gestation, whereas normal gestation is 40 weeks. Preterm birth (PTB) is a contributor to other adverse birth outcomes, particularly low birth weight (LBW; defined as 2,500 grams or less) and infant mortality. Rates of these three correlated outcomes (PTB, LBW, and infant mortality) are high in the United States, particularly compared to other developed countries (MacDorman & Mathews, 2008). The United States typically ranks 27th. However, there has been a decline in overall infant mortality rates in the United States over the past few decades, with a simultaneous increase in PTB and LBW (Alexander & Slay, 2002), due largely to advances in neonatal intensive care. From 1990 to 2004, the rates of preterm birth rose from 10.6% to 12.5% of live births in the United States, an increase of more than 15% (Alexander, 2006, see Appendix A in 2006 IOM report). In 2005, there were over 4 million births in the United States of which 12.7% were preterm (about 1 in 8 births) and 8.2% were LBW (MacDorman & Mathews, 2008).[2]

Adding to the complexity of this issue is a striking ethnic disparity in both PTB and LBW, with African Americans at much higher risk. In 2005, the rate of preterm birth among Black women in the United States was 18.1% compared to rates of 10.5% for Asian and Pacific Islander women and 11.5% for White women. The Hispanic rate was 12% overall. These disparities are not fully explained by socioeconomic status, maternal risk behaviors, genetics, or prenatal care (Lu & Halfon, 2003). Reducing rates of PTB, LBW, and infant mortality, along with eliminating disparities in these rates, are top public health priorities in the United States and have been for some time. Healthy People 2010 (www.healthypeople.gov), a set of federal objectives for increasing the health of the population, included the goal of reducing total preterm births to no more than 7.6% of live births. Still, high PTB and LBW rates persist despite considerable effort directed at their reduction. Thus, further research on both etiology and prevention is essential.

High rates of PTB and related adverse outcomes are of public health concern because of their severe consequences. Besides risk of death (i.e., neonatal and infant mortality) for those born especially early and/or small, PTB poses significant risk of complications at birth, pediatric problems in infancy and childhood, developmental disorders, adult health risks, and lifelong disabilities. Preterm (PT) infants are often hospitalized in the intensive care unit (ICU) for several weeks and suffer higher rates of respiratory problems, infection, and feeding difficulties, together with disrupted parent–infant contact. When they go home, caring for preterm infants presents special challenges. For example, they may be frightening for parents to care for and difficult to comfort (Affleck, Tennen, & Rowe, 1991). Depending on how early the delivery is and the presence of any complications at birth, infants born preterm have more pediatric visits for illness, suffer higher rates of cognitive and learning difficulties, and show poorer growth and development. There are higher risks of short- and long-term pulmonary, ophthalmologic, and neurologic morbidity and delayed psychomotor development (Kramer, 2003). Higher economic costs to families and society are further consequences of PTB. An Institute of Medicine (IOM) report estimated the cost of PTB to be $26.2 billion in 2005, two thirds of which

[2] One reason for increased rates of preterm birth is an increase in multiple gestation or multiple births (e.g., twins, triplets). However, this does not account entirely for the increase in preterm birth, which remains high in singleton births.

was for medical care (Zupancic, 2006, see Appendix D in 2006 IOM report).

PATHOPHYSIOLOGY OF PRETERM LABOR AND DELIVERY

It is important to distinguish the various proximal causes of preterm birth. First, *spontaneous preterm labor* is the natural onset of labor defined as premature contractions before 37 weeks' gestation. When it cannot be arrested by intervention, early labor may result in a preterm birth before 37 weeks. Approximately half of all preterm births occur in this way. In another 30% of cases, labor is preceded by preterm premature rupture of the membranes (referred to as PPROM),[3] which leads to the onset of early labor either spontaneously or by induction to protect the fetus. The causes of PPROM are overlapping with those of spontaneous preterm labor without early rupture of membranes, and both may involve a role for maternal stress. In contrast, medically induced preterm birth, also called "indicated delivery," is physician-initiated delivery for the benefit of the fetus or the mother via Caesarian section or by induction of labor (estimated as 20% of PTB cases). With a few exceptions, maternal prenatal stress is not relevant to early delivery for this last group. Certain conditions of pregnancy such as pregnancy-induced hypertension and preeclampsia that are direct contributors to indicated preterm birth (Klonoff-Cohen, Cross, & Pieper, 1996; Landsbergis & Hatch, 1996) may involve maternal stress as a precursor. Our focus in this chapter and in most research presently is on spontaneous preterm birth with or without PPROM, rather than indicated preterm birth.

Until recently, the pathophysiology of early labor was believed to be a single process regardless of how and when early labor began (anywhere from 22 weeks to 37). However, it is now accepted that there are multiple physiological pathways to preterm labor distinguishable, in part by when in gestation labor begins. This can be characterized as multiple upstream processes leading to a single downstream pathway to labor. According to a panel of experts preterm birth has heterogeneous origins that result in common biological pathways and that lead to relatively few clinical presentations (IOM, 2006).

INFLAMMATORY/IMMUNE PATHWAY

Inflammation is a primary process through which tissues deal with both infectious and noninfectious insults. The inflammatory response consists of increases in blood flow, increases in permeability of blood vessels, and migration of fluids, proteins, and white blood cells to the site of an injury or infection. Inflammation is central to reproductive success, playing a role in implantation of the embryo, maintenance of pregnancy, and parturition (Romero, Gotsch, Pineles, & Kusanovic, 2007). However, an exaggerated inflammatory response is a recognized contributor both to preterm labor and PPROM (Goldenberg, Hauth, & Andrews, 2000). For example, proinflammatory cytokines are involved in the ripening of the cervix in term deliveries, but overproduction of these cytokines is associated with PTB (Keelan et al., 2003). Bacterial intrauterine infections are the leading cause of infection-related preterm birth. The most common microorganisms found in the amniotic cavity are genital *Mycoplasma* species, which reflects the finding that the most frequent pathway through which intrauterine infections occur is ascension from the vagina and cervix (Goldenberg, Culhane, Iams, & Romero, 2008). Other known sources of infection related to PTB include lower genital tract infections, systemic maternal infections (e.g., malaria, kidney infection), and periodontal disease (Romero et al., 2007; Xiong, Buekens, Fraser, Beck, & Offenbacher, 2005). (There is little evidence supporting a role of viral infections such as influenza in PTB [Goldenberg et al., 2008].)

Inflammation due to bacterial systemic or maternal genital tract infections is estimated to account for 25% to 40% of PTB cases (Goldenberg et al., 2000) and may be responsible for up to 50% of PTB before 28 weeks (IOM). It now is believed that infection results in spontaneous preterm labor through stimulation of prostaglandins (lipid compounds with a wide range of strong physiological functions, including promotion of uterine contractility) and increased production of proinflammatory cytokines by the mother and/or fetus in response to microbial invasion (Romero et al., 2006).

THE HYPOTHALAMIC-PITUITARY-ADRENOCORTICAL PATHWAY

A second, neuroendocrine pathway, involving the maternal hypothalamic-pituitary-adrenocortical (HPA) axis and its effects on the fetal-placental unit, has been labeled the "stress pathway" by some obstetric researchers. Corticotropin-releasing hormone (CRH) is a neuropeptide primarily of hypothalamic origin that plays a central role in the control of pituitary-adrenal function and regulation of the physiological response to stress exposure (Vale, Spiess, Rivier, & Rivier, 1981). CRH stimulates the pituitary gland to produce adrenocorticotropic hormone (ACTH), which, in turn, activates the production of cortisol, a major stress hormone, by the adrenal cortex. During pregnancy this stress-sensitive peptide is synthesized by the placenta and rises exponentially in the maternal circulation over the course of normal gestation (Petraglia, Florio, Nappi, & Genazzani, 1996). Placental CRH (pCRH) levels during pregnancy

[3] PROM is referred to, colloquially, as "her water breaking." It is important to note that PPROM is not a redundant term. PROM (premature rupture of membranes) refers to rupture of membranes prior to initiation of labor. PPROM (preterm PROM) means that this occurs before 37 weeks' gestation.

have repeatedly been linked to timing of onset of parturition and may be involved in the causal pathway (Smith, Mesiano, & McGrath, 2002). Premature elevations (perhaps beginning as early as 16–18 weeks' gestation) and steeper trajectories in CRH are reliable predictors of eventual preterm labor and delivery (Holzman, Jetton, Siler-Khodr, Fisher, & Rip, 2001; McLean et al., 1995; Smith et al., 2009; Wadhwa et al., 2004; Wadhwa, Porto, Garite, Chicz-DeMet, & Sandman, 1998). Further, elevated CRH in the presence of lower levels of CRH-binding protein may be particularly likely to increase the risk of PTB, presumably because of the increased availability of biologically active CRH (Hobel, Arora, & Korst, 1999; Petraglia et al., 1997). In vitro studies suggest that when released into the maternal compartment, the myometrium is a primary target for pCRH and its actions there could influence uterine contractility (Markovic et al., 2007; Yang, You, Tang, Gao, & Ni, 2006; You, Yang, Tang, Gao, & Ni, 2006). Placental CRH also is released into the fetal circulation, where it likely stimulates the production of dehydroepiandrosterone sulfate (DHEA-S), the precursor for placental estriol synthesis, from the fetal adrenals, providing an additional route through which pCRH might affect uterine contractility (Smith, Mesiano, Chan, Brown, & Jaffe, 1998). Given these associations, it is probable that pCRH is a causal determinant in the pathway leading to preterm birth. However, to date, its precise role in this complex process has yet to be fully elucidated. The activation of the maternal HPA axis due to stress exposure early in pregnancy, with consequences for the fetal HPA axis and the placenta, is believed to be a primary stress pathway to PTB.

TWO ADDITIONAL PATHWAYS

A third pathway that may also be sensitive to stress involves abnormalities in placental vascular development that are commonly observed in women who exhibit spontaneous PTB and also PPROM. Vascular lesions of the placenta have been detected in 34% of women with preterm birth and 35% of women with PPROM, compared to 12% in women with uncomplicated term deliveries (Arias, Rodriquez, Rayne, & Kraus, 1993). Placental lesions can include those resulting from improper early placental development (specifically, failure of trophoblast invasion and physiological transformation of the spiral arteries), acute atherosis, or maternal or fetal thrombosis (Khong, 2004). Vascular lesions may lead to PTB by causing placental ischemia or alterations in the microcirculation of the placenta. Plausible potential mechanisms exist that could account for such an association and include the renin-angiotensin system and thrombin. However, to date, the precise mechanism through which ischemia would result in spontaneous PTB has not been demonstrated (Romero et al., 2006).

Finally, PTB is associated with multiple gestation (carrying more than one fetus). Multiple gestation can lead to uterine overdistention and premature rupture of membranes. There is little or no recognized contribution of stress in this multiple gestation pathway.

Before further exploring mechanisms further, we examine the evidence for stress as a contributor to preterm birth.

EVIDENCE FOR STRESS CONTRIBUTING TO PTB

For decades, there have been studies published suggesting that women who are under stress are at higher risk of adverse birth outcomes (Dunkel-Schetter, Gurung, Lobel, & Wadhwa, 2000). However, the evidence has been only suggestive until recently because of imprecision and lack of replication. An earlier careful review by Savitz and Pastore (1999) of 20 of the more rigorous studies concluded that it was difficult to draw conclusions due to methodological limitations. Study designs until that time had been a mix of retrospective and case-control investigations, with relatively few utilizing prospective studies. Approximately, half of the studies reviewed found associations of stress and preterm birth or length of gestation. One expert summed it up thus: "Maternal psychosocial processes in pregnancy are at least as important and warrant the same degree of further consideration and study as other established obstetric risk factors because the overall magnitude of their independent effect size on prematurity-related outcomes is comparable" (Wadhwa et al., 2002, p. 152).

In recent years, many more studies have been published on this topic, often with prospective designs, large sample sizes, and appropriate controls. Recent reviews concur that the evidence regarding stress as a significant independent risk factor for spontaneous preterm labor and delivery is now clearer (Beydoun & Saftlas, 2008; IOM, 2006). Beydoun and Saftlas (2008) report that 9 of 11 studies between 2000 and 2006 found significant effects of prenatal maternal stress on length of gestation or risk of preterm labor or birth, although not all studies adjusted for appropriate control variables. They conclude that evidence consistently suggests that exposure to stressful stimuli increases the risk of preterm birth.

Another review was published in an Institute of Medicine report on causes and consequences of PTB (Savitz & Dunkel-Schetter, 2006). That review of about two dozen studies is organized according to life events, chronic and catastrophic stress exposures, emotional and affective states (anxiety, depression), and other forms of exposure (occupational stress and personal violence). It concludes that the most consistent evidence is for anxiety as a risk factor, particularly anxiety regarding pregnancy. The present chapter's review of the evidence is updated to include many recent studies and is organized similarly by stress concepts: episodic stressors, catastrophic/traumatic events, chronic stress, emotional states, and pregnancy anxiety/stress. Tables 24.1 through 24.4 categorize

Table 24.1 ■ Episodic Forms of Stress

Studies	Sample	Design	Findings
Stressor: Life events			
Barbosa (2000)	472 African American women	Prospective	Significant effect for loss events but not total life events
Dole et al. (2003)	1,962 North Carolina women	Prospective	Negative impact of life events predicted PTB (RR = 1.8)
Goldenberg et al. (1996)	1,491 pregnant women with previous PTB, 69% Black	Prospective	Nonsignificant association between LE and PTB
Hedegaard, Henriksen, Secher, Hatch, and Sabroe (1996)	5,873 Danish women	Prospective	1 or more stressful LE between 16 and 30 weeks gestation associated with PTB (OR = 1.76)
Lobel et al. (2000)	129 high-risk pregnant women	Prospective	Nonsignificant association between LE number and impact with GA
Kramer et al. (2009)	5,337 Canadian women	Prospective	Negative LE not associated with PTB
Lobel et al. (2008)	279 pregnant women	Prospective	Nonsignificant association for LE number and impact with GA
Lu & Chen (2004)	33,542 PRAMS cohort	Retrospective	Nonsignificant association between LE and PTB
Messer et al. (2005)	1,908 pregnant women in NC	Prospective	Highest quartile of negative LE associated with PTB
Nordentoft et al. (1996)	2,432 Danish women	Prospective	Severe life events predicted PTB (OR = 1.14 controlling for covariates)
Parker-Dominguez et al. (2005)	178 African American women assessed at three times in pregnancy starting at 18–20 weeks	Prospective	Number of LE predicted GA
St. Laurent et al. (2008)	1,602 Montreal	Prospective	11-item measure in French indirectly predicted GA in path model via smoking
Whitehead et al. (2002)	70,840 U.S.	Retrospective, two cohorts	>2 LE predicted PTB in women in 1994–1995 cohort who had not given birth before; >5 LE predicted PTB in women in 1990–1993 cohort who had previously given birth
Zambrana et al. (1999)	1,071 low-income Mexican immigrant, Mexican American, & Black pregnant women	Prospective	Number and impact of LE predicted GA as part of latent factor

Studies	Sample	IV	Findings
Stressor: Catastrophic/traumatic events			
Berkowitz et al. (2003); see also Engel et al. (2005)	187 pregnant women exposed to disaster and 2,367 control women not exposed in pregnancy	Exposure to World Trade Center disaster in NYC	Nonsignificant differences in GA and PTB between groups
Eskenazi et al. (2007)	1,660,401 NY state birth records from 1996 to 2002	Present on Sept 11th terrorist attacks in NYC or upstate NY	Increase in delivery of infants weighing <2,000 g in week after Sept 11 and no effect in comparison area
Glynn et al. (2001)	40 women experiencing Northridge, CA earthquake	Time in gestation or postpartum when earthquake occurred	Shortest gestation among women experiencing earthquake in first trimester
Huizink et al. (2008)	121 adolescent Finnish twins exposed in utero; 157 unexposed controls	Chernobyl nuclear disaster exposure during second trimester	Longer GA among exposed twins
Kuvacic et al. (1996)	Croatian pregnant women grouped as free (712) or expatriated (593 refugees)	Free or experienced stress due to expatriation during occupation in Croatia	Expatriated women delivered PT twice as often as those free
Lederman et al. (2004)	300 women in NYC during World Trade Center attack	Trimester when occurred and distance from WTC	Women in first trimester had shorter GA
Levi et al. (1989)	86 pregnant women exposed to Chernobyl nuclear disaster in Sweden early in gestation	Retrospective	Shorter GA (not PTB) associated with anxiety
Noll et al. (2007)	Case/control study: 68 child sexual abuse, 56 without	History of child sexual abuse	Higher risk of PTB in those with history of childhood sexual abuse
Rich-Edwards et al. (2005)	606 Boston women pregnant during the Sept 11th terrorist attacks	Comparison to women who delivered before Sept 11	Longer GA and lower risk of PTB among those in first trimester in Boston during Sept 11 attacks
Xiong et al. (2008)	Hurricane Katrina	High versus low exposure to the hurricane during pregnancy or immediately before conception	Increased risk of PTB

GA, gestational age at birth; LE, life events; OR, odds ratio; PRAMS, a specific pregnancy cohort study; PTB, preterm birth (<37 weeks); RR, relative risk.

the studies accordingly. When multiple measures of stress could be evaluated individually, a study may appear in more than one table.

Table 24.1 includes studies on *episodic forms of stress*. The largest numbers of studies have examined *life events* or major episodes that happen to individuals. In total, 8 of the 14 studies on life events showed significant effects in the expected direction. Of the 8, 6 involved very large sample sizes. Considered together, these studies suggest that exposure to certain types of life events (loss events, more severe events) and to very high numbers of life events increase risk of PTB. An additional study in a large Canadian sample showed indirect effects of life events on gestational age that were mediated by cigarette smoking (St. Laurent et al., 2008).

A second form of episodic stress shown in Table 24.1 is *catastrophic events*, referring to large-scale, destructive occurrences that fall outside the normal range of life experiences. Five of the nine studies on exposure in pregnancy document adverse effects of catastrophic events on gestational age (GA) or PTB. Several of these focused on the effects of the terrorist attacks in the United States on Sept 11th; most demonstrated significantly shorter gestational length among women exposed to the attack (e.g., Lederman et al., 2004), but in one study exposure to the terrorist attacks was associated counterintuitively with longer gestation (Rich-Edwards & Grizzard, 2005). Similar yet contrasting findings were obtained in two studies on the Chernobyl nuclear disaster; in one study, women who were exposed experienced shorter gestations (Levi, Lundberg, Hanson, & Frankenhaeuser, 1989), but in a second study of twins exposed in utero compared to twins not exposed, *longer* gestation occurred among those exposed (Huizink et al., 2008). Untangling stress-related physiological effects of the catastrophe from other possible effects, such as positive changes in behavior, increased support, and improved medical care, is necessary and may explain these contradictory results. More than half of the studies on catastrophes, however, are fairly consistent in demonstrating adverse effects on GA or PTB.

A final form of episodic stress is *daily hassles*. None of the four studies we located on this form of stress (not shown in table) had significant associations with GA or PTB (Jesse, Seaver, & Wallace, 2003; MacKey, Williams, & Tiller 2000; Paarlberg, Vingerhoets, Heinen, Dekker, & Can Geijn, 1996; Wadhwa, Sandman, Porto, Dunkel-Schetter, & Garite, 1993).

Table 24.2 lists studies of various *chronic forms* of stress, including chronic strain, perceived stress, perceived racism, and neighborhood or community stressors. All five of the studies on *chronic strain,* measured either in general or in specific forms such as homelessness severity or household strain, show effects on PTB. These are mostly retrospective or case-control studies, but some involve controlled, prospective analyses in larger samples of high-risk women (e.g., Misra, O'Campo, & Strobino, 2001).

In contrast to these studies on chronic strain, only 4 of the 12 studies that measured *appraised or perceived stress* (see Table 24.2) showed effects on PTB. All of these studies used the Perceived Stress Scale (PSS) (Cohen, Kamarck, & Mermelstein, 1983), which is not stressor specific and captures perceived strain and inability to control stress or cope. The largest study, conducted in the Netherlands, found PSS was associated with babies who were small for gestational age but not with PTB (Krabbendam et al., 2005). Three others with large samples, however, do report significant associations of PSS and PTB (Kramer et al., 2009; Messer, Dole, Kaufman, & Savitz, 2005; Zambrana, Dunkel-Schetter, Collins, & Scrimshaw, 1999). Thus, the utility of the PSS measure of perceived stress in predicting PTB remains unclear. In addition, two studies found that changes in PSS—but not levels at single time points—predicted PTB (Glynn, Dunkel-Schetter, Hobel, & Sandman, 2008; Ruiz, Fullerton, Brown, & Schoolfield, 2001).

Perceived racism, another chronic form of stress shown in Table 24.2, has been hypothesized to contribute to disparities in PTB and low birth weight. Yet, only one of the three studies measuring racism that we located suggests effects on preterm birth. Nonetheless, an interesting study of California births before and after the 9/11 terrorist attacks, showed that the rates of preterm, LBW births were significantly higher after the attacks in women with Arabic surnames. Many additional studies (not listed in the table) have reported effects of perceived racism on birth weight (see review by Giscombe & Lobel, 2005). More rigorous research in this area is needed to draw conclusions about the effects of racism in African American and other minority groups on PTB as compared to effects on fetal growth or LBW.

Neighborhood- or community-level stress has been highlighted as an important group variable that may affect birth outcomes independent of individual-level factors and may account for race and social-class disparities (Culhane & Elo, 2005; IOM, Chapter 6, 2006). As shown in Table 24.2, seven of the eight studies on neighborhood stress factors show significant results on GA or PTB. For example, at the aggregate level, poverty, crime, and the racial composition of a community were all significant predictors of PTB in communities. The mechanisms through which neighborhood structural factors are associated with PTB and related outcomes presumably involve individual-level experiences of stress and adaptation (Morenoff, 2003). More research on this pathway is needed.

Occupational stress is another form of chronic stress, but a review of the many studies on this topic is beyond the scope of this chapter and can be found elsewhere (Mozuekewich, Luke, & Avni, 2000; Saurel-Cubizolles & Kaminski, 1986; Woo, 1997). There appear to be no risks associated with employment per se, but various characteristics of employment or housework are critical to understanding the effects of chronic strain in pregnancy. For example, both physical strain and psychological stressors, such as lack of control and work overload, have

Table 24.2 ■ Chronic Forms of Stress

Studies	Sample	Design	Findings
Chronic strain			
Hollander (2005)	496 women incarcerated during pregnancy	Case control study	Risk of PTB increased compared to matched controls in women 30 years or older; but not among younger women
Misra et al. (2001)	739 low-income African American women	Retrospective	Multidimensional chronic strain measure predicted PTB (adj OR = 1.86) with many control variables
Pritchard and Teo (1994)	393 Swedish pregnant women	Prospective at 20 and 30 weeks gestation	Household strain at 20 weeks associated with PTB
Stein et al. (2000)	237 Homeless women	Retrospective	Severity of homelessness (percent of life homeless) predicted PTB controlling for substance use, trauma, distress, race and ethnicity, income, medical risk

Studies	Sample	DV	Findings
Appraised/perceived stress			
Glynn et al. (2008)	415 pregnant women assessed at 19 and 31 weeks gestation	GA	Change in PSS, but not level predicted PTB
Krabbendam et al. (2005)	5,511 pregnancies in Netherlands 2001–2003, 14–30 weeks	PTB	PSS small but nonsignificant effects on SGA at 14 weeks
Kramer et al. (2009)	5,337 Canadian women	PTB	PSS not associated with PTB
Lobel et al. (1992)	130 pregnant women	GA	PSS predicted GA as part of latent factor
Lobel et al. (2000)	129 high-risk pregnancies	GA	PSS not associated with GA
Lobel et al. (2008)	279 pregnant women	GA	PSS associated with GA at only one of three waves (late pregnancy)
Messer et al. (2005)	1,908; 24–29 weeks (PIN study in N. Carolina)	PTB	Highest quartile of PSS associated with PTB
Parker-Dominguez et al. (2005)	178 African American women assessed at three times in pregnancy starting at 18–20 weeks	GA	PSS not associated with GA
Rondo et al. (2003)	865 Brazilian pregnant women assessed < 16 weeks, 20–26, 30–26.	PTB	No association with PTB
Ruiz et al. (2001)	78 pregnant low-income women assessed 23–26 and 31–35 weeks	Preterm labor with or without PTB	PSS levels not associated with preterm labor/birth (changes in PSS were significant)
Ruiz et al. (2006)	N = 106 pregnant women at 22–25 weeks	GA, BW	PSS associated with CRH but not GA
Zambrana et al. (1999)	1,071 low-income Mexican immigrant, Mexican American and Black pregnant women	GA	PSS associated with GA

Studies	Sample	DV	Findings
Perceived Racism			
Dole et al. (2003)	1,962 North Carolina women	PTB	Not associated with PTB
Lauderdale (2006)	CA births 2000–2002 compared pre and post 9/ll terrorist attacks; racism imputed by name	PTB	RRs of preterm LBW were higher pre/post 9/11 for Arabic-named compared to non-Hispanic White women
Parker-Dominguez et al. (2008)	124 African American and White women	GA	Associated with LBW adjusted for GA, but not with GA

Continued

Table 24.2 ■ *Continued*

Studies	Sample	Findings
Neighborhood/Community		
Ahern et al. (2003)	417 African American births 1,244 White births	Adverse neighborhood conditions predicted PTB with controls in model
Bell et al. (2006)	2002 African American births in major metropolitan areas (434,376) linked to census tract data	Greater isolation from other African Americans and lower clustering of African Americans associated with PTB and other adverse outcomes
Dole et al. (2003)	1,962 North Carolina women	No association with PTB
Masi et al. (2007)	1991 birth data in Chicago linked to neighborhood characteristics (55,130 live births)	PTB higher in Whites and Hispanics living in census tracts with higher proportion of Blacks vs. same race tracts (group density)
Messer et al. (2006)	Wake County, NC geocoded for birth and crime records (13,960 births)	Neighborhood crime and deprivation associated with PTB for White and Black non-Hispanic women
Pickett et al. (2002)	417 African American and 1,244 White women delivering in San Francisco 1980–1990	Neighborhood SES factors and changes in neighborhoods over time were related to PTB in exploratory analysis
Pickett et al. (2005)	1,991 births in Chicago to African American mothers (25,286)	PTB effects of SES at group level and racial composition of tracts (qualified by interactions)
Reagan and Salsberry (2005)	1,033 Blacks; 1,664 Whites; 602 Hispanics	Neighborhood poverty rates and housing vacancy rates positively associated with rate of very PTB and inversely associated with rate of moderate PTB for Blacks only?

BW, birth weight; CRH, corticotrophin-releasing hormone; GA, gestational age at birth; LBW, low birth weight; PSS, perceived stress scale; PTB, preterm birth (<37 weeks); RR, relative risk.

been examined. A large study of 16 European countries (Saurel-Cubizolles et al., 2004) found that women working more than 42 hours per week, standing more than 6 hours per day, and with low levels of job satisfaction were at greater risk of PTB (cf. Escrib-Arguir, Perez Hoyos, & Saurel-Cubizolles, 2001).

Table 24.3 lists studies on emotional states, including separate lists for anxiety, depression, and general distress. A total of 6 of the 11 studies on *general or state anxiety* show some impact on preterm birth or gestational age, although in all cases the effects are somehow qualified. For example, one reports effects for White women but not for Black women (Goldenberg, Cliver, & Mulvhill, 1996). Another showed effects in Hispanic and White women when state anxiety was combined with a measure of pregnancy anxiety (Rini, Dunkel-Schetter, Wadhwa, & Sandman, 1999). Lobel et al. (2008) found significant correlations at two of three time points in mid-to-late pregnancy. A large Swedish study examined clinical diagnoses of anxiety disorders but found no significant link to PTB (Andersson, Sundstrom-Poromaa, Wulff, Astrom, & Bixo, 2003). A sixth study found that trait anxiety was associated with spontaneous preterm labor in women with a history of PTB (Dayan et al., 2002).

Only 3 of the 14 studies in Table 24.3 that tested *depressed mood or symptoms of trauma* show effects on GA or PTB. Depressed mood or depressive symptoms were typically measured using the Center for Epidemiological Studies Depression scale. Two studies involved clinical diagnoses of depressive disorders, but neither found significant associations with PTB or GA (Andersson et al., 2003; Suri et al., 2007). Only one of the three studies showing effects of depressed mood had a large sample size (Orr, James, & Blackmore Prince, 2002), whereas 6 of the 11 studies with no effects had large samples. Compared to these relatively modest results supporting a link between depression and PTB, many more studies show effects of depressed mood on fetal growth or low birth weight (e.g., Diego et al., 2006).

Three studies (shown in Depression section of Table 24.3) tested the effects on PTB of posttraumatic stress disorder symptoms (PTSD), often associated with depression. These show equivocal results. One found no association of PTSD symptoms to PTB or GA in 187 women who were near the World Trade Center when it was attacked (Berkowitz et al., 2003). A second study found that a measure combining PTSD and depression was associated with significantly *longer* GA among a small sample of 52 pregnant women who were near the World Trade Center (Engel, Berkowitz, Wolff, & Yehuda, 2005). A third study found a marginally significant effect of symptoms of nonspecific trauma on PTB in a sample of 1,100 pregnant women but no effect of depressed mood (Rogal et al., 2007).

Table 24.3 ■ Emotional States

Study	Sample	IV	Results
Anxiety (general)			
Andersson et al. (2003)	1,465 women in Sweden in two clinics	Clinical diagnostic assessment in second trimester	No differences in PTB between women with anxiety disorders in pregnancy and those without
Copper et al. (1990)	2,593 (63% Black; 35% White)	2 items on feeling nervous, tense and strained at 26 weeks gestation	Predicted PTB with controls for race, age, marital status, insurance, education, substances
Dayan et al. (2002)	634 French women	Trait anxiety at 20–28 weeks gestation	Associated with spontaneous preterm labor in those with a history of PTB
Glynn et al. (2008)	415 Pregnant women	State anxiety assessed at 19 and 31 weeks	Change in anxiety, but not level, predicted PTB
Goldenberg et al. (1996)	1,491 pregnant women who had previously given birth; 69% African American	Trait Anxiety (retrospective)	Significantly associated with PTB in White women, not in AA women
Lobel et al. (1992)	130 pregnant women	State anxiety over pregnancy	Associated with GA as part of latent factor
Lobel et al. (2000)	129 high-risk pregnant women	State anxiety combined three assessments mid to late gestation	Not associated with GA
Lobel et al. (2008)	229 pregnant women	State anxiety mid to late gestation	Associations with GA? at 2 of 3 time points in mid to late pregnancy
Parker-Dominguez et al. (2005)	178 African American women	State anxiety assessed at three times in pregnancy starting with 18–20 weeks	Not associated with GA
Perkin et al. (1993)	1,515 White pregnant women in London	GHQ anxiety subscale assessed at 3 time points (17–36 weeks)	No association with PTB
Rini et al. (1999)	230 Hispanic and White	State anxiety assessed at 28–30 weeks	Associated with PTB in combination with pregnancy anxiety (OR = 1.6)
Depression			
Andersson et al. (2003)	1,465 women in Sweden in two clinics	Clinical diagnostic assessment in second trimester	No association between depressive disorders in pregnancy and PTB
Berkowitz et al. (2003)	187 women near World Trade Center; 2,367 controls	PTSD	No association with PTB or GA
Copper et al. (1990)	2,593 (63% Black; 35% White)	Depression symptoms	No association with PTB
Dayan et al. (2002)	634 French women	EPDS at 20–28 weeks	Associated with spontaneous preterm labor in women who were underweight before pregnancy (BMI <19)
Dole et al. (2003)	1,962 pregnant women	CESD	No association with PTB
Engel, Berkowitz et al. (2005)	52 pregnant women near WTC during terrorist attacks	PTSD/Depression	PTSD associated with longer GA and smaller head circumference
Goldenberg et al. (1996)	1,491 pregnant women who had previously given birth; 69% Black	CESD	No association with PTB
Jesse et al. (2003)	120 rural pregnant women	Two depression screening items at 16–28 weeks	Associated with PTB
Kramer et al. (2009)	5,337 Canadian women	CESD score over 16	Not associated with PTB
Messer et al. (2005)	1,908 women at 24–29 weeks' gestation (PIN study in N. Carolina)	CESD	Not associated with PTB
Orr et al. (2002)	1,399 low-income African American pregnant women	CESD	Women in top 10% at greater risk of spontaneous PTB (adj OR = 1.96)
Perkin et al. (1993)	1,515 White pregnant women in London	GHQ depression subscale assessed at 3 time points (17–36 weeks)	No association with PTB
Rogal et al. (2007)	1,100 pregnant women	Depression/PTSD	Higher rate PTB for PTSD ($p < .055$)
Suri et al. (2007)	90 women assessed prospectively (49 under treatment for MDD; 22 MDD without treatment; 19 comparisons)	SCID, Beck, Hamilton	No association with GA
Other emotions/general distress			
Hedegaard et al. (1993)	5,872 Danish women	GHQ at 16 and 30 weeks gestation	Distress at 30 weeks associated with PTB
MacKey et al. (2000)	35 pregnant women hospitalized for preterm labor; 35 controls	POMS	Tension/anxiety and depression subscales associated with preterm labor
Neggers et al. (2006)	3,149 low-income predominately African American pregnant women	28 item psychosocial risk scale including negative affect, worry, and stress	Negative affect associated with PTB
Peacock et al. (1995)	1,513 White women assessed 17–36 weeks at three times	GHQ and 2 items on "trouble with nerves and depression"	No association with PTB
Rondo et al. (2003)	865 Brazilian pregnant women	GHQ assessed < 16 weeks, 20–26, 30–26.	Associated with PTB

CESD, Center for Epidemiological Studies Depression scale; EPDS, Edinburgh Postpartum Depression Scale; GA, gestational age at birth; GHQ, General Health Questionnaire; OR, odds ratio; POMS, Profile of Mood States; PTB, preterm birth (<37 weeks); PTSD, posttraumatic stress disorder; SCID, Schedule of Clinical Indicators of Depression.

Studies on general distress use measures that combine symptoms of depression, anxiety, and other forms of psychopathology. Of the five studies on general distress shown in Table 24.3, four found adverse effects on PTB. The most recent is a study of 3,149 low-income and predominantly African American pregnant women in which negative affect was associated with PTB (Neggers, Goldenberg, Cliver, & Hauth, 2006). The largest, a 1993 study in Denmark, utilized a common general distress measure, the General Health Questionnaire (GHQ), which at 30 weeks predicted PTB but not at 16 weeks.

Table 24.4 contains all of the published studies we could locate on *pregnancy anxiety and pregnancy stress.* Notably, all but 1 is prospective, and 10 of 11 show effects on PTB. The 3 with the largest samples all confirmed the role of pregnancy anxiety in PTB (Dole et al., 2003; Kramer et al., 2009; Orr, Reiter, Blazer, & James, 2007). Thus, of all the emotional states covered in Table 24.4, pregnancy anxiety emerged as the strongest predictor.

There are a few studies in the literature that used combined measures of stress to test effects on preterm birth. Overall, they are mixed in their findings. About half show effects of unique composite indices on gestational age or preterm birth (Lobel et al., 1990; Rini et al., 1999; Zambrana, Scrimshaw, Collins, & Dunkel-Schetter, 1997) and the other half do not (Diego et al., 2006; Hobel, Dunkel-Schetter, Roesch, Castro, & Arora, 1999; Lobel, DeVincent, Kaminer, & Meyer, 2000; Lobel et al., 2008). For example, 130 pregnant women were followed throughout pregnancy with multiple measures of stress (perceived stress, state anxiety, distress from life events) that were later aggregated into a composite index summed over second and third trimester assessments (Lobel et al., 1992). This stress composite predicted earlier delivery as well as low birth weight with medical risk factors controlled, including smoking. This finding was then replicated in a subsequent study in Los Angeles County with a much larger and more homogeneous sample of pregnant women of Mexican origin or descent and similar though slightly different stress measures (Zambrana et al., 1997). In one further study of this type, three stress measures were compared in their predictive power; together, they predicted gestational age among a sample of 418 women delivering mostly at term; however, once again, the predictor that accounted for most of the effect was pregnancy anxiety (Roesch et al., 2004). As these studies illustrate, combining different stress measures has both advantages and disadvantages. If a set of stress measures are intercorrelated, their combined use as a measured variable or latent factor should increase the quality of the stress measure and the power to detect effects on the outcome. However, combining stress measures of different conceptual natures may not achieve this goal and can sacrifice the ability to determine which components have effects and which do not. Comparative analyses of different stress measures are valuable in pinpointing the relevant risk factors and in developing theories of mechanisms that are psychologically precise. Thus, we recommend the use of multiple stress measures in future research for the purpose of comparative analyses and, in some cases, for the formation of composite indices, but with a careful eye to how the individual components are interrelated, and with full reporting of their individual effects.

In addition to considering multiple measures of stress, it also is important to consider the pattern of stress, or stress profile, across gestation because there are predictable changes in stress responding as pregnancy progresses. On average, women show a decline in psychological and physiological stress responding during gestation (DiPietro, Costigan, & Gurewitsch, 2005; Glynn, Dunkel-Schetter, Wadhwa, & Sandman, 2004; Glynn, Wadhwa, Dunkel-Schetter, Chicz-DeMet, & Sandman,

Table 24.4 ■ Pregnancy-Specific Anxiety or Stress

Study	Sample	Design	Results
Dole et al. (2003)	1,962 pregnant women	Prospective	Anxiety at 24–29 weeks predicted PTB (RR = 2.1) adjusted for alcohol and tobacco use
Kramer et al. (2009)	5,337 Canadian women	Prospective	Anxiety predicted PTB (OR = 1.5)
Lobel et al. (2000)	129 high-risk pregnant women	Prospective	Not associated with GA
Lobel et al. (2008)	279 pregnant women	Prospective	Pregnancy specific stress more strongly associated with GA than PSS or state anxiety
Mancuso et al. (2004)	282 diverse ethnicity	Prospective	Anxiety at 28–30 weeks (not at 18–24 weeks) predicted GA.
Misra et al. (2001)	739 low-income African American women	Retrospective	Pregnancy hassles not associated with PTB
Orr et al. (2007)	1,820 pregnant women (3/4 African American)	Prospective	Predicted risk of spontaneous preterm birth (OR = 2.7)
Parker-Dominguez et al. (2005)	178 African American pregnancies assessed at 3 times in pregnancy starting with 18–20 weeks	Prospective	Anxiety not associated with GA
Rini et al. (1999)	230 Hispanic and White at 28–30 weeks	Prospective	Combination of state and pregnancy-specific anxiety sig predicted GA
Roesch et al. (2004)	418 African American, Latino and White pregnant women, mostly term deliveries	Prospective	Pregnancy specific stress predicted GA controlling for perceived stress and state anxiety
Wadhwa et al. (1993)	90 pregnant women	Prospective	Anxiety predicted GA and PTB

GA, gestational age at birth; OR, odds ratio; PTB, preterm birth (<37 weeks).

2001; Kammerer, Adams, von Castelberg, & Glover, 2002; Schulte, Weisner, & Allolio, 1990). However, not all women show this expected decline. Further, those women who do not may be more susceptible to the adverse influences of stress exposures. One of our studies followed over 400 women during pregnancy examining *patterns of stress* as well as *levels* at different intervals in pregnancy (Glynn et al., 2008). Consistent with this rationale, we found that an increase in perceived stress or anxiety was associated with a twofold increase in risk for PTB. That is, among 400 women, those who did not show the expected dampening of stress reactivity were at increased risk for PTB.

Viewed collectively, the evidence is quite clear that stress, conceived of as a broad multidimensional concept, contributes to the etiology of preterm birth. However, some conceptions or dimensions are now emerging as more important than others. By far, the most consistent results are found for pregnancy-related stress and anxiety, and a close second is major life events. Also notable are chronic strains, catastrophes, community stressors, and racism, but these literatures are still in the early stages.

OTHER RISK FACTORS FOR PRETERM BIRTH

The role of stress as an independent risk factor for PTB must be tested with appropriate control of other known risk factors. Although there are many medical risk factors for PTB, the amount of variance they explain, either individually or in combination, is typically low. These include various *medical history* factors (LBW or PTB in a previous pregnancy; multiple second trimester spontaneous abortions [i.e., miscarriages]; prior first trimester induced abortion; history of infertility; nulliparity [i.e., no prior births]; cervical, uterine, and placental abnormalities; and DES exposure), and *current pregnancy conditions* (gestational bleeding, intrauterine growth retardation, preeclampsia, urogenital infections, inadequate weight gain). In addition, short stature and low prepregnancy weight or low body mass index are also risk factors (IOM, chapter 4, 2006).

Prenatal care has also been studied extensively, showing that late or no prenatal care generally increases risk of preterm birth, disproportionately so for Black and Hispanic women (Masi, Hawkley, Piotrowski, & Pickett, 2007) and high-risk pregnancies. Demographic factors associated with higher risk of PTB are single marital status, low SES (usually income/education), and age (under 17 years of age or over 40). SES is associated with PTB in studies abroad as well as in the United States. This link is attributed most often to associations of SES with work and physical activity, health behaviors (nutrition, smoking, substance use), medical conditions (gastrointestinal and sexually transmitted infections), prenatal care, and stress (see IOM, Chapter 6, for review). SES is predictive of PTB at both the individual and community level. That is, the socioeconomic characteristics of a woman (e.g., her education, occupational status, household income) and of her community (average household income in a neighborhood) both contribute to risk.

Proposed behavioral risk factors for PTB include tobacco use; use of cocaine, marijuana, and other illicit drugs; alcohol consumption; caffeine intake; dietary intake; sexual activity during late pregnancy; and physical activity. Many of these health behaviors have not proved to be as strongly associated with PTB as presupposed. For example, a "health practice" score combining alcohol, tobacco use, medical and dental care, vitamin use, and exercise was not associated with PTB in one large study (Neggers et al., 2006). The 2006 Institute of Medicine Review of the behavioral contributors to preterm birth concluded that "there is clear evidence that a favorable lifestyle and a greater degree of health consciousness are associated with reduced risk of preterm birth above and beyond what can be measured effectively and controlled in observational studies . . . continued efforts are needed to better understand and ultimately pinpoint the aspects of favorable lifestyle that are associated with a reduced risk of preterm birth" (IOM, 2006, p. 89).

Of these lifestyle factors, smoking is one of the more robust behavioral predictors of PTB and LBW (Ahern, Pickett, Selvin, & Abrams, 2003; Masi et al., 2007; McCormick et al., 1990; Paarlberg et al., 1999). A recent study in the Netherlands with a large sample found that smoking (especially late in pregnancy) was associated with LBW and PTB (Jaddoe et al., 2007). In addition, smoking contributes to PPROM.

Lobel, Hamilton, and Cannella (2008) provide a cogent review of the role of physical activity in the form of exercise and strenuous leisure activities. They argue that moderate physical activity is advantageous for pregnant women. Insufficient research is available to determine the effects of different levels or types of activity on PTB, although this remains an area of great interest. Another risk factor of growing emphasis is environmental exposure to toxic substances. Documented risk factors for preterm birth include exposure to lead, air pollutants, and tobacco smoke (Ritz, Yu, Chapa, & Fruin, 2000).

EVIDENCE FOR THE ROLE OF STRESS IN BEHAVIORAL PATHWAYS TO PRETERM BIRTH

There is considerable evidence that stress is associated with higher risk health-related behaviors in adults in general, and there is some evidence that stress is a contributor to poorer health behavior in pregnancy (Lobel et al., 2008). For example, Rodriguez, Bohlin, and Lindmark (2000) examined health behaviors in 350 nulliparious pregnant women and found that perceived stress at weeks 12 and 32 predicted smoking at weeks 20 and 32 of gestation.

St. Laurent et al. (2008) found that stress predicted gestational age at birth indirectly through its association with smoking. In a sample of 279 pregnant women,

Lobel et al. (2008) found that pregnancy-specific stress predicted health behaviors (cigarette smoking, caffeine consumption, unhealthy eating, vitamin use, and exercise) and also gestational age at delivery, but they found no evidence for a mediational pathway. There was, however, a mediated pathway from stress to birth weight; pregnancy-specific stress predicted birth weight through effects on smoking and preterm birth.

Hobel and Culhane (2003) reviewed evidence on maternal psychosocial stress, strenuous activity, and fasting as independent risk factors for PTB and LBW and noted plausible biological pathways. Another behavioral pathway, involves possible stress effects on low utilization of prenatal care. If women are overwhelmed by chronic strain and lack support, they may be unable to find time or transportation, manage the cost, or obtain low-cost services for prenatal care. In addition, highly stressed pregnant women may miss visits and show poor compliance with recommendations such as prenatal vitamins. Language problems and discrimination in health care settings can also pose barriers for minority and immigrant women. Understanding the multiple ways in which stressors pose barriers to prenatal care is an important understudied area.

EVIDENCE FOR THE ROLE OF STRESS IN IMMUNE, NEUROENDOCRINE, AND CARDIOVASCULAR PATHWAYS TO PRETERM BIRTH

Few studies have examined both exposures to psychosocial stress and potential neuroendocrine mediators in conjunction with birth outcomes. Despite this, there is some evidence to support the view that one avenue through which stress exposures result in preterm birth is through activation of the maternal HPA axis. First, during the prenatal period, exposures to or perceptions of psychosocial stressors, and also depression, have been linked to elevations in circulating stress hormones, including CRH, ACTH, and cortisol (Field et al., 2008; Mancuso, Dunkel-Schetter, Rini, Roesch, & Hobel, 2004; Rich-Edwards et al., 2008; Sarkar, Bergman, O'Connor, & Glover, 2008; Wadhwa, Dunkel-Schetter, Chicz-DeMet, Porto, & Sandman, 1996; Yim et al., 2009). Second, both in vitro and in vivo studies provide evidence that cortisol can stimulate the production of placental CRH (Petraglia, Sutton, & Vale, 1989; Sandman et al., 2006). Third, those studies that have utilized multiple prospective measures of both biological and psychological stress are consistent with the idea that the link between maternal psychosocial stress exposure and PTB may be mediated by alterations in HPA axis and placental function. For example, we have shown that elevations in stress and anxiety are associated with elevated CRH, which in turn predicts PTB (Hobel, Dunkel-Schetter et al., 1999; Mancuso et al., 2004). There are at least two other studies that have included measures of both psychosocial stress and HPA and placental hormones that have not replicated these associations (Erickson et al., 2001; Kramer et al., 2009). However, both of these studies measured psychosocial stress at only one prenatal time point, and this most likely poses a critical limitation on the ability to detect such associations.

Indirect evidence for a role of the immune pathway in the relation between stress and PTB is derived from our understanding of the relations between stress exposures and immune function in the nonpregnant state. It is well documented that both the sympathetic adrenomedullary (SAM) and HPA axes interact with the immune system and that chronic activations of these systems are associated both with inflammatory processes and immunosuppression (Malarkey & Mills, 2007). Further, exposures to stressors, in both humans and nonhuman animals, are associated with reduced natural killer cell and lymphocyte function, increased cytokine production, and increased susceptibility to, and duration of, illness (Cohen, Doyle, & Skoner, 1999; Glaser & Kiecolt-Glaser, 2005). Accumulating evidence also provides direct support for the hypothesis that the immune pathway mediates the relation between stress exposure and PTB. Among pregnant women, higher levels of chronic stress at both the individual and community levels (Culhane, Rauh, McCollum, Elo, & Hogan, 2002; Culhane et al., 2001), and also reports of higher levels of perceived stress over the previous month (Nelson et al., 2008), have been linked to the presence of bacterial vaginosis. In addition, high levels of prenatal stress are associated with elevated proinflammatory cytokines and C-reactive protein and also specifically influence lymphocyte production of proinflammatory cytokines (Coussons-Read, Okun, & Nettles, 2007; Coussons-Read, Okun, Schmitt, & Giese, 2005; Herrera, Alvarado, & Martinez, 1998). Both the findings linking stress exposures to susceptibility to infection during pregnancy, and the findings linking stress exposures to immune functions relevant to the physiological control of normal parturition and to PTB, provide support for the proposition that the adverse consequence of prenatal stress exposure on PTB operate, in part, through the immune/inflammatory pathway.

Although relatively few studies have examined the role of stress in the HPA and immune pathways to preterm birth, even less is known about the potential for stress to influence vascular processes associated with PTB. When vascular abnormalities of the placenta occur, they may be reflected in heightened resistance in the microcirculation of the placenta (Adamson, Morrow, Bascom, Mo, & Ritchie, 1989; Hossain & Paidas, 2007). Some studies have demonstrated an association between both biological and psychosocial indicators of stress and alterations in placental vascular resistance. Both CRH and cortisol levels have been linked to alterations in uterine and umbilical artery blood flow

(Florio et al., 2003; Giles, McLean, Davies, & Smith, 1996; Harville et al., 2008). Further, higher maternal state and trait anxiety, and also exposure to negative life events, predict increased umbilical/uterine artery resistance (Harville et al., 2008; Kent, Hughes, Omerod, Jones, & Thilaganathan, 2002; Sjostrom, Valentin, Thelin, & Marsal, 1997; Teixeira, Fisk, & Glover, 1999).

Pregnancy-induced hypertension (PIH) and preeclampsia are associated with fetal growth restriction and are a primary cause of PTB for maternal indications (Goldenberg et al., 2008). It has been proposed that stress can hasten or exacerbate the development of PIH and preeclampsia, and some empirical evidence exists to support this assertion (Klonoff-Cohen et al., 1996; Landsbergis & Hatch, 1996; Leeners, Neumaier-Wagner, Kuse, Stiller, & Rath, 2007; Marcoux, Berube, Brisson, & Mondor, 1999), although not all studies demonstrate such a link (Vollebregt et al., 2008). Little is known about the relationship of subclinical blood pressure levels to either fetal growth restriction or spontaneous PTB. However, we have shown that, among nonhypertensive African American women, elevations in resting blood pressure were related to higher levels on a composite measure of stress that included chronic socioenvironmental stress exposures and reports of perceived stress and mood. Further, those African American women who exhibited both the highest stress levels and the highest blood pressure levels gave birth to those infants who, on average, had the lowest birth weights (Hilmert et al., 2008). There is little known about the role of stress-induced cardiovascular reactivity in spontaneous PTB. During pregnancy, blood pressure and heart rate responses to stress decrease (Matthews & Rodin, 1992), and women who possess stress-buffering resources such as self-efficacy and favorable coping strategies show less exaggerated cardiovascular responses to stress during gestation (Nierop, Wirtz, Bratsikas, Zimmerman, & Ehlert, 2008; Urizar, Milazzo, Le, Delucci, & Munoz, 2004). Three published studies have demonstrated that women who exhibit larger blood pressure excursions in the face of a stressor, either social or physical, also exhibit shortened gestational lengths. McCubbin et al. (1996) initially demonstrated that women who showed larger blood pressure responses to a social stressor delivered earlier on average. Similarly, women who showed an exaggerated response to a cold pressor task also exhibited shorter gestational lengths (Gomez Ponce de Leon, Gomez Ponce de Leon, Coviello, & De Vito, 2001). Most recently, Hatch et al. (2006) showed that, among African American women, but not White women, exaggerated blood pressure responses to stress were associated with spontaneous PTB. To date, it is not known whether these exaggerated stress responses are a marker of some other underlying dysregulation that causes preterm birth or are a direct contributor to shortened gestational lengths. The mechanism through which exaggerated cardiovascular reactivity might directly influence spontaneous preterm birth has yet to be elucidated.

THEORY AND ANALYSIS OF STRESS AND PRETERM BIRTH MECHANISMS

THREE PART MECHANISTIC PATHWAY

The simplest schema for a theoretical approach to the study of stress processes in preterm birth is a three-part causal chain involving stressor–mediators–preterm birth. Table 24.5 indicates possible stressors, mediators, and outcomes in a model of spontaneous preterm birth.

As can be seen in the Table 24.5, there are many forms of stressors, many possible mechanisms, and one outcome, measured either continuously (GA, or gestational age, also called length of gestation) or as a dichotomy (PTB). A related trichotomy is term birth (>37 weeks), preterm birth (32–36 weeks), and very preterm birth (<32 weeks). Birth weight (BW) should always be studied in combination with PTB given the high degree of overlap as noted earlier. In the majority of studies of prenatal stress and preterm birth, the X variable (stress) is treated as unidimensional despite the range of different possibilities. In other words, the "upstream" factors in this schema (e.g., stressors) are usually treated somewhat simplistically, while the "downstream" factors (e.g., neuroendocrine and immune parameters) are much more differentiated.

Most studies examine only two of the three components in the chain, stress and outcome, stress and mediators, or mediators and outcome. Intensive, well-designed, prospective investigations evaluating the full mediated model are rare. As noted above, there is limited evidence for the three-part causal chain (mediational model), and some studies that have tested the

Table 24.5 ■ Schematic of the X-Y-Z Mediational Chain for the Stress-Preterm Birth Relation

X (Stressors)	Y (Hypothesized Mediators)	Z (Outcomes)
Episodic major events	Neuroendocrine	Gestational age (weeks)
Chronic strain	Cortisol	Preterm birth (<37 weeks)
Trauma/loss	CRH	Birth weight (grams)
Racism	ACTH	
Neighborhood stressors	Immune	
Emotional states	Proinflammatory cytokines	
Depressed mood	Immune suppression	
Anxiety (state or trait)	Cardiovascular	
General distress	Resting and ambulatory BP	
PTSD	Cardiovascular reactivity	
Pregnancy anxiety	Behavioral	
Pregnancy-specific stress	Physical activity/exercise	
Composite indices	Smoking/nicotine	
	Alcohol	
	Substances (e.g., cocaine)	
	Diet/nutrition	
	Weight gain	
	Fasting	
	Overeating	
	Nutrients	
	Interactions of these	
	Studied as levels or changes in levels over time (trajectories)	

mediational model have not found significant effects. For example, our most recent work with a large cohort of women (N = 400 or more) tested four times prenatally beginning at 15-weeks gestation; we found no concurrent relations between measures of stress or negative affect and hormones of the HPA axis or placenta (cortisol, ACTH, CRH) at any time point. Thus, evidence for a simple neuroendocrine mechanism is not necessarily consistent (cf. Kramer et al., 2009).

We have pondered why there is not stronger evidence for the hypothesized mediation of the stress–preterm birth link. There are several possibilities. One observation is that research teams tend to be skilled in one piece of the pathway and not in others, so studies are imbalanced in rigor. Most studies are strong in either the study of psychosocial stress or the biological mediators, but not both. Some are weak in both areas but strong in their understanding of preterm birth and labor. Very few studies are strong in their approach to studying the health behavior mediators. Thus, unevenness in rigor of all components is a possible explanation for the lack of evidence for the mediational pathways. The solution is obviously to conduct better designed studies involving further collaboration among experts from the relevant disciplines. Another possible explanation is that the design and analytical strategies are not fully capturing the dynamic relations between physiological and psychosocial processes during pregnancy. To understand these complex relations, both longitudinal designs and analytic techniques such as multilevel modeling are needed in order to examine interrelationships over time.

IMPROVING THE STUDY OF STRESS AND PRETERM BIRTH

To improve existing research paradigms, perinatal researchers need to study stress more rigorously, relying more on theory and examining the multiple dimensions of stress. Measurement issues regarding reliability and validity must be addressed more adequately than in past. Many studies do not provide Cronbach's alpha coefficients reflecting internal consistency estimates of the reliability of multi-item measures of stress, or the reliability estimates reported are marginal or too low to test hypotheses with adequate power. Stress instruments that are designed and validated in English must be translated into foreign languages with greater attention to whether the original concept is captured validly and reliably. Reliability of psychosocial instruments in different languages is often lower than in English, providing only weak tests. For example, research on Hispanic pregnancies is now being conducted in Spanish, but the quality of translations is frequently unknown or poor. Furthermore, some stress concepts do not generalize well across ethnic, cultural, and foreign populations (validity issues). These issues must be addressed thoughtfully to provide good tests of the stress–preterm hypotheses in the diverse populations that happen to be those of greatest risk and attention by policy makers. We have found this to be a rich area for basic researchers interested in culture as well (Campos et al., 2008).

If some dimensions of stress apply only to specific groups, it does not mean they are not valuable to study. Racism, for example, is a salient stressor for African Americans that may contribute to disparities in preterm birth. Similarly, anxiety in pregnancy has been shown to characterize Latina women in particular, especially new and unacculturated immigrants from countries with poor medical care (Rini et al., 1999; Scrimshaw, Zambrana, & Dunkel-Schetter, 1997). We must continue to develop population-specific concepts and measures of stress in order to improve our ability to test hypotheses well. In addition, we need stress concepts and measures that generalize well over ethnic, cultural, and international populations, with validation in different languages. The emergence of pregnancy-specific validated measures of stress and anxiety may help to abet this particular issue (cf. Huizink, Mulder, Robles de Medina, Visser, & Buitelaar, 2004; Lobel et al., 2008; Rini et al., 1999).

Insufficient sample sizes, heterogeneity within samples, and lack of control of confounding variables in tests of mediation also contribute to the weak evidence thus far. For instance, researchers must study either high-risk pregnancies or a mix of high and low risk because predominately low-risk populations usually have insufficient variability in stress or gestational age to test hypotheses well. Also, studies typically control for only some of the many risk factors (e.g., medical risk factors, health behaviors, demographics) or control for only a subset within a risk category (e.g., previous preterm birth but not other medical conditions, smoking but not other health behaviors, age but not education). This is often due to small sample size, but control for risk factors can be achieved by other means such as greater homogeneity in sampling. Sampling only one ethnic group or a group with common medical risk characteristics may require more time to recruit but may be a stronger research design, especially if the sample size is not in the thousands. These problems in study design and analyses render many previous tests of the meditational chain from stress to preterm birth underpowered to obtain significant results.

Researchers must also ask whether they are studying the HPA and immune systems in pregnancy carefully enough. Intensive, rigorous, prospective studies involving biological sampling with large samples are very rare (cf. Harville et al., 2008). Further, CRH, which has been such a promising marker in stress–PTB research, is very difficult and expensive to assay and is viewed as impractical for population studies in general (Latendresse, 2009; Latendresse & Ruiz, 2008). Furthermore, we should be examining diurnal cortisol rhythms (i.e., repeated assessments over the day), and cortisol response under challenge conditions (laboratory stress paradigm or waking responses), rather than taking a single snapshot of cortisol. In addition, behavioral health researchers who are expert in the study of

smoking, alcohol and drug use, nutritional analyses, and physical activity are needed to refine the measurement and analytical approaches to the study of these mediators (cf. Roelands, Jamison, Lyerly, & James, 2009; Zammit, Skouteris, Wertheim, Paxton, & Milgrom, 2008).

Regarding the outcome variables, the focus must zero in on spontaneous early labor, and theory must be applied to distinguish mechanisms involved in effects of stress on very early preterm birth versus later preterm birth. For example, if early birth results more often from immune dysregulation, one might examine pathways from prepregnancy and early pregnancy forms of stress hypothesized to influence specific immune factors.

Existing Models. For many years, there were no biopsychosocial conceptual models guiding work in this research area. Currently, there are several published papers specifying pathways to preterm birth, ranging from simple conceptual diagrams or schemes to complex frameworks. For example, Dr. Calvin Hobel, who published among the first mapping of hypothesized pathways from stress to preterm birth (Bragonier, Cushner, & Hobel, 1984), has detailed these pathways in a recent paper reflecting advances in our knowledge (Hobel, Goldsmith, & Barrett, 2008). Wadhwa et al. (2001) have spelled out the infection pathways in detail (see also Coussins-Read, Okun, & Simms, 2003). Wang et al. (2001) have laid out the pathogenic pathways to PTB focusing on gene–environment interactions and effects on mechanisms. In this excellent paper, social environmental risk and maternal and fetal genes interact to influence inflammation, HPA activity, uteroplacental vasculopathy, and susceptibility to toxins, all leading to preterm labor, PPROM, induction, and ultimately, to PTB. Each of these models, however, focuses in detail on the biomedical side of the equation and is much sketchier on the psychosocial side.

Other models have developed the psychosocial pathways a bit further and incorporated sociodemographic factors usually with the goal of public health prevention. Hogue, Hoffman, and Hatch (2001) and Kramer, Goulet, Lydon, Seguin, and McNamara (2001), for example, both emphasized socioeconomic status and ethnic disparities in pathways from stress to PTB. Lu and Halfon (2003) applied a life-course perspective incorporating SES, behavior, prenatal care, stress, infection, race, and racism. Misra, Guyer, and Allston (2003) propose a multiple determinants model that also takes a life-span approach and incorporates preconception and interconception factors to improve perinatal health. This paper includes social, psychological, behavioral, environmental, and biological forces operating during pregnancy and influencing short- and long-term maternal and infant disease and complications, health and functioning, and well-being. Culhane and Elo's (2005) conceptual framework includes neighborhood factors (social environment, service environment, physical characteristics) as well as individual-level factors (SES and demographic), which together lead to further individual-level factors (psychosocial and behavioral), stress physiology, and birth outcomes. Some approaches are even larger in scope, such as that of Halbreich (2005), which includes postpartum outcomes, offspring development, offspring long-term disorders, and next generation vulnerability in one comprehensive model.

In sum, there are now many models available to guide research. Nonetheless, we still need integration of these models into more comprehensive biopsychosocial frameworks with equal emphasis on biomedical, psychosocial, sociodemographic, and sociocultural factors. As with any good model, future frameworks must generate hypotheses that are testable. Since one comprehensive model may not be ideal, partial analyses are also valuable but, ideally, with further biopsychosocial linkages specified. In general, pregnancy research is not utilizing existing social and behavioral science theories or the newest empirical findings on stress and health (e.g., Gallo & Matthews, 2003; Hobfoll, Schwarzer, & Koo Chon, 1998). One prominent biopsychosocial theory regarding effects of stress on health via allostatic load (McEwen, 1998) has useful implications for the study of stress in pregnancy (cf. Shannon, King, & Powell Kennedy, 2007). Allostatic load is conceptualized as the cumulative biological effect of stress over time. If stressors over a lifetime pose wear and tear on the body's systems, then we should study the level of "load" or past chronic strain a woman has had prior to pregnancy, not only her exposures during pregnancy. This dictates research designs that involve life history and preconception approaches together with biomarkers that capture chronic strain such as body mass index, waist–hip ratio, cholesterol, and blood pressure. The use of this and other ways of understanding how stress in the environment gets "under the skin" (Repetti, Taylor, & Seeman, 2002) and poses risk in pregnancy can offer both novel approaches and more focused hypotheses. Both broad theoretical approaches and narrower, well-specified conceptual models for the study of stress in PTB are needed at this juncture.

As noted above, existing models of stress and preterm birth are often simplistic regarding psychological processes. We suggest that the weak theoretical basis of inquiry on psychological and behavioral factors contributes to inability to test powerfully the meditational models linking prenatal stress to immune or HPA processes as mediators of effects of preterm birth. How does strong theory contribute to improving research on this topic? Theories can guide many of the issues that have plagued this area of research, such as definitions of stress, measurement or assessment tools, and low power in tests of mediation.

THEORETICAL SPECIFICITY REGARDING STRESS

Regarding the stress side (X variables), specificity means a focus on specific stressors, such as pregnancy anxiety or pregnancy-related stress, which has proven to be a consistent predictor of earlier delivery. Little attention has been directed to severity of anxiety symptoms, cognitive components, anxiety treatments, or other aspects of anxiety

that may be linked to physiological mediators and onset of labor. Littleton, Brietkopf, and Berenson (2007) note that a nearly exclusive focus has been on anxiety symptoms and not on pathological levels of anxiety. Ross and McLean (2006) discuss the prevalence of anxiety disorders in the perinatal period, but studies on prevalence and implications for fetal development and birth outcomes have not been done. Various measures of pregnancy anxiety have also been developed (e.g., Huizink, Mulder, & Buitelaar, 2004) but with little theoretical basis and no tests of convergent validity to see if they assess the same concepts.

THEORETICAL SPECIFICITY REGARDING BIOLOGICAL PROCESSES

The physiological state of pregnancy is complex and dynamic. All of the potential mediational pathways linking stress to preterm birth show predictable and dramatic changes in function during gestation. For example, we and others have demonstrated that as pregnancy progresses, women become less reactive both physiologically and psychologically to these exposures (de Weerth & Buitelaar, 2005; Glynn et al., 2004). This suggests two additional points of refinement to the study of the effects of prenatal stress on preterm PTB. First, at the group level, it suggests that as pregnancy progresses the strength of association between a stress exposure and length of gestation should be lessened. This is due to the fact that as pregnancy progresses, the probability that a stress exposure translates into a shortened gestation is diminished because both the physiological and psychological response to stress are dampened. Second, at the level of the individual, there are differences in the propensity to show this dampening in stress responding. That is, there is individual variability in the probability that an individual woman shows reduced responding. It follows, then, that those women who remain relatively more sensitive to stress will be more likely to deliver preterm, even in the absence of differences in stress exposures. It further follows that when these women are exposed, the consequences will be more profound for them. There exist empirical demonstrations that are consistent with both of these premises. It has been shown that timing of stress exposure during pregnancy is not uniform and that early exposures may be more likely to produce a preterm birth (Glynn et al., 2001; Lederman et al., 2004). Further, as noted earlier, we have shown that women who do not exhibit the expected decrease in reports of generalized stress and anxiety during pregnancy are at increased risk for PTB (Glynn et al., 2008).

MODERATORS OF THE STRESS–PRETERM BIRTH ASSOCIATION

A further point is that we are not paying sufficient attention to potential moderating variables. Dispositional factors appear to interact with or moderate the three primary factors. For example, genetic risk factors are gaining increasing attention. There is growing evidence that genetic susceptibility and gene–environment interactions figure into models of early preterm birth (Crider, Whitehead, & Buus, 2005; Menon, Fortunato, Thorsen, & Williams, 2006) via single gene variants, candidate genes, and gene–environment interactions including stress. This is a very important area for theory to incorporate. Our group has been focusing on two sets of potential moderators of the mediation of stress–preterm birth relations: (1) demographic and cultural factors and (2) susceptibility to stress. Demographic factors such as SES and age are important as antecedents and modifiers of behavior, immune function, and stress hormone activity. Ethnic and cultural variables in particular are implicated throughout the process and call for innovative approaches and creativity. Specific models for specific ethnic groups at risk, such as African Americans, may be the most useful (Hogue & Bremner, 2005). Not only are specific stressors relevant only to certain cultural groups in terms of their ability to predict birth outcomes but it also appears that the proposed biological mediators may exert stronger or weaker relations with both the X or Z variables. For example, Dominguez, Dunkel-Schetter, Glynn, and Sandman (2008) have shown that lifetime exposures to racism are predictive of restricted fetal growth but only among African American women. Further, Holzman et al. (2001) have shown that the threshold of CRH exposure that is associated with preterm birth is lower among African American women, and Glynn, Dunkel-Schetter, Chicz-DeMet, Hobel, and Sandman (2007) have shown that elevated prenatal cortisol is more likely be associated with an accelerated CRH trajectory in African American women than among White women.

As discussed previously, pregnancy affects the physiological and psychological response to stress exposure, and there are meaningful individual differences in these processes during pregnancy (Glynn et al., 2008). Important influences on these differences in susceptibility to stress during pregnancy are lifetime exposures to either chronic or traumatic stress and exposures during the preconception period. Some women may enter pregnancy with a latent vulnerability to stress that is expressed as gestation progresses (Glynn et al., 2007). Exposure to stress in the preconception period and over a woman's lifetime may disregulate her physiology and increase risk of adverse outcomes of pregnancy and for the child (Astone, Misra, & Lynch, 2007; Lu & Halfon 2003; Noll et al., 2007). The existence of such a preexisting vulnerability is consistent with the view that lifelong exposures to stress among women of ethnic minority status may increase the likelihood of poor reproductive outcomes even before a pregnancy is conceived (Rich-Edwards & Grizzard, 2005) and also that fetal programming may contribute to adult reproductive health (Barker, 1998; Lu & Halfon, 2003). These premises call for moderated meditational analyses that to date have not been used in prenatal research.

The above differences suggest, for example, that among those women who are more vulnerable before pregnancy, stress exposures during pregnancy will have more potent effects on birth outcome.

Differences in environmental or genetic vulnerability to stress and the role of culture and ethnicity represent only two possible avenues for exploration of the moderated mediation of stress–PTB connection. However, it seems clear that complete models must consider the fact that the relations between stressors, mediators, and birth outcomes are best understood in the context of potential moderators of these X–Y–Z relations.

OTHER EMERGING FRONTIERS

There are a number of emerging areas in the study of preterm birth that pertain to this chapter. We spotlight only one of these very briefly, the effects of stress in pregnancy on development and health after delivery. There is enormous attention directed now to the topic of *fetal programming*, which refers broadly to the notion that many physiological systems are programmed in the womb in ways that influence later development and health throughout the life span. This notion is attributed mainly to Barker (1998), whose work pointed in the direction of adult health effects of prenatal events such as preterm birth. More recently, Gluckman and Hansen (2004) have contributed an elegant model of prenatal programming in the context of the Predictive Adaptive Response (PAR), which describes the process by which the developing organism draws from early experience to express a phenotype that maximizes fitness based on the expected future environment. It has been proposed that prenatal experience prepares the fetus for challenges in the postnatal environment and that it is the consistency (or lack of consistency) between the pre- and postnatal environments that determine the adaptability of the prenatal programming (Gluckman & Hanson, 2004; Hales & Barker, 2001; Horton, 2005). Thus, the adaptability of the response depends on the accuracy of the prediction. When the PAR does not match the postnatal environment, the mismatch results in reduced fitness (or disease states in the case of humans) (Gluckman & Hanson, 2004; Hales & Barker, 2001).

Empirical evidence supporting the link between prenatal experience and later health and development continues to accumulate and underscores the importance of prospective studies with human mothers and their fetuses and offspring. Coe and Lubach (2008) review animal and human studies indicating that the stimulation and priming occurring in utero guide optimal maturation of the nervous, endocrine, and immune systems and set regulatory set points governing physiology in adulthood. Talge, Neal, and Glover (2007) provide an excellent review of prospective studies on maternal stress in pregnancy and child emotional and cognitive effects, including ADHD, anxiety, and language delay, which supports clinically significant effects of maternal stress on child neurodevelopment (see also Beydoun & Saftlas, 2008). Research by our group has shown that maternal stress exposure reflected as changes in maternal affect and stress levels, as well as maternal HPA axis and placental hormones, influences the fetal environment with developmental consequences. We have shown that prenatal hormone exposures and also maternal psychological state during gestation predict fetal behavior and development (Class et al., 2008; Sandman et al., 2003), newborn neurodevelopment (Ellman, Dunkel-Schetter, Hobel, Glynn, & Sandman, 2008), and infant temperament and cognitive development (Davis et al., 2004, 2007; Davis, Glynn, Dunkel-Schetter, Hobel, & Sandman, 2005; Davis & Sandman, 2010). Importantly, each of these findings is independent of birth outcomes (length of gestation and birth weight), indicating direct fetal programming effects. The growing interest in the potential power of maternal stress factors in pregnancy to predict profoundly important outcomes in the offspring is hard to overestimate. It has the potential to strongly influence theory in both developmental and health psychology and to transform child and maternal health policies around the world.

In closing, we propose that a generation of new interdisciplinary biopsychosocial scientists is needed to work at multiple levels with multiple goals in mind to advance the study of stress in pregnancy. Past collaborations were among individuals of different disciplines, but the next decade will see more and more researchers trained in multiple disciplines of research. We hope this chapter informs and inspires those who might take up and carry this torch for the benefit of parents and children in the future.

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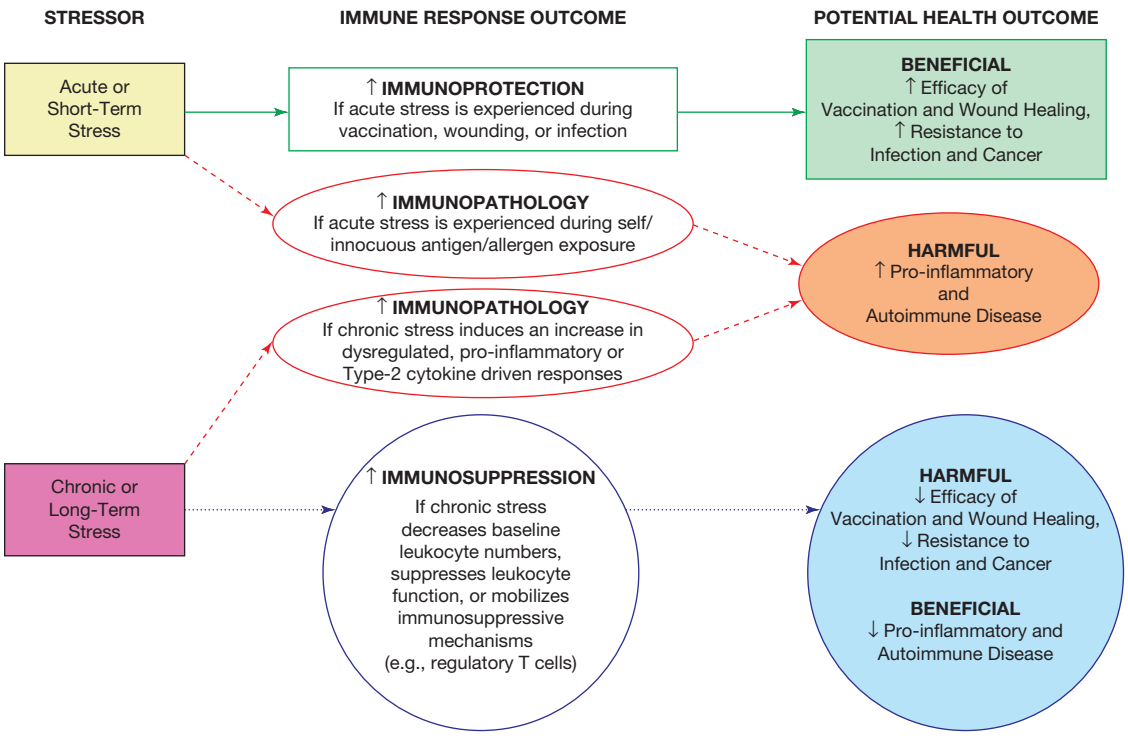

Figure 4.1 ■ The relationship among stress, immune function, and health outcomes.

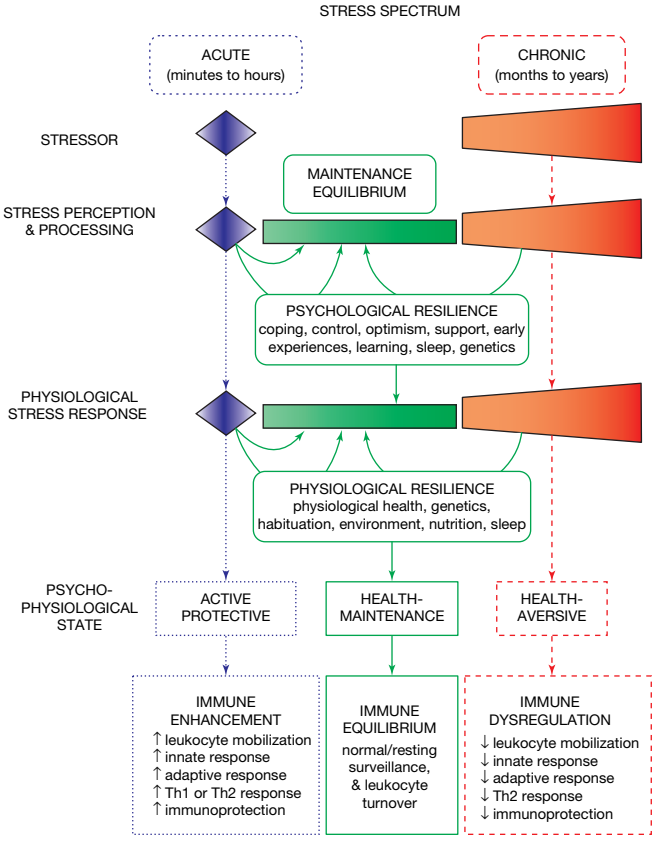

Figure 4.2 ■ The stress spectrum model. Reprinted from Dhabhar & McEwen, 2006.

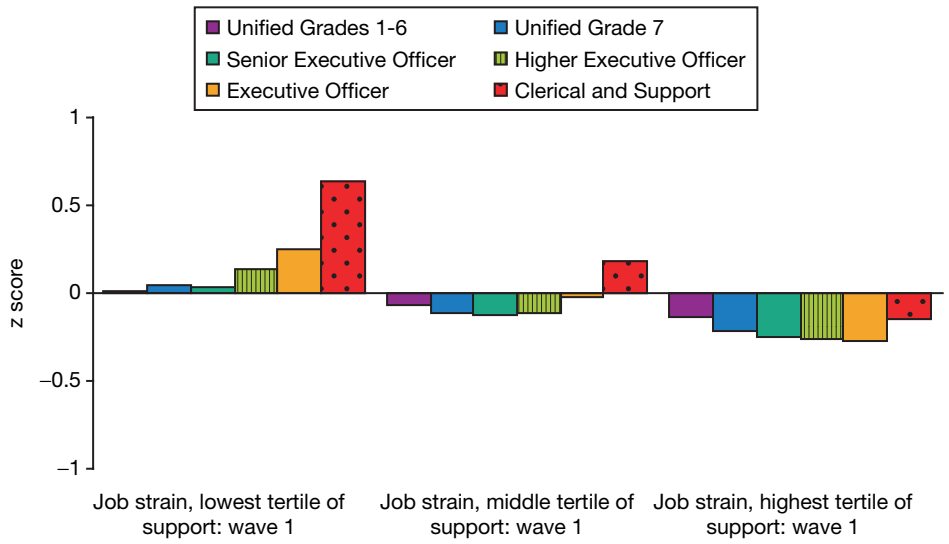

Figure 14.5 ■ Mean job strain and SES by tertiles of social support at work in the Whitehall II Study (Wave 1).

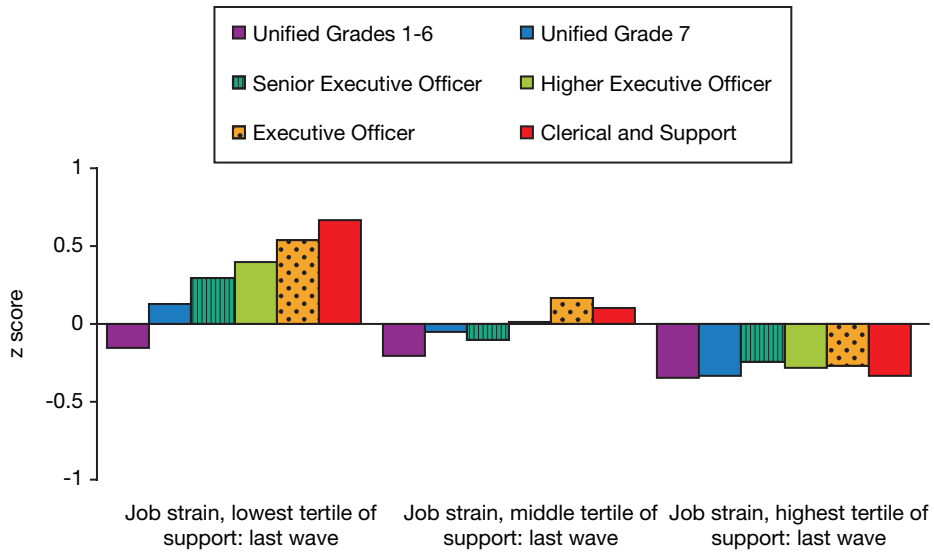

Figure 14.11 ■ Mean job strain and SES by tertiles of social support at work in the Whitehall II Study (Last wave).

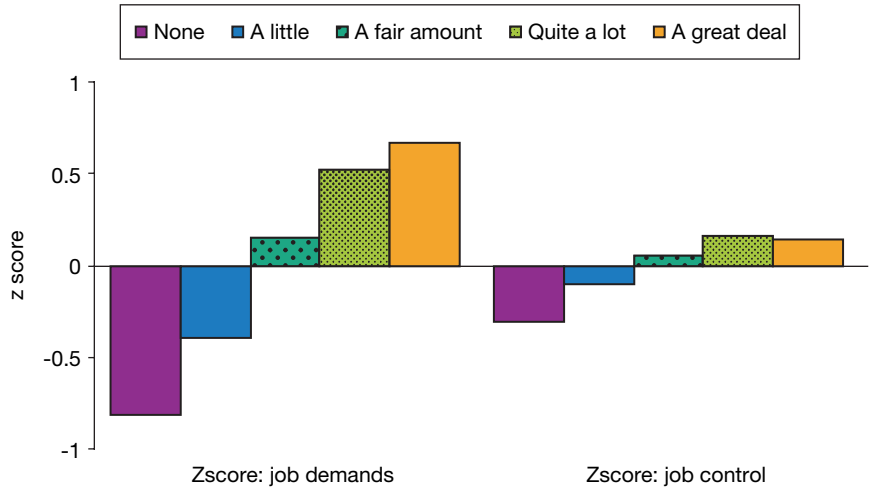

Figure 14.12 ■ Mean job demands and job control by levels of perceived stress in the Whitehall II Study (Wave 3).

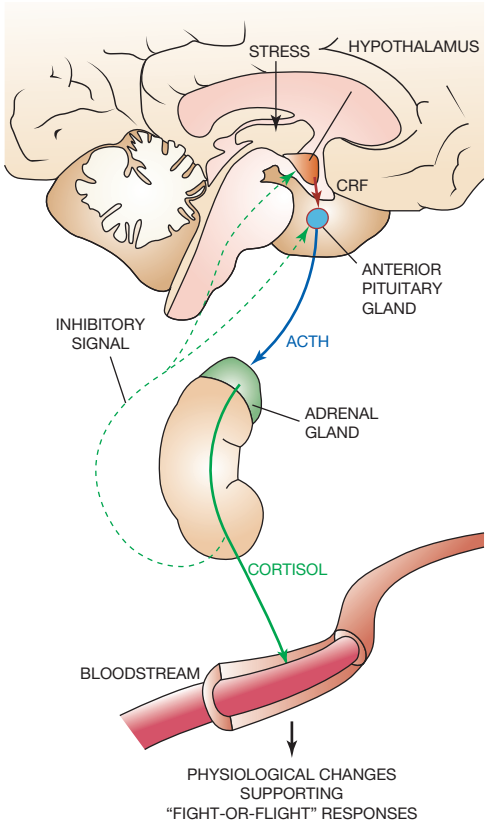

Figure 25.1 ■ *Overview of the HPA axis*: Following relevant stimuli, including stress, CRF is released from the hypothalamus into the hypophyseal portal vessels, where it is transported in high concentrations to the pituitary gland. CRF then promotes the release of ACTH, which in turn promotes the release of cortisol from the adrenal glands. Cortisol acts as an inhibitory signal at both the hypothalamus and pituitary, preventing further CRF and ACTH release, respectively. Reproduced from Nemeroff, 1998.

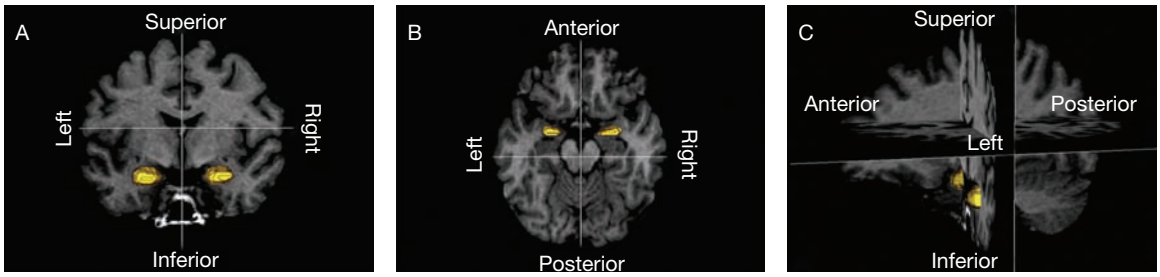

Figure 39.1 ■ The amygdala (highlighted in yellow) is shown in three spatial planes: **(A)** coronal, **(B)** horizontal (or axial), and **(C)** sagittal. Image provided by Dr. Robert Tamburo.

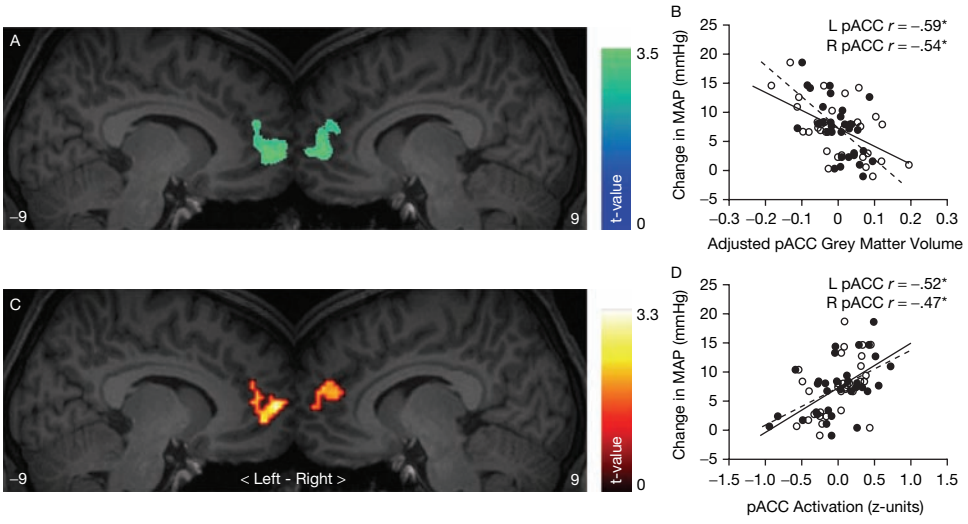

Figure 39.2 ■ Mean arterial pressure (MAP) reactivity to a Stroop color-word interference stressor is shown as a function of gray matter volume and fMRI BOLD activation in the prefrontal cortex, encompassing Brodmann area (BA) 32 of the perigenual anterior cingulate cortex (pACC) and BA 10 of the medial prefrontal cortex. Reprinted from Gianaros, et al., 2008.

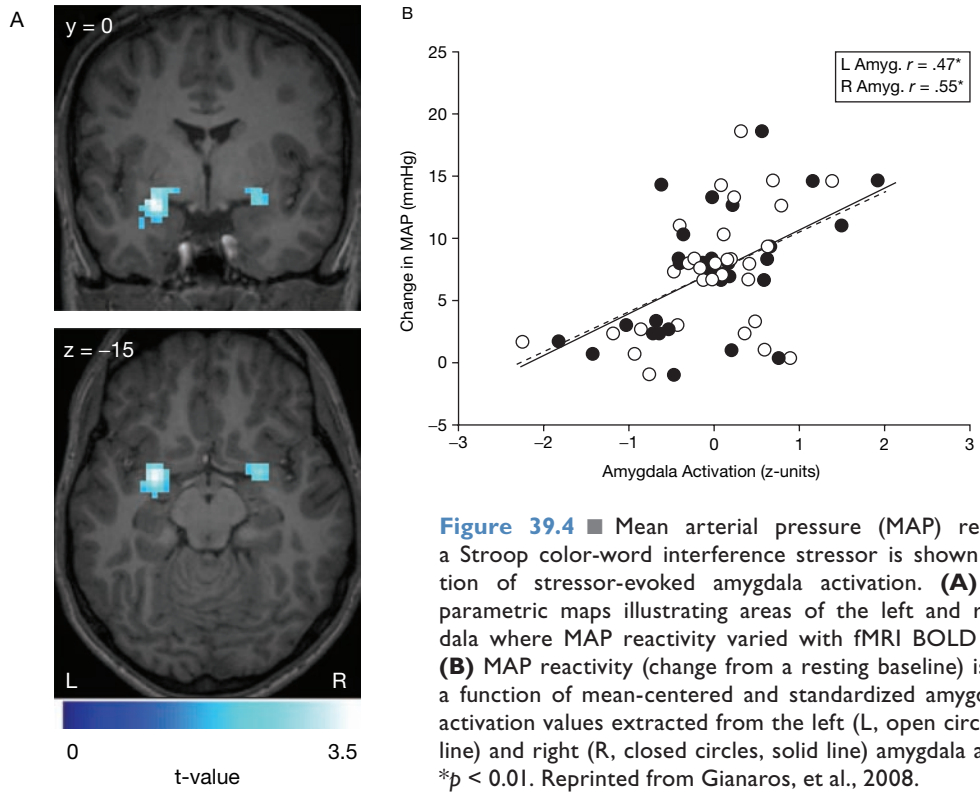

Figure 39.4 ■ Mean arterial pressure (MAP) reactivity to a Stroop color-word interference stressor is shown as a function of stressor-evoked amygdala activation. **(A)** Statistical parametric maps illustrating areas of the left and right amygdala where MAP reactivity varied with fMRI BOLD activation. **(B)** MAP reactivity (change from a resting baseline) is shown as a function of mean-centered and standardized amygdala BOLD activation values extracted from the left (L, open circles, dashed line) and right (R, closed circles, solid line) amygdala areas in (a). *$p < 0.01$. Reprinted from Gianaros, et al., 2008.

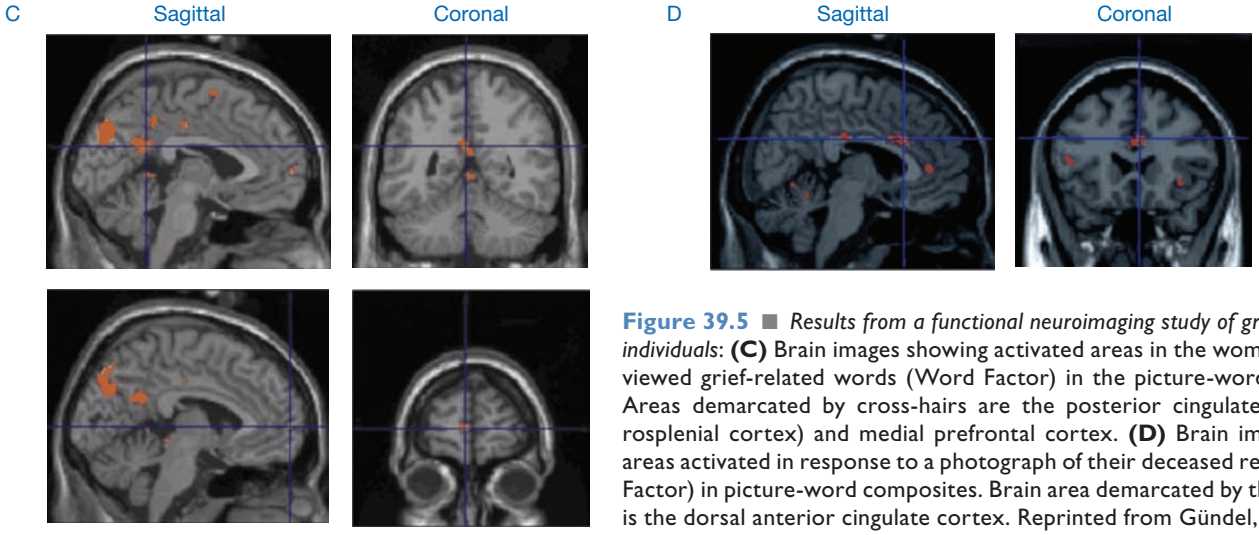

Figure 39.5 ■ *Results from a functional neuroimaging study of grief in bereaved individuals*: **(C)** Brain images showing activated areas in the women when they viewed grief-related words (Word Factor) in the picture-word composites. Areas demarcated by cross-hairs are the posterior cingulate cortex (retrosplenial cortex) and medial prefrontal cortex. **(D)** Brain images showing areas activated in response to a photograph of their deceased relative (Person Factor) in picture-word composites. Brain area demarcated by the cross-hairs is the dorsal anterior cingulate cortex. Reprinted from Gündel, et al., 2003.

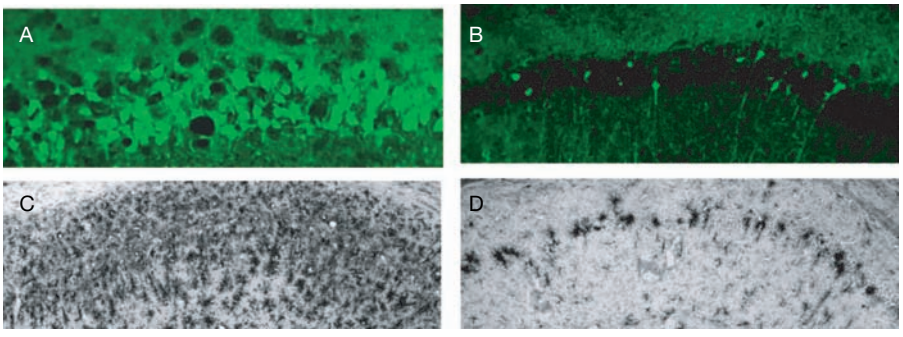

Figure 43.5 ■ *Social isolation potentiates ischemic damage*: Fluoro Jade staining of hippocampal cell degeneration in socially isolated **(A)** and socially housed mice **(B)**. Microglial activation in the socially isolated **(C)** and socially housed animals **(D)**. Adapted from Weil, et al., 2008.

25 Stress and Depression

David A. Gutman and Charles B. Nemeroff

INTRODUCTION

Depression ranks among the largest contributors to both morbidity and lost productivity in the developing world. A recent survey conducted by the World Health Organization in 60 countries and published in the *Lancet* highlights this point. Depression produces larger declines in health than other chronic diseases including angina, arthritis, asthma, and diabetes (Moussavi et al., 2007). Despite the enormous public health implications, our understanding of the pathophysiology of depression is surprisingly limited. The identification of both environmental and genetic factors that either increase or decrease vulnerability to stress-related disorders, including depression, is therefore a critical public health issue.

No experienced practitioner would doubt the fact that stress and depression are inexorably linked. Stress causes a disruption in the organism's normal homeostatic processes, and the effects of chronic stress cumulatively result in wear and tear on both the body and the brain. In genetically vulnerable individuals, stress can precipitate depression, whereas the same stressful experience in more resilient individuals may be without serious long-term consequences. Moreover, previously depressed patients who have recovered and are euthymic after treatment often unexpectedly relapse when confronted with severe stressful life events.

The link between stress and depression has received increasing attention in recent years (Heim, Bremner, et al., 2006). Of the two thirds of the contribution of environmental factors to the pathogenesis of major depression, stress likely contributes to most of the burden. This takes the form of recent life stressors, the cumulative effects of life stress, and most important, the very significant impact of early life stress (Penza, Heim, & Nemeroff, 2005). In one sense, depression can be conceptualized as a maladaptive response to acute or chronic stress.

This chapter reviews the pertinent literature demonstrating a relationship between the neurotransmitter and neurohormonal systems that modulate the stress response and those implicated in the pathophysiology of depression. Subsequently, we discuss literature demonstrating that early life stress (ELS) increases the likelihood of developing depression later in life. Finally, we review the emerging literature suggesting that interactions between genetic and environmental factors are of paramount importance in mediating risk for depression.

BASIC BIOLOGY OF THE STRESS RESPONSE

Although reviewed elsewhere in this volume, a brief review of the basic mammalian stress response will be useful. The concept of what constitutes a stressor to a given individual or organism varies, but globally one can view stress as a "threat to the organism's homeostasis" with the goal being a return of internal stability. There are myriad forms of stress. So-called interoceptive stressful stimuli provide a direct disturbance to the physiological homeostasis of the body. These include, for example, direct physical injury, hypoglycemia, infection, pain, and hemorrhage. Among these, physical illness stressors such as myocardial infarction (Whyte & Mulsant, 2002; Rasmussen et al., 2003), stroke (Godding, McAnulty, Wittrock, Britt, & Khansur, 1995; McDaniel, Musselman, Porter, Reed, & Nemeroff, 1995; Guo et al., 2006), and cancer (Godding et al., 1995; McDaniel et al., 1995; Guo et al., 2006) are often associated with the development of depression. However, it is critical to note that not everyone with these disorders develops clinical depression. Environmental threats, be they real or perceived, are also extremely potent activators of the stress response. These so-called exteroceptive stressors include traumatic events such as war and terrorism, natural disasters, and physical and/or sexual abuse. Moreover, even relatively milder events such as novel environments, public speaking, and so forth, can also activate the stress response, particularly in vulnerable individuals.

Although the number of stimuli that can activate the stress response is very broad, the biological stress response is well defined. When confronted with a stressful stimulus, a number of physiological alterations occur in order to maximize both available energy and likelihood for a safe outcome. Following the detection of a stressful stimulus, the body activates two separate but interrelated systems, the sympathoadrenal medullary (SAM) system

and the hypothalamic-pituitary-adrenal (HPA) axis (see Figure 25.1).

THE SAM SYSTEM

Activation of the SAM system results in the release of catecholamines [epinephrine (EPI) and norepinephrine (NE)] from sympathetic nerve terminals and from the adrenal medulla, which produces a number of rapid physiologic responses. Circulating EPI released from the adrenal medullae produces rapid increases in heart rate. In parallel, NE released from nerve endings throughout the body produces selective vasoconstriction, shifting blood away from the skin and viscera toward the skeletal muscles, coronary arteries, liver, and brain. The activation of the SAM system, which elicits the so called "fight or flight" response, occurs on a very short time scale (within milliseconds); the neurotransmitters regulating these processes, EPI and NE, have a short half-life of 1–3 minutes within the blood. Therefore, the effects of SAM activation diminish rapidly once the stressor decreases in intensity.

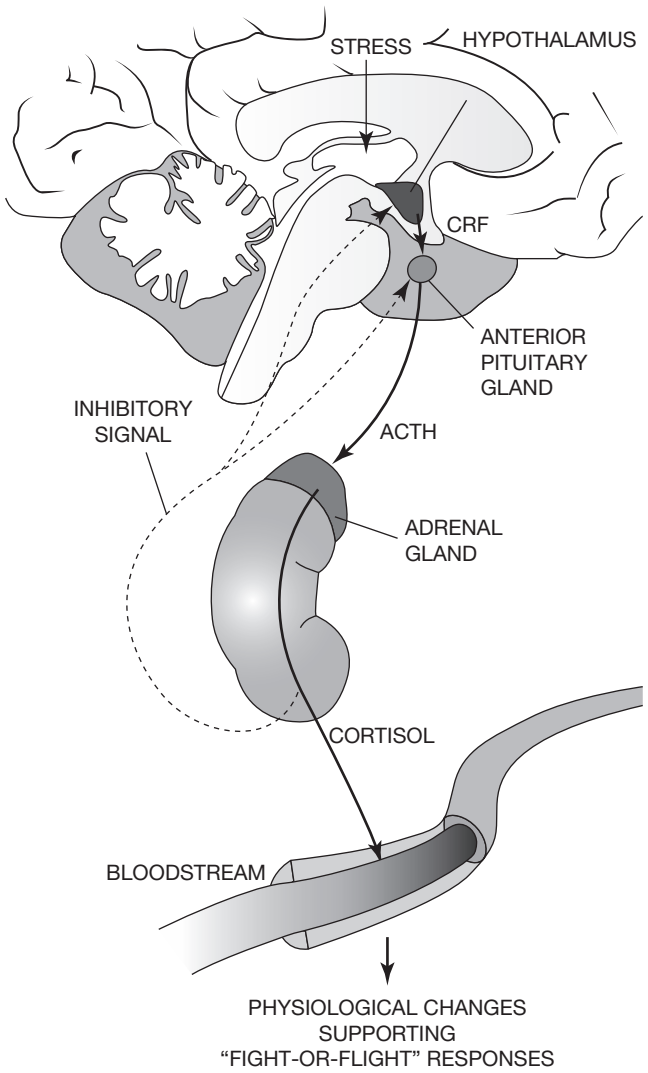

Figure 25.1 ■ *Overview of the HPA axis*: Following relevant stimuli, including stress, CRF is released from the hypothalamus into the hypophyseal portal vessels, where it is transported in high concentrations to the pituitary gland. CRF then promotes the release of ACTH, which in turn promotes the release of cortisol from the adrenal glands. Cortisol acts as an inhibitory signal at both the hypothalamus and pituitary, preventing further CRF and ACTH release, respectively. Reproduced with permission of Tomo Narashima from Nemeroff, C.B., 1998, *Scientific American,* June, p. 47. (*See color insert.*)

HPA AXIS AND CRF

The activation of the HPA axis occurs in synergy with the response of the SAM system. The former takes significantly longer (seconds to minutes) but persists for a much longer period of time (minutes to hours). At the pinnacle of this system is the neuropeptide, corticotropin-releasing factor (CRF), also known as corticotropin-releasing hormone (CRH), which is distributed throughout the central nervous system (CNS) and serves as the critical mediator of the stress response. As will be discussed in more detail below, CRF provides a key link between stress and depression. For example, intracerebroventricular injection of CRF in laboratory animals reproduces many of the hallmark symptoms of depression and anxiety in laboratory animals including decreased libido, reduced appetite and weight loss, sleep disturbances, and neophobia (Dunn, Berridge, Lai, & Yachabach, 1987; Kalin Shelton, & Barksdale, 1989).

Corticotropin-releasing factor is a 41-amino acid peptide. Although Saffron and Schally identified a crude extract that promoted the release of adrenocorticotropic hormone (ACTH) from the pituitary in 1955 (Saffran, 1955), CRF was not isolated and chemically characterized until 1981. Working with extracts derived from 500,000 sheep hypothalami, Vale, Spiess, Rivier, and Rivier (1981) isolated, synthesized, and elucidated the structure of CRF. This neuropeptide not only is the major physiological regulator of the HPA axis, but serves to coordinates the immune, autonomic, and behavioral responses of mammals to stress.

Corticotropin-releasing factor is primarily synthesized in parvocellular paraventricular nucleus (PVN) neurons of the hypothalamus (Hauger, 2000). These neurons (see Figure 25.1 for an overview of HPA axis) receive input from a variety of brain nuclei including the amygdala, bed nucleus of the stria terminalis, and other brain stem nuclei (Swanson, Sawchenko, Rivier, & Vale, 1983). Hypothalamic CRF-containing neurons project primarily to the median eminence (Swanson et al., 1983). In response to stress, this neural circuit is activated, releasing CRF from the median eminence into the hypothalamo-hypophyseal portal system where it

activates CRF receptors on corticotrophs in the anterior pituitary. This promotes the synthesis of proopiomelanocortin (POMC) and the release of its posttranslation products, ACTH and β-endorphin. The ACTH released from the anterior pituitary then acts directly on the adrenal cortex, stimulating the production and release of glucocorticoids, cortisol in humans.

Cortisol acts in synergy with catecholamines to mobilize energy stores during periods of acute stress. The net effect is to increase glucose production and availability and maximize its availability for the heart, brain, and skeletal muscles, which have greater physiological demands for energy during times of stress. Glucocorticoids also promote the breakdown of lipids (fats) and inhibit other bodily functions that are less essential during these periods of increased stress, such as gastrointestinal motility (i.e., digestion of food), inflammation, and reproduction. As will be discussed later, these mechanisms may have life-saving properties when activated acutely, but when chronically active or dysregulated, may cause deleterious effects.

The actions of CRF are mediated primarily by two CRF receptor subtypes, CRF_1 and CRF_2, which have distinct anatomical localization and receptor pharmacology (Chalmers, Lovenberg, et al., 1996; Chang, Pearse, et al., 1993; Chen, Lewis, et al., 1993; Grigoriadis, Lovenberg, et al., 1996; Lovenberg, Liaw, et al., 1995) in rats and humans. Both receptors are G-protein-coupled receptors and are positively coupled to adenylyl cyclase via G_s. The CRF_1 receptor is predominantly expressed in the pituitary, cerebellum, hippocampus, amygdala, and neocortex in the rat (Primus, Yevich, Baltazar, & Gallager, 1997). A growing body of evidence suggests that CRF_1 receptors may specifically mediate some of the anxiogenic-like behaviors observed after administration of CRF (Heinrichs et al., 1997; Steckler & Holsboer, 1999). The CRF_2 receptor family is composed of two primary splice variants, CRF_{2A} and CRF_{2B}. The CRF_{2A} receptor is more prevalent in subcortical regions, such as the ventromedial hypothalamus, lateral septum, and dorsal raphe nucleus, whereas CRF_{2B} is more abundantly expressed in the periphery. In addition to CRF, other endogenous peptide ligands for CRF receptors have been discovered including urocortin (Vaughan et al., 1995), urocortin II, and urocortin III (Lewis et al., 2001; Reyes, 2001).

THE HPA AXIS AND DEPRESSION

Because activation of the HPA axis is a key component of the stress response, stress plays a preeminent role in both mood and anxiety disorders and is among the most intensely studied systems in psychiatric disorders generally. An abundance of evidence dating back over 100 years has demonstrated that dysfunction of the HPA axis may lead to specific psychiatric disturbances. One impetus to scrutiny of HPA axis function in psychiatric disorders was the observation of depression and other psychiatric symptoms in patients with Cushing's syndrome or Addison's disease. Based on the work of several research groups, including those led by Board, Bunney, and Hamburg, as well as by Sachar, Stokes, and Besser, literally thousands of reports have been published in this area. Early studies demonstrated increased HPA activity in depressed patients, including elevations in plasma cortisol concentrations (Carpenter & Bunney 1971; Gibbons, 1962), 24-hour urinary free cortisol concentrations, and urinary levels of cortisol metabolites (Sachar, Hellman, Fukushima, & Gallagher, 1970). Elevated cortisol secretion in depression is among the most reproducible findings in all of psychiatry. In this section, the alterations in HPA-axis function in depressed patients are described in detail.

Structural changes in the components of the HPA axis have been documented in depressed patients, believed to be at least in part due to the effects of chronic activation of the axis. Perhaps in part due to the trophic effects of chronic CRF hypersecretion, pituitary gland enlargement has been documented in depressed patients as measured by MRI (Krishnan et al., 1991). Enlargement of the adrenal glands, presumably due to chronic ACTH hypersecretion, has repeatedly been demonstrated in both depressed patients (Amsterdam, Marinelli, Arger, & Winokur, 1987; Nemeroff et al., 1992) and in suicide victims (Dorovini-Zis & Zis, 1987). An ever-increasing preclinical (McEwen & Magarinos, 1997; Murray, Smith, & Hutson, 2008) and clinical literature (Fuchs, Czeh, Kole, Michaelis, & Lucassen, 2004; Lucassen et al., 2006) also suggests that high levels of circulating glucocorticoids, commonly observed in depression, may also cause reductions in the volume of the hippocampus, a region essential for information processing and memory.

FUNCTIONAL TESTS OF HPA AXIS ACTIVITY

The measurement of nonstimulated (basal) levels of stress hormones has been extremely informative in our overall understanding of stress neurobiology. Over the past quarter century, in part spurred by the identification and ability to produce synthetic CRF, a number of provocation tests have been developed to test the function of the HPA axis.

DEXAMETHASONE SUPPRESSION TEST

In order to evaluate HPA axis function, one commonly used test is the dexamethasone suppression test (DST). In this test, 1 mg of dexamethasone is administered at 11 p.m. and blood samples are collected the following day at 8 a.m., 4 p.m., and 11 p.m. for cortisol measurement. Dexamethasone is a synthetic steroid structurally similar to cortisol that suppresses ACTH secretion,

and subsequently cortisol release, in healthy volunteers. This test was originally developed for the diagnosis of Cushing's syndrome. Nonsuppression of plasma glucocorticoid levels following the administration of dexamethasone is also very common in depression. The rate of cortisol nonsuppression after dexamethasone administration generally correlates with the severity of depression (Evans & Nemeroff, 1987); in fact, nearly all patients with major depression with psychotic features exhibit DST nonsuppression (Arana, Baldessarini, & Ornsteen, 1985; Evans & Nemeroff, 1983). While the test is primarily used for research and not for diagnostic purposes, the conclusion from myriad studies indicates that a sizeable percentage of depressed patients exhibit HPA axis hyperactivity. Unfortunately, DST nonsuppression was also observed in patients with psychiatric disorders other than depression, such as mixed bipolar disorders (Swann et al., 1992), anorexia nervosa (Herpertz-Dahlmann & Remschmidt, 1990; Neudeck, Jacoby, & Florin, 2001), and Alzheimer's disease (Molchan et al., 1990).

CRF STIMULATION TEST

Shortly after elucidating the structure of CRF, a standardized CRF stimulation test was developed to assess HPA axis activity. In this paradigm, CRF is administered intravenously (usually a 1 μg/kg dose or a fixed 100 μg dose) and the ensuing ACTH and cortisol response is measured at 30-minute intervals over a 2- to 3-hour period (Hermus, Pieters, Smals, Benraad, & Kloppenborg, 1984). Numerous studies have demonstrated a blunted ACTH and β-endorphin response to exogenously administered ovine CRF (oCRF), or human CRF (hCRF) in depressed compared with nondepressed subjects, though the cortisol responses in these two groups did not consistently differ (Amsterdam et al., 1988; Gold et al., 1984; Holsboer et al., 1984; Kathol, Jaeckle, Lopez, & Meller, 1989; Young et al., 1990). The blunted ACTH response to CRF occurs in depressed DST nonsuppressors but not in DST suppressors (Krishnan et al., 1993). The attenuated ACTH response to CRF is presumably due either to chronic hypersecretion of CRF from nerve terminals in the median eminence, which results in downregulation of CRF receptors in the anterior pituitary, and/or to chronic hypercortisolemia. The CRF receptor down-regulation results in a reduced responsivity of the anterior pituitary to CRF, as has been demonstrated in laboratory animals (Aguilera et al., 1986; Holmes, Catt, & Aguilera, 1987; Wynn, Aguilera, Morell, & Catt, 1983; Wynn et al., 1984; Wynn, Harwood, Catt, & Aguilera, 1988). Following recovery from depression, the disturbances in the HPA axis generally remit.

DEX/CRF TEST

A combined dexamethasone/CRF test has also been developed. In this test, 1.5 mg of dexamethasone is administered orally at night (11 p.m.), and subjects receive an intravenous bolus of 100 μg of hCRF at 3 p.m. the following day. Patients with HPA axis dysfunction display an increased release of ACTH and cortisol following the DEX/CRF challenge relative to controls. These abnormalities disappear following remission of depression, and normalization of HPA axis function seems to precede full clinical remission (Heuser, Yassouridis, & Holsboer, 1994; Holsboer, 2000). The combined DEX/CRF test appears to have much higher sensitivity for detecting subtle alterations in HPA axis function; approximately 80% of patients with major depression exhibit an abnormal response to the DEX/CRF test. In contrast, only approximately 44% of patients with major depression demonstrate an abnormal response in the DST (Holsboer, Lauer, Schreiber, & Krieg, 1995).

The current evidence suggests that both environmental and genetic factors may influence the response to the DEX/CRF test. Otherwise healthy individuals with first degree relatives with an affective illness, which greatly increases their own risk for mood disorders, demonstrated cortisol and ACTH responses to the DEX/CRF test that were intermediate between a control group and patients with major depression. This suggests that a genetically transmittable defect may render these individuals more susceptible to developing affective disorders (Van Den Eede et al., 2006). A later study found no differences in the DEX/CRF responses between healthy controls and patients who had remitted from major depression, though a small subset (13%) of the depressed patients (13%) demonstrated altered cortisol responses (Kirschbaum, Pirke, Hellhammer, 1993). Abnormal responses to the DEX/CRF prior to discharge, despite symptomatic improvement, also predict the relapse of depression; an abnormal DEX/CRF response was associated with a four- to six-fold increase in the likelihood for relapsing (Zobel et al., 2001). A later study by this same group indicated that normalization of the DEX/CRF response 2–3 weeks after the initiation of antidepressant treatment was associated with higher treatment response rates at 5 weeks (Ising et al., 2007). Further work is certainly needed to clarify the state-trait contributions to DEX/CRF test results.

PSYCHOLOGICAL CHALLENGE TESTS: TSST

In contrast to provocative endocrine tests to assess the activity of the HPA axis are tests that have been developed to assess the HPA axis responsivity to psychological stressors. One such well-characterized paradigm is the Trier Social Stress Test (TSST). This standardized laboratory-based paradigm involves a simulated 10-minute public speech and a mental arithmetic task. These stressful stimuli provide no direct physical harm to the subjects but reliably activate the HPA axis (Kirschbaum et al., 1993). Our group has reported increased plasma ACTH and cortisol concentrations, presumably due to hypersecretion of CRF, after exposure to the TSST in depressed women, and increased ACTH in nondepressed women

previously exposed to severe physical and emotional trauma as children (Heim et al., 2000). These data provide indirect evidence for hyperactivity of CRF systems secondary to early adverse life events.

EXTRA-ENDOCRINE ROLES OF CRF

Although CRF is the primary regulator of the HPA axis activity, it also plays a key role in modulating the autonomic, immune, and behavioral responses to stress in mammals. Results from both clinical and preclinical studies, the latter primarily in rodents and nonhuman primates, have revealed the importance of extrahypothalamic CRF containing neural circuits in these critical functions (Heim et al., 2000). In rodents, primates, and humans, CRF and its receptors are heterogeneously distributed in a variety of brain regions including the amygdala, thalamus, hippocampus, and prefrontal cortex (Charlton, Ferrier, & Perry, 1987; Sanchez, Young, Plotsky, & Insel, 1999; Suda et al., 1984; Van Pett, 2000). These brain areas are important in regulating both the mammalian stress response and affect. The presence of CRF receptors in both the dorsal raphe and locus coeruleus, the two sites for the serotonergic- and noradrenergic-containing perikarya, respectively, and that project to the forebrain, also deserves comment. Because most available antidepressants, including the tricyclics (TCAs) and selective serotonin reuptake inhibitors (SSRIs), are believed to act on these noradrenergic and/or serotonergic systems, the neuroanatomical proximity of CRF and monoaminergic systems suggests a possible role for CRF systems in the mechanism of action of antidepressants.

Involvement of extrahypothalamic CRF systems in the pathophysiology of depression is supported by numerous studies showing elevated CRF concentrations in the cerebrospinal fluid (CSF) of drug-free patients suffering from depression (Arato, Banki, Bissette, & Nemeroff, 1989; Banki, Bissette, Arato, O'Connor, & Nemeroff., 1987; France, Urban, et al., 1988; Nemeroff, 1988; Risch, Lewine, et al., 1992). Elevated concentrations of CRF in the CSF have also been observed in depressed suicide victims (Arato et al., 1989). A reduction in the CRF concentrations in CSF has been reported in healthy volunteers treated with the TCA desipramine (Veith, Lewis, et al., 1993), and in depressed patients following treatment with fluoxetine (De Bellis, Gold, et al., 1993) or amitriptyline (Heuser et al., 1998), providing further evidence of a possible connection between antidepressants, monoaminergic neurons, and CRF circuits. Similar effects of ECT have been noted in depressed patients (Nemeroff, Bissette, Akil, & Fink, 1991). Elevated CSF CRF concentrations appear to represent a state, rather than a trait, marker of depression, that is, a marker of the state of depression rather than a marker of vulnerability to depression. Furthermore, high and/or increasing CRF concentrations in the CSF, despite symptomatic improvement of major depression during antidepressant treatment, may be the harbinger of early relapse (Banki, Karmasci, Bissette, & Nemeroff, 1992), as was previously reported for DST nonsuppression (Charles, Schittecatte, Maes, Rush, & Wilmotte, 1986; Ribeiro, Tandon, Grunhaus, & Greden, 1993).

Postmortem studies have demonstrated increased CRF concentrations in depressed patients (Nemeroff, Owens, Bissette, Andom, & Stanley, 1988). Reduced CRF_1 receptor binding density was observed in the prefrontal cortex of suicide victims (Merali et al., 2004), which would be expected as a consequence of increased CRF availability (Nemeroff et al., 1988). In a later study, Merali et al. (2006) confirmed this early result, demonstrating a specific decrease in CRF_1 mRNA expression in the frontal cortex of depressed patients. Increased CRF mRNA concentrations have also been demonstrated in the hypothalamus of depressed patients (Bao, Meynen, & Swaab, 2007; Raadsheer et al., 1994, 1995). This concatenation of findings provides overwhelming evidence of CRF hypersecretion in depression.

Recently, studies from our group and others have documented long-term persistent increases in HPA axis activity and extrahypothalamic CRF neuronal activity after exposure to early untoward life events. These include studies of child abuse and neglect in both laboratory animals (rat and nonhuman primates) and in humans (Coplan et al., 1996; Holsboer et al., 1987, 1995; Nemeroff, 1999). The role of early life stress in depression is discussed next.

EARLY LIFE STRESS AND DEPRESSION: INSIGHTS FROM ANIMAL MODELS

As noted earlier, approximately 30% to 40% of the risk for depression is believed to be heritable, with the remaining variability imparted by environmental factors. Responses to stressful life events, in part regulated by CRF and the HPA axis, are known to precipitate depression in vulnerable individuals. Moreover, early life stress, such as child abuse and neglect, occurring during neurobiologically vulnerable periods of development, has been posited to be one means by which the environment influences vulnerability to depression. The concept that stressful life events render one vulnerable to psychiatric disorders has been a mainstay of the psychiatric literature for more than a century. This thinking was initiated in part by the pioneering work of Freud, who explored the relationship between stressful life events and psychopathology. These concepts slowly evolved into more biologically based theories with the early work of Selye, who studied the relationships between stress, illness, and emotions. Harlow further highlighted the critical influence of the early environment on behavior in his seminal studies of maternally deprived rhesus monkeys (Ruppenthal, Arling, Harlow, Sackett, & Suomi, 1976). Rhesus monkeys that spent the first 6 months of their life in partial isolation (i.e., raised

with peers in the absence of the mother) exhibited a number of exaggerated oral behaviors, stereotypic movements, heightened fear and aggression, and a reduced ability to deal with daily stressors (Levine, Wiener, & Coe, 1993). Early work in primate models was soon replicated in other species in the late 1950s and 1960s (Levine, 1975). More recent studies in rodents (Francis, Diorio, Liu, & Meaney, 1999; Francis & Meaney, 1999; Ladd et al., 2000) and nonhuman primates have further highlighted the long-term impact of early life stress.

The predictability and stability of the mother–child bond during early childhood and adolescence appear to be important variables in modulating the long-term effects of stress. Adult nonhuman primates maternally deprived during infancy demonstrate elevated HPA axis and behavioral responses to stressful stimuli (Suomi, 1991). Exposing mother/infant bonnet macaques to varying levels of foraging demand over a 12-week period induced severe behavioral disturbances in the infants. The study involved three experimental conditions: a low foraging demand (LFD) condition where the mothers could easily obtain food; a high foraging demand (HFD) condition where mothers had to complete a daily task in order to obtain food; and a variable foraging demand (VFD) condition where the accessibility of food was unpredictable. It is believed that the lack of predictability of the VFD condition results in a diminished sense of security as to the availability of food, producing an increase in anxiety in the mother and a subsequent reduction in the quality of maternal care, creating a state analogous to parental neglect in humans. As adults, VFD reared monkeys demonstrated an anxious temperament and significantly elevated CSF CRF concentrations relative to LFD or HFD reared primates (Coplan et al., 1996), elevations that persisted for the lifetime of the animal (Coplan, Rosenblum, & Gorman, 1995). The VFD-reared animals also exhibited alterations in noradrenergic and serotonergic function as a result of early life stress (Coplan et al., 2000; Rosenblum & Andrews, 1994). Primate models elucidating the effects of direct physical abuse early in life, while still ongoing, suggest similarly devastating long-term consequences of adverse early life events (McCormack, Sanchez, Bardi, & Maestripieri, 2006; Sanchez, 2006).

EARLY LIFE STRESS: CHILD ABUSE AND CHILD NEGLECT

The rate of child abuse and neglect has reached epidemic proportions in our country and worldwide, with epidemiological studies revealing a disturbingly high rate of child maltreatment in the United States. The National Center of Child Abuse and Neglect reports over 1.5 million confirmed cases of child maltreatment each year. More than 50% of these cases represent neglect, and about 700,000 cases involve sexual, emotional, or physical abuse (Sedlack & Broadhurst, 1996).

EARLY LIFE STRESS AND DEPRESSION

The vast majority of the studies evaluating altered HPA axis responses in depression predated recognition of the critical role that early experiences may play in the development of the stress axis. It is likely that some, but not all, of the variability in these studies may be explained by failure to account for the effects of early life stress (ELS). As discussed above, our group has demonstrated that depressed women with a history of prepubertal sexual abuse exhibit persistently increased HPA axis activity as evidenced by a blunted ACTH response to CRF infusion, and both hypercortisolemia and increased ACTH secretion in response to a standardized laboratory stressor (Heim et al., 2000). A multiple regression model of this data set demonstrated that a history of childhood abuse, the number of separate abuse events, the number of adulthood traumas, and the severity of depression predicted the peak ACTH response to the psychosocial stress. Interestingly, the strongest predictor for ACTH response was a term that coded for the interaction between childhood (past) and adult (present) trauma. This correlation fits well with our model in which early untoward life events sensitize the stress responsive circuitry, so that upon reexposure to traumatic events later in life, there is a hyperactive (and maladaptive) response in which CRF is hypersecreted, ultimately leading to the signs and symptoms of a major depressive episode.

We have recently demonstrated similar findings in adult men with childhood trauma histories; in this study, increases in ACTH and cortisol responses to DEX/CRF were observed in males with ELS when compared with nonabused men (Heim et al., 2008). The most robust difference in stress responsiveness was seen when abused men with current major depressive disorder (MDD) were compared with both control subjects and with depressed men without childhood abuse experience. Furthermore, the magnitude of the increased response was associated with the severity, duration, and earlier onset of the abuse.

Studies have also suggested that these effects are not specific to abuse and neglect, with other early life stressors not involving physical and sexual abuse potentially producing similar long-term sequelae. Individuals who experienced parental loss (prior to age 16) demonstrated elevated cortisol responses in a public-speaking task as well as in response to exposure to a video-clip depicting the loss of a parent (Luecken, 1998). A subsequent, larger study, which assessed not only early parental loss but also assessed self-reported measures of abuse and family conflict, found higher plasma cortisol concentrations in individuals with early parental loss and family conflict, whereas no association between cortisol and family conflict was seen in a control group that did not experience early parental loss (Luecken, 2000; Luecken & Appelhans, 2006). While the above-mentioned studies examined subjects who were not currently depressed, the results provide further evidence that early life stress may sensitize

the HPA axis, potentially resulting in greater vulnerability to depression later in life.

CURRENT LIFE STRESSORS AND DEPRESSION

While depression can develop without the prior occurrence of any identifiable stressors, ongoing adverse life events often serve as the precipitant for a full-blown major depression. For example, work stress has been demonstrated to provoke depression and anxiety in young men and women (Melchior et al., 2007). A causal relationship between stressful life events and depression appears to have been demonstrated. In a month in which a stressful life event was identified, the odds ratio for the development of MDD increased more than fivefold (Kendler, Karkowski, & Prescott, 1999). However, the authors noted that up to one third of the association between stressful life events and the development of depression was noncausal, as patients prone to MDD often place themselves in high-risk situations.

Although conceptualized as a syndrome, striking variations exist in the severity and clinical presentation of depression seen within patient populations. Clinically, the diagnosis of MDD is made by assessing for the presence of depressed mood or anhedonia (inability to experience pleasure) together with at least 5 out of 9 other specific symptom clusters (see Table 25.1 for a description of the diagnostic criteria for MDD). Further highlighting the complexity of the link between stress and depression is a study indicating that specific clusters of depressive symptoms were predicted by the nature of the preceding life event (Keller, Neale, & Kendler, 2007). For example death of a loved one and romantic breakups were associated with high levels of anhedonia, sadness, and appetite lost, as were romantic breakups, which were also associated with guilt. Among subjects unable to identify a specific stressor prior to the onset of depression, symptoms of fatigue, appetite gain, and thoughts of self-harm were more common, but sadness was reported less often. Chronic stress was associated with symptoms of fatigue and hypersomnia, but sadness, anhedonia, and appetite loss were less often reported. Furthermore, one might predict that within a given patient, the specific pattern of depressive symptoms would likely be similar between individual bouts of depression. However, the specific stressor preceding the onset of depression was a stronger predictor of the pattern of depressive symptoms than was the set of depressive symptoms seen in the previous episode (Keller et al., 2007).

Table 25.1 ■ Major Criteria for a Major Depressive Episode (MDE)

A diagnosis of MDE can be made when at least five of the following symptoms have been present for the same 2-week period, and at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

(1) Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful)
(2) Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation made by others)
(3) Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day
(4) Insomnia or hypersomnia nearly every day
(5) Psychomotor agitation or retardation nearly every day
(6) Fatigue or loss of energy nearly every day
(7) Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day
(8) Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others)
(9) Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide

The above criteria are adapted from the *DSM-IV-TR*.

THE ROLE OF GENETICS

The preponderance of evidence would suggest that environmental factors (i.e., "nurture") can clearly influence the development and set point of the stress axis. In particular, a strong case has been made for the deleterious effects of early untoward life events. However genetic factors are clearly of relevance as well. Depression is highly heritable, with rates of concordance between monozygotic twins between 30% to 40% (Kendler, Gatz, Gardner, & Pedersen, 2006) versus a prevalence rate of ~15% in the general population (Kessler, Merikangas, & Wang, 2007). However, a discordance rate of 60% to 70% between genetically identical siblings and the development of MDD highlights the complex interplay between genetics and environment and further demonstrates that depression is not simply the result of a single gene abnormality.

ROLE OF THE SERT GENE

It is very unlikely a single gene will ever be identified that, in and of itself, is responsible for vulnerability to depression. Nevertheless, the identification of genes that may act either to buffer or to amplify the effects of various stressors, which in turn may mediate the risk for developing depression, is an area of active research. Arguably, one of the most remarkable observations of the past decade is the finding that variations within the promoter region of the serotonin transporter (SERT) gene interact with early adversity to influence vulnerability to depression. Serotonin is one of the major monoamine neurotransmitters known to play a role in the pathogenesis of depression. The SERT is the primary target of the SSRIs, which are the most widely prescribed class of antidepressants. The SSRIs, as their name implies, primarily act by blocking the reuptake of 5-HT into the presynaptic

nerve terminal; this in turn increases the concentration of 5-HT within the synapse, subsequently potentiating postsynaptic serotonergic neurotransmission.

Minor variations in the sequence of genes, so-called genetic polymorphisms, are quite common within the human genome. A three-base pair repeat polymorphism has been identified within the promoter region sequence of the SERT gene (Bradley & Blakely, 1997; Heils et al., 1996), termed the 5HTTLPR. This polymorphism results in the production of two different allelic forms of the SERT gene, a short variant that contains fewer repeats, the so called "s" variant, as well as a long or "l" variant, with a greater number of repeats. As these polymorphisms do not occur within the transcribed region of the gene, the SERT produced by these alleles is identical. However the polymorphism occurring within the promoter region of the SERT gene appears to alter transcriptional efficiency, with the "s" variant showing reduced transcriptional efficiency of the SERT and thus reduced SERT expression (Lesch et al., 1996).

Studies appearing shortly after the discovery of these variants demonstrated an association between the number of copies of the s allele and anxiety-related personality traits (Lesch et al., 1996). Variations in the 5HTTLPR have also been associated with activation of the amygdala, a region critical for the recognition and processing of fearful stimuli. Increased amygdala activation has been observed in individuals with two copies of the "s" allele in response to fearful stimuli compared with individuals with two copies of the "l" allele (Hariri et al., 2002).

Most relevant to this discourse on the link between stress and depression is the seminal work of Caspi (2003) in which the incidence of early traumatic events and depression was assessed as well as the SERT genotype. Individuals with the "s" allele of the promoter region of the SERT gene are unusually vulnerable to the now very well-documented depressogenic effects of early life stress, that is, child abuse or neglect and, moreover, that this effect is "dose dependent," both in terms of the "s" allele (one copy or two) and in terms of the frequency and severity of the abuse. Thus the most vulnerable to depression are individuals with the s/s genotype and the least vulnerable are those with the l/l genotype, with s/l individuals being of intermediate risk. This finding is all the more extraordinary because this polymorphism has been shown to be functional: The s/s and s/l individuals exhibit reduced SERT binding sites in PET imaging studies compared to l/l individuals (Graff-Guerrero et al., 2005). The s/s genotype increased sensitivity to the effects of early life stress and, moreover, the l/l genotype protected against the depressogenic effects of early life trauma, representing a disease-resistant haplotype. Recently another allele of this gene, the Lg variant, was identified, which, similar to the s allele, also confers vulnerability to the effects of adverse early life events (Frodl et al., 2008). The isolation of other genes that confer both susceptibility and resilience (stress buffering genes) is an area of considerable interest. This original observation by Caspi and colleagues has now been replicated in most (Kendler, Kuhn, Vittum, Prescott, & Riley, 2005) but not all subsequent studies (see Vergne & Nemeroff, 2006, for a review). One of the key points of this work that is worth underlining is that the SERT polymorphism only appears to increase vulnerability to depression in the presence of significant adverse early life events; in the absence of ELS, no difference in the prevalence rates of depression is noted among individuals with different SERT polymorphisms.

ROLE OF THE CRF_1 GENE

As noted above, a preponderance of evidence has demonstrated a key role for CRF neural circuits in the stress response. Although there is often considerable variability in the association between specific allelic variants and depression, a number of polymorphisms have been suggested to confer an increased risk for the development of MDD. These include variations within the CRF_1 receptor gene itself (Liu et al., 2006) as well as polymorphisms within the CRF Binding Protein (CRF-BP), a protein involved in regulating the availability of the peptide (Van Den Eede et al., 2007). Variations within the glucocorticoid receptor gene (FPKP5) (van Rossum et al., 2006), which regulates the effects of cortisol, as well as in a chaperone protein involved in the regulation of glucocorticoid receptor functioning (Binder et al., 2004), have also been associated with an increased risk of developing of depression.

A direct link between genotype, ELS, and depression has also recently been identified in the CRF_1 gene, analogous to the finding showing an association between SERT polymorphisms, ELS, and depression (Bradley et al., 2008). In this study, a large sample of patients were recruited from an urban medical clinic waiting room within a large inner-city hospital. Self-reported measures of both childhood trauma history as well as symptoms of current depression were assessed, and saliva was collected for DNA analysis. Within this primarily African American sample, there was a strong interaction between specific single nucleotide polymorphisms (SNPs), child abuse, and the subsequent risk for developing depression. The authors' results were confirmed in a separate independent sample that was distinct both ethnically (88% White) and socioeconomically (less impoverished) (Bradley et al., 2008). Similar to the results from the investigations in polymorphisms seen in the SERT, specific CRF_1 receptor polymorphisms were only associated with increased risk for depression in individuals with a history of moderate to severe childhood physical or sexual trauma (see Figure 25.2). These findings further both bolster the putative role for CRF in modulating depression and further highlight the critical role of both genetics and the environment indicating the long-term effects of early life stress. Of note, polymorphisms of another gene (FKBP5) in the same population predicted vulnerability

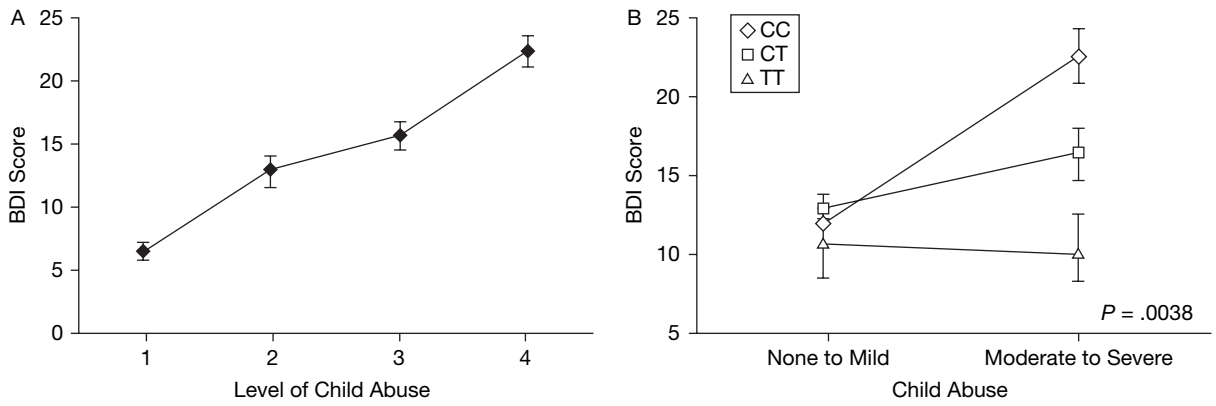

Figure 25.2 ■ Panel (A) indicates a correlation between the number of traumatic life events and scores on the Beck Depression Inventory (BDI). In panel (B), an interaction between traumatic life events and CRF_1 polymorphisms is demonstrated, indicating that genotype was only associated with BDI in the presence of ELS. Adapted from Bradley, R. G., Binder, E. B., Epstein, M. P., Tang, Y., Nair, H. P., Liu, W., et al. (2008). Influence of child abuse on adult depression: Moderation by the corticotropin-releasing hormone receptor gene. *Archives of General Psychiatry*, *65*(2), 190–200.

to posttraumatic stress disorder (PTSD) but not depression (Binder et al., 2008).

CONCLUSION

It is evident that an inexorable link exists between stress and depression, and new research has dramatically increased our understanding of the relationship between the two. Perhaps most compelling have been the results demonstrating a clear relationship between ELS and depression. With the recent work specifically implicating disturbances in CRFergic neurotransmission as a direct result of adverse early experiences in both rat and primate studies, a stress–diathesis model is compelling. Indeed, analogous to the well-established critical periods in the development of the visual system (Kandell, Schwarz, et al., 1998), severe stress during the critical childhood years can cause persistent abnormalities of stress-responsive neural circuitry and alter the "set point" of the HPA axis to later stressful events. This renders victims of abuse more susceptible to developing depression or anxiety disorders later in life. The recent work demonstrating an increased risk for depression in individuals with the s/s genotype of the SERT who were exposed to ELS, together with similar findings for CRF_1 receptor polymorphisms, further bolster this concept.

Advancing our understanding of the neurobiology of stress and depression also has the potential to increase the effectiveness of our treatments. Our current pharmacological treatments for depression and anxiety primarily modulate the activity of monoaminergic neurotransmission. Drugs that modulate these three target neurotransmitter systems have been available for more than 50 years, with most of the newer antidepressant compounds developed over the last 10 to 20 years showing improved side-effect profiles and safety by comparison with older drugs, but a similar overall mechanism of action. Currently available antidepressants are effective in many patients; however, overall remission rates remain disappointingly low. Understanding the neurobiology of depression will surely implicate new targets for drug development. Based on this premise, newly developed CRF_1 receptor antagonists represent a novel putative class of antidepressants and anxiolytics. Such compounds exhibit activity in many preclinical screens for antidepressants and anxiolytics. A small, open-label pilot study examining the effectiveness of R121919 (a CRF_1 receptor antagonist) in major depression (Zobel et al., 2000) showed that severity measures of both anxiety and depression were reduced in the depressed patients. Although this drug is no longer in clinical development, it is clear that CRF_1 antagonists may represent a new class of psychotherapeutic agents to treat anxiety and affective disorders.

Going forward, the role of stress in the pathophysiology of depression, particularly the role of early life stress, will allow for the identification of at-risk populations. This may lead to the development of interventions that may prevent the long-term effects of ELS on the subsequent development of depression. Because the "s" allele of the SERT in the context of ELS appears to be associated with depression, one could envision a strategy where compounds that modulate the function of the SERT (such as SSRIs) given at critical times (after an incident of abuse comes to the attention of the relevant social services or mental health practitioners) may prevent the long-term sequelae of ELS. With growing recognition of the morbidity and mortality associated with depression (Moussavi et al., 2007), furthering our understanding of stress and depression is a critical public health issue.

NOTES

In the past 3 years, Dr. Nemeroff served on the Speakers' Bureau and/or Board of Directors, has been a grant recipient, and/or owned equity in one or more of the following: Abbott Laboratories, Acadia Pharmaceuticals, American Foundation for Suicide Prevention (AFSP), American Psychiatric Institute for Research and Educations (APIRE), AstraZeneca, BMC-JRLLC, Bristol-Myers-Squibb, CeNeRx, Corcept, Cypress Biosciences, Cyberonics, Eli Lilly, Entrepreneur's Fund, Forest Laboratories, George West Mental Health Foundation, GlaxoSmithKline, i3 DLN, Janssen Pharmaceutica, Lundbeck, National Alliance for Research on Schizophrenia and Depression (NARSAD), Neuronetics, NIMH, NFMH, NovaDel Pharma, Otsuka, Pfizer Pharmaceuticals, Quintiles, Reevax, UCB Pharma, Wyeth-Ayerst.

Currently, Dr. Nemeroff serves on the Scientific Advisory Board for Astra-Zeneca, Johnson & Johnson, Pharma NeuroBoost, Forest Laboratories, Quintiles, and NARSAD. He is a grant recipient from NIH, NARSAD, and AFSP. He serves on the Board of Directors of AFSP, APIRE, NovaDel Pharmaceuticals, and the George West Mental Health Foundation. He owns equity in CeNeRx and Reevax. He owns stock or stock options in Corcept, Cypress Biosciences, and NovaDel.

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26 Stressors and Mental Health Problems in Childhood and Adolescence

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Stressors occupy a central role in the field of developmental psychopathology. At the theoretical level, prevailing models of child and adolescent psychopathology recognize the potential importance of environmental stressors in the etiology and maintenance of both internalizing and externalizing disorders in youth (Cicchetti & Toth, 1991, 1997; Haggerty, Sherrod, Garmezy, & Rutter, 1994; Hammen & Rudolph, 2003; Hankin & Abela, 2004). At the practical level, numerous events and conditions pose threats to children and adolescents. This stems from high levels of poverty, violence, and family adversity (Children's Defense Fund, 1999, U.S. Census Bureau, 2003) and is reflected in high rates of emotional and behavioral problems in young people (Achenbach & Howell, 1993; Achenbach, Dumenci, & Rescorla, 2002). Policies to reduce exposure to stressors in the lives of children and adolescents and interventions to enhance the adaptive capacities of children and adolescents to manage life stressors are a high priority (Compas, 1995; Hammen & Rudolph, 2003; Hankin & Abela, 2004).

In spite of the potential significance of stressors for understanding and influencing child development and psychopathology, research on stress in childhood and adolescence has lagged behind similar research with adults. Reviews of the child/adolescent stress literature published in the past two decades present a picture of a field early in its development (e.g., Cohen & Park, 1992; Compas, 1987; Johnson, 1986; Johnson & Bradlyn, 1988), with research in preliminary stages in all areas, including measurement development, epidemiological research, prospective investigations of the etiological significance of stressors, and research on possible mediators and moderators of the association between stressors and psychopathology (Grant et al., 2003).

To evaluate progress that has been made in the past 15 years, we have examined the child and adolescent stress literature in a series of four articles. These include reviews of conceptualization and measurement of stressors (Grant et al., 2003), evidence of prospective effects (Grant, Compas, Thurm, McMahon, & Gipson, 2004), evidence of specificity in the relation between stressors and child/adolescent psychopathology (McMahon, Grant, Compas, Thurm, & Ey, 2003), and evidence of moderating and mediating effects in the relation between stressors and child and adolescent psychopathology (Grant et al., 2006). In this chapter, we will discuss the results of these reviews and provide recommendations for future research that builds upon them.

DEFINING STRESS FOR CHILD AND ADOLESCENT RESEARCH

Prevailing definitions of stress focus on environmental circumstances or conditions that threaten, challenge, exceed, or harm the psychological or biological capacities of the individual (see Cohen, Kessler, & Gordon, 1995 and Dohrenwend, 2006 for reviews). These demands may occur in the form of change in the social environment or in persistent environmental conditions that present ongoing threats and challenges. In this sense, all definitions of stress include an environmental component. Definitions of stress differ, however, in the degree to which they emphasize psychological processes that occur in response to the environment. One approach has focused on exposure to environmental events (e.g., loss of a loved one, natural disaster) and chronic conditions (e.g., poverty) that represent objective measurable changes in, or characteristics of, individuals' environments, in the tradition originally outlined by Holmes and Rahe (1967). This perspective emphasizes the importance of objectively documenting the occurrence and effects of environmental events and conditions independently of the individual's cognitive appraisals, which are subjective and potentially confounded by the stress response (Brown & Harris, 1989; Cohen et al., 1995; Dohrenwend, 2006; Dohrenwend & Shrout, 1985).

In contrast, a second approach is reflected in transactional models, which posit that stress is dependent on the degree to which individuals appraise environmental demands as threatening, challenging, or harmful (Lazarus & Folkman, 1984). Although the transactional theory that Lazarus and Folkman (1984) proposed has been seminal in advancing our understanding of stress processes, there are some inherent problems with including appraisal in the definition of stress, particularly for research with children and adolescents (Grant et al., 2003).

Results of research on stress during infancy indicate there are clear negative effects of maternal separation, abuse, and neglect on infants (e.g., Field, 1995; Goldberg et al., 2003; Perry, Pollard, Blakley, Baker, & Vigilante, 1995) that occur, presumably, without the cognitive appraisal component that is central to the transactional definition. In addition, preliminary research indicates that cognitive appraisal processes that play a significant role later in development do not play the same role for young children exposed to stressors (Nolen-Hoeksema, Girgus, & Seligman, 1992; Turner & Cole, 1994).

Furthermore, in recent years, theoretical models of the etiology of developmental psychopathology have become more sophisticated, with a greater emphasis on moderating and mediating processes that influence or explain the relation between stressors and psychopathology across development (Cicchetti & Cohen, 1995; Pearlin, 1999). Reliance on a definition of stress that "lumps" together with stressors potential mediating or moderating processes, such as cognitive appraisal, is conceptually unclear and empirically problematic (Reiss & Oliveri, 1991). To understand fully how stressful experiences, moderating factors, and mediating processes relate to one another in the prediction of psychopathology, it is important to discretely define and measure each of these variables (Aneshensel, 1999). This is particularly true in child and adolescent research, because the role of specific mediating and moderating processes is likely to shift across development (Grant et al., 2003).

A final reason for moving beyond a transactional definition of stress is that the individually based focus of such an approach may accentuate confounding of genetic and environmental contributions to mental health problems in stress research (Grant & McMahon, 2004). From a transactional perspective, whether an experience is defined as a stressor is based on whether the individual appraises it as such. Appraisal processes, however, may reflect genetic or other vulnerability contributions to risk, thereby exacerbating potential confounding of vulnerabilities and environmental contributions to symptomatology (Brown, 1990; Dohrenwend, 2006; Dohrenwend & Shrout, 1985; Skodol, Dohrenwend, Link, & Shrout, 1990).

Therefore, in our view, the single essential element of stress research—distinct from moderators and mediators, psychological symptoms, and other sources of risk or vulnerability—is external, environmental threat to the individual (Cohen et al., 1995). For this reason, Grant and colleagues (2003) propose that *stress* be defined as "environmental events or chronic conditions that objectively threaten the physical and/or psychological health or well-being of individuals of a particular age in a particular society" (p. 449). Such a definition is consistent with traditional "stimulus-based" definitions of stress (Holmes & Rahe, 1967) and more recent definitions of stressors (McCubbin & Patterson, 1983) and *objective stress* (Brown & Harris, 1989; Dohrenwend, 2006; Dohrenwend & Strout, 1985; Hammen, 1997).

Given the historical association of the term *stress* with a wide array of psychological phenomena and definitions, Grant and colleagues (2003) recommend use of the word *stressor* to refer to the environmental experiences that should be the defining feature of stress research. The broader term *stress* is more useful as an inclusive term that refers not only to the environmental stressors themselves but also to the range of processes set in motion by exposure to environmental stressors. Thus *stress research* refers to the body of literature that examines environmental stressors as well as reciprocal and dynamic processes among stressors, mediators, moderators, and psychological symptoms.

MEASURING STRESSORS IN CHILD AND ADOLESCENT RESEARCH

STRESSOR CHECKLISTS

The most widely used method for assessing stressors affecting children and adolescents is the self-report checklist. Checklists are relatively easy to administer and allow investigators to collect data on large samples, thereby increasing statistical power to detect relations among stressors, mediating and moderating variables, and psychological outcomes. General checklists assess a broad range of stressful experiences, whereas specialized checklists assess specific types or domains of stressful events in the lives of young people (Grant et al., 2004).

General Checklists of Stressful Events

Advances have been made in the development and refinement of general stressor checklists for adolescents, but less progress has been made in the development of checklists for children. At least 11 such measures for adolescents (Burnett & Fanshawe, 1997; Cheng, 1997; Coddington & Troxell, 1980; Compas, Davis, Forsythe, & Wagner, 1987; Johnson & McCutcheon, 1980; Masten, Neeman, & Andenas, 1994; McCubbin & Patterson, 1983; Newcomb, Huba, & Bentler, 1981; Swearingen & Cohen, 1985; Tolor, Murphy, Wilson, & Clayton, 1983; Yeaworth, York, Hussey, Ingle, & Goodwin, 1980) and at least 5 for children (Byrne, Velamoor, Cernovsky, Cortese, & Losztyn, 1990; Coddington, 1972; Deutsch & Erickson, 1989; Sandler, Wolchik, Braver, & Fogas, 1986) are relatively well established in the literature (see Grant et al., 2004, for a review).

These general checklists are all similar in that they present respondents with a sample of negative and, in some cases, positive events that are representative of the types of events that researchers deem relevant. None of the inventories are designed to be exhaustive; rather, they are intended to offer a sufficiently broad sampling to be representative of stressful events and experiences in childhood and adolescence. Although early versions of these measures offered little information on their psychometric

qualities (Compas, 1987), more recent studies have documented the test-retest reliability, internal consistency, and concurrent validity of several general life events checklists for adolescents (e.g., Burnett & Fanshawe, 1997; Cheng, 1997; Cohen & Park, 1992; Compas et al., 1987), though basic psychometric data are not available for many of the other adolescent stressor measures that have been reported in the literature (e.g., Tolor et al., 1983; Yeaworth et al., 1980; see Grant et al., 2004, for a review).

Specialized Checklists

Specialized stressor checklists have generally been developed with two related issues in mind: the need for specific measures for specific populations and the need for measures of specific types of events.

With some notable exceptions (e.g., Allison et al., 1999; Cheng, 1997; Gil, Vega, & Dimas, 1994; Nyborg & Curry, 2003; Richters & Martinez, 1993), measures of cumulative life stressors have been developed in European American middle-class samples. These measures have been criticized for lacking items pertinent to youth of color, particularly those living in disadvantaged urban communities (Miller, Webster, & MacIntosh, 2002). A small number of measures have been developed to address this issue, particularly with regard to exposure to community violence among minority youth (e.g., Richters & Martinez, 1993). Although exposure to violence scales are important sources of information on stressors affecting low-income urban youth, they do not represent comprehensive measures of stressors likely to affect youth of color or other minority youth (Allison, Martin, Bergen, & Roeger, 2004; Miller et al., 2002). Broader measures are needed that are inclusive of exposure to racism, discrimination, acculturation stressors (Gil, Vega & Dimas, 1994; Nyborg & Curry, 2003), and specific economic stressors (Grant et al., 2004).

Critiques of the Checklist Approach

Most stressor checklists are consistent with an objective conceptualization of environmental stressors; however, the degree to which stressor checklists actually assess objective threat is unclear. The items included on stressor checklists have typically been selected by researchers based on their personal opinion, or information generated in small focus groups. Thus the items themselves have not been empirically generated relative to objective threat. In addition, as cumulative stressor checklists include a list of brief items (e.g., death of a grandparent), it is unclear to what degree each item assesses the same objective experience for different children and adolescents. For example, the death of a grandparent who has had little contact with a child represents less threat and disruption than the death of a grandparent who has served as that child's primary caregiver (Duggal et al., 2000; Rudolph & Hammen, 1999).

Stressor checklists also have been criticized for limiting the number and types of stressful events that may be examined (Duggal et al., 2000). Measures for adolescents have included from 30 items (Swearingen & Cohen, 1985) to more than 200 items (Compas et al., 1987). Although longer measures can be assumed to be more comprehensive, abbreviated versions of longer checklists have also been found to be valid (e.g., Grant & Compas, 1995). Thus the number and type of stressors necessary to adequately assess the effects of stressors on youth is unclear (Grant et al., 2004).

Another critique of stressor checklists is that they do not require respondents to provide information about the date of occurrence or timing of the events (Duggal et al., 2000; Rudolph & Hammen, 1999). Most checklists focus on a particular period of time (e.g., events that have occurred in the previous 6 months) without specifying at what point during that period the event took place. This limits the usefulness of checklists in determining the role of the occurrence of stressors in relation to the onset or remission of psychiatric disorders (Grant et al., 2004; Rudolph & Hammen, 1999).

Finally, stressor checklists have been criticized for failing to distinguish between stressors that are independent of the individual's behavior (e.g., death of a parent, parental divorce, moving) and those that are not (e.g., break-up of a romantic relationship, school failure, incarceration; Hammen, 1997). Independent events are generally considered less confounded with psychopathology and therefore, represent "cleaner" markers of environmental effects. On the other hand, there is increasing evidence of a reciprocal relation between stressors and psychological symptoms (Grant et al., 2003), indicating the importance of examining dependent stressors as well.

STRESSOR INTERVIEWS

Stressor interviews address some of the shortcomings of checklists and are designed to provide relatively objective indices of the degree of contextual threat that is associated with stressful events and conditions in the lives of children and adolescents. Interviews are used to generate a list of stressful events that have been encountered and the conditions that surround these events. Probes for each event that has occurred include requests for a description of what happened, when it happened (using a calendar to establish the dates of occurrence), who was involved, and the objective consequences of the event (Rudolph & Hammen, 1999; Rudolph, Hammen, & Burge, 1997). External raters then evaluate the level of threat associated with each event and condition or the severity of impact of each event. These ratings are then summed to form an objective index of stressors that each child or adolescent has encountered. Interrater reliability of these ratings has typically been quite high (Adrian & Hammen, 1993; Garber & Robinson, 1997; Rudolph et al., 1997; Rudolph & Hammen, 1999; Williamson et al., 2003).

Although many potential advantages of the stressor interview have been identified, there have been few

empirical comparisons of the relative merits of interviews and checklists. Some preliminary evidence suggests that interviews may be more useful for research on particular severe events. Duggal and colleagues (2000) found that a similar total number of stressors were identified by the Bedford College Life Events and Difficulties Schedule interview (Brown & Harris, 1989) modified for adolescents (Monck & Dobbs, 1985) and the Life Events Checklist (LEC; Johnson & McCutcheon, 1980) and that the two methods were equally effective at distinguishing between depressed adolescents and controls. These findings are consistent with the high correlations between checklist and interview approaches reported in other studies (Lewinsohn, Roberts, Hops, & Andrews, 1991; Lewinsohn, Rohde, & Gau, 2003; Wagner, Abela, & Brozina, 2006). Nonetheless, Duggal and colleagues (2000) found that different events appear to have been tapped by the two measures, and many of the severe stressors coded on the interview were not identified on the stressor checklist.

There also is some preliminary evidence that stressor interviews may be better predictors of changes in symptomatology. Garber and Robinson (1997) found that although significantly correlated, the Life Events Interview for Adolescents (LEIA) was a stronger predictor of changes in depressive symptoms in prospective analyses than either the LEC (Johnson & McCutcheon, 1980) or the Family Inventory of Life Events (McCubbin & Patterson, 1983).

Critiques of the Interview Approach

Despite their potential advantages, stressor interviews have been used less frequently than pencil-and-paper measures. Grant and colleagues (2004) examined more than 500 studies in their review of child and adolescent stressors and found that fewer than 2% used interviews to assess stressors. This is likely due to the increased time demands and person power associated with interview administration, which bring substantially increased costs to the researcher and the participants. Given this reduced cost-effectiveness, interviews do not offer a complete solution to the problems identified with existing survey measures. Sole reliance on stressor interviews would limit the field by reducing the participation of some researchers and by reducing sample sizes of those studies that are conducted.

Beyond concerns about cost-effectiveness, interviews have been criticized as less likely to elicit information that may be embarrassing or have potential negative consequences if reported (Singleton & Straits, 1999). This may be a particular concern with child and adolescent samples. For example, children and adolescents may be less likely to answer questions about physical or sexual abuse truthfully in an interview format (to an interviewer who may be required to report such abuse) than they would in an anonymous survey (Grant et al., 2004).

Nonetheless, there are research questions for which stressor interviews are essential. In particular, interviews are recommended to better understand the complexity of the relation between the temporal course of psychological symptoms/disorders and stressors. For example, identifying the onset, course, duration, severity, and remission of psychological symptoms in relation to the specific nature, duration, and severity of stressors would be more easily accomplished through an interview process. In addition, interviews can be particularly helpful when the outcome examined is a categorical diagnosis rather than symptoms of psychopathology, such as diagnoses based on *Diagnostic and Statistical Manual of Mental Disorders* (4th ed. [*DSM-IV*]) (American Psychiatric Association, 1994) criteria in which the emphasis is on the onset, course, duration, and remission of a disorder. In this circumstance, researchers need to document the timing of stressful events in relation to changes in diagnostic status. This requires the use of measures of both stressful events and psychopathology that are sensitive to timing and duration and research designs that are able to identify the specific timing of events in relation to the onset or termination of an episode of disorder (Cohen et al., 1995).

GENERAL CRITIQUES OF STRESSOR MEASUREMENT IN CHILD AND ADOLESCENT RESEARCH

In addition to critiques that are specific to either survey or interview method, two significant problems apply to both approaches to measurement. A first general concern involves possible confounding of stressors and symptoms of psychopathology due to similar items appearing on measures of both constructs (e.g., Dohrenwend, 2006; Dohrenwend & Shrout, 1985). For example, fights or conflicts with others and worries or concerns about one's life situation have not only been included on some measures of stressors but are also symptoms of some forms of psychopathology (e.g., disruptive behavior disorders and anxiety). The development of an empirically based taxonomy of stressors, inclusive only of stressors that are not overly confounded with symptoms, might address this problem (described further below). In the meantime, researchers should evaluate existing stressor measures for degree of overlap with symptomatology (Grant et al., 2004).

A second area of concern centers on the lack of standardization of stressor measurement for children and adolescents. For example, in Grant and colleagues' (2004) review, approximately 500 studies were exemplary in that each moved beyond examination of a simple association between stressors and symptoms to examine prospective, moderating, mediating, or specificity relations among stressors and outcome. Nevertheless, very few of these studies used comparable stressor measures. Approximately 60% used cumulative stressor checklists or interviews (as opposed to measures of specific stressors

such as sexual abuse or exposure to a hurricane). Of these studies, fewer than 10% used one of the well-validated measures cited above, and no single measure was used in more than 3% of studies (Grant et al., 2003). Forty-five percent of studies indicated the authors developed their own measure of cumulative stressors. Psychometric data on most of these measures were not provided, and few of the authors who developed their own scales provided information about their method of measurement development or items included on their scales (Grant et al., 2004).

This lack of standardization highlights a central difference between the state of the field of child and adolescent stressor measurement and the state of the field of child and adolescent psychopathology measurement. Specifically, taxonomies of child and adolescent psychopathology have been developed, but no such taxonomy exists for child and adolescent stressors. Two well-established taxonomies for child and adolescent psychopathology have been developed (1) *DSM-IV* and (2) the Achenbach System of Empirically Based Assessment (ASEBA; Achenbach & Rescorla, 2001). Although the *DSM-IV* is generally regarded as the gold standard of diagnostic systems, the ASEBA (and earlier versions of the measures on which the ASEBA is based) has been used more frequently in stress research on children and adolescents. The development of such taxonomies represents an important achievement in the past half century, which has dramatically improved the ability of researchers to communicate with one another and to replicate one another's work (Grant et al., 2004).

The progress made in stressor measurement over the past 15 years suggests it may be possible to also develop a taxonomy of stressors. In particular, the development of reliable and valid stressor interviews indicates that it is possible to achieve agreement about events and conditions that pose a threat to children and adolescents in our society. Evidence for the reliability and validity of stressor surveys also has emerged, in spite of the fact that these measures have been developed independently of empirically based objective threat ratings. These achievements suggest that a standardized measure of stressors, which builds on the strengths of each of these methodologies, could be developed (Grant et al., 2004).

CONCEPTUALIZING THE ROLE OF STRESSORS IN THE DEVELOPMENT OF PSYCHOPATHOLOGY

As argued above, stressors remain central to current etiological theories of child and adolescent psychopathology. This is evident in that more than 1,500 empirical investigations of the relation between stressors and psychological symptoms among youth have been conducted in the past 15 years alone (Grant et al., 2004). This large body of research has led to some notable progress in the field. Earlier literature reviews concluded there was insufficient evidence demonstrating that stressors predict psychopathology in children and adolescents over time (Cohen & Park, 1992; Compas, 1987; Johnson, 1986; Johnson & Bradlyn, 1988) and consistently yielded recommendations for additional prospective studies (Grant et al., 2004). Since those earlier reviews, more than 60 published studies have tested for a prospective association between stressors and psychological symptoms (e.g., Time 1 stressors predict Time 2 symptoms, controlling for Time 1 symptoms) and evidence for prospective effects have been reported in the vast majority of those studies (see Grant et al., 2004, for a review).

Unfortunately, there has been substantially less progress in other areas of stress research. Many of the questions raised in earlier reviews have yet to be answered. For example, earlier reviews reported the need for more research examining (1) moderators of the relation between stressors and psychological problems (including the need for research examining changes in the association between stressors and psychopathology across development), (2) mediating processes in the relation between stressors and psychopathology, (3) specificity in the relation between particular types of stressors and particular types of psychopathology, and (4) reciprocal relations between stressors and psychopathology (Cohen & Park, 1992; Compas, 1987; J. H. Johnson, 1986; Johnson & Bradlyn, 1988). Reviews of these areas of research (Grant et al., 2003, 2004, 2006; McMahon et al., 2003) have revealed a general lack of substantial progress (with the exception of a group of studies testing mediating processes that are discussed later in this chapter).

Reasons for lack of progress include the variability in conceptualization and operationalization of stressors described above. Few studies have used comparable measures of stressors, and even fewer have used comparable measures of stressors and psychopathology (Grant et al., 2004). Underlying these specific measurement concerns is the broader issue that most studies of the relation between stressors and psychological problems in children and adolescents have not been theory driven. Earlier reviews recommended the development and analysis of complex theoretical models of the role of stressors in the etiology of child and adolescent psychopathology (Cohen & Park, 1992; Johnson, 1986). Unfortunately, beyond the broad theoretical notion that stressors pose a risk factor for psychopathology, most studies conducted over the past 15 to 20 years have not placed their investigation within a theoretical context (Grant et al., 2003).

A GENERAL MODEL

To address this problem, Grant and colleagues (2003) have proposed a general conceptual model of the role of stressors in the etiology of child and adolescent psychopathology. This model builds on previously proposed models of specific forms of psychopathology (e.g., Albano, Chorpita, & Barlow, 1996; Asarnow & Asarnow,

1996; Hammen & Rudolph, 2003) and includes five central propositions (see Figure 26.1): (1) stressors contribute to psychopathology; (2) moderators influence the relation between stressors and psychopathology; (3) mediators explain the relation between stressors and psychopathology; (4) there is specificity in the relations among stressors, moderators, mediators, and psychopathology; and (5) relations among stressors, moderators, mediators, and psychopathology are reciprocal and dynamic. None of these propositions are mutually exclusive. All may operate at once or in dynamic interactions.

EVIDENCE FOR CENTRAL PROPOSITIONS OF GENERAL MODEL

Stressors Contribute to Psychopathology

The first proposition of this conceptual model, that stressors contribute to psychopathology, provides a fundamental conceptual basis for all studies of the relation between stressors and psychological problems in children and adolescents. As briefly described above, Grant and colleagues (2004) reviewed the evidence for prospective effects in 60 studies conducted with children and adolescents. They found consistent evidence that stressful life experiences predict psychological problems in children and adolescents over time (Grant et al., 2004). Cumulative measures of stressors and particular stressful experiences (e.g., poverty, divorce) were both found to predict psychological symptoms. Furthermore, positive associations were reported for both internalizing problems, such as depression and anxiety, as well as externalizing problems, such as aggression and delinquency (e.g., Robinson, Garber, & Hilsman, 1995), though the associations were typically stronger with internalizing than externalizing problems (Compas, Howell, Phares, Williams, & Ledoux, 1989), and externalizing symptoms were examined less frequently (Grant et al., 2004).

Moderators Influence the Relation Between Stressors and Psychopathology

The notion that moderators influence the relation between stressors and psychopathology has been examined in numerous studies (see Grant et al., 2006, for a review). Moderators may be conceptualized as diatheses, or as protective factors, as they represent preexisting characteristics (i.e., in existence prior to exposure to the stressor) that increase or decrease the likelihood that stressors will lead to psychopathology (Baron & Kenny, 1986; Holmbeck, 1997). Moderators may also be viewed as the mechanisms that explain variability in processes and outcomes ranging from equifinality to multifinality (i.e., the mechanisms that explain why varying predictors/processes may lead to similar outcomes and why similar predictors/processes may lead to varying outcomes; Egeland, Carlson, & Sroufe, 1993; Sameroff, Lewis, & Miller, 2000). Potential moderating variables include demographics (e.g., age, sex/gender, race/ethnicity, and socioeconomic status), social factors (e.g., social support, parent relationships, school and neighborhood contexts), and "fixed" emotional and cognitive styles (e.g., temperament, attributional, and coping styles).

Moderating variables may be the result of genetic vulnerabilities (or protective factors), nonstressor environmental influences (e.g., parenting or peer influences), or in some cases, stressful experiences. For example, exposure to severe and chronic stressors may lead to the development of a stable attributional style that interacts with future stressors to predict psychopathology (Grant et al., 2003, 2006). In a review of the literature on moderators of the association between stressors and psychological problems in young people, Grant and colleagues (2006) found that age and sex are the two variables that have most frequently been tested as moderators (Grant et al., 2006). Both represent "fixed" individual characteristics in

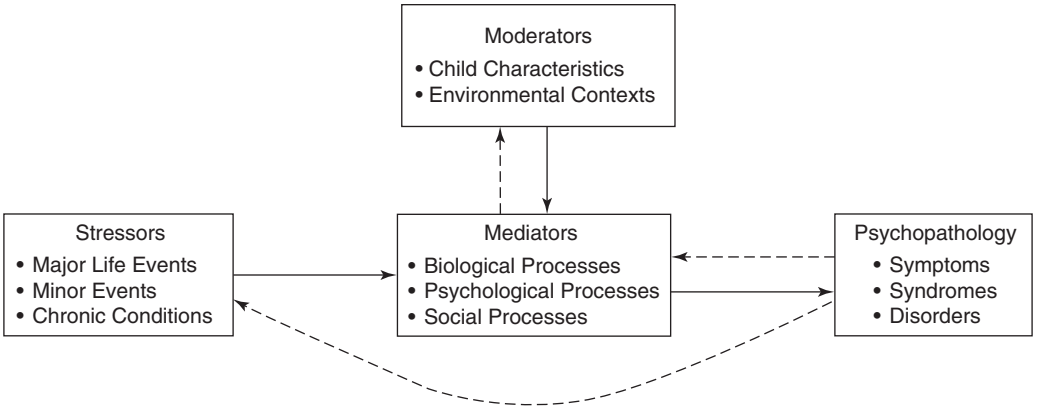

Figure 26.1 ■ General conceptual model of the role of stressors in the etiology of child and adolescent psychopathology. From Grant, K. E., Compas, B. E., Stuhlmacher, A. F., Thurm, A. E., McMahon, S. D., & Halpert, J. A. (2003). Stressors and child and adolescent psychopathology: Moving from markers to mechanisms of risk. *Psychological Bulletin, 129*, 447–466.

that neither is likely to be influenced by stressors (Grant et al., 2006).

Despite the potential importance of understanding developmental effects on the relation between stressors and psychopathology, few consistent findings have emerged from the more than 60 studies that have tested age as a moderator (Grant et al., 2006). A little over half of these studies found age to moderate the relation between stressors and symptoms (Grant et al., 2006). One pattern emerged across several of those studies (Black, Dubowitz, & Harrington, 1994; Chandy, Blum, & Resnick, 1996; DiGallo, Barton, & Parry-Jones, 1997; Fitzpatrick, 1993; Hibbard & Hartman, 1992; Johnston, 1990; Larson & Ham, 1993; Masten, Miliotis, Graham-Berman, Ramirez, & Neemann, 1993; O'Keefe, 1994a, 1994b; Patton et al., 1996; Seidman et al., 1998; Yule, 1992): Stressors appeared to be more strongly associated with parent-report symptoms among younger children and more strongly associated with self-report symptoms among older youth (Grant et al., 2006).

Sex has been examined as a moderator in over 100 studies (Grant et al., 2006). A little over half of these studies found sex to moderate the relation between stressors and mental health problems (Grant et al., 2006). One expected pattern of results was that boys were more likely to exhibit externalizing symptoms, and girls were more likely to exhibit internalizing symptoms in response to stressors (Grant et al., 2006). In addition to this pattern, it appears that risk for negative outcomes for boys versus girls may also vary as a function of the specific stressor experienced. For example, among studies reporting moderating effects for sex, boys were found to be at greater risk when exposed to poverty, divorce, and abuse, whereas girls were found to be at greater risk when exposed to violence and disaster. This pattern may reflect specificity between particular stressors and particular outcomes more common for a particular sex. For example, poverty, divorce, and abuse all may involve heightened exposure to conflict, which may be specifically linked to aggression (Sandler, Reynolds, Kliewer, & Ramirez, 1992), an externalizing outcome for which boys are at heightened risk. On the other hand, exposure to the particular types of violence examined in many of the studies conducted in this area (e.g., suicide, murder) and exposure to disaster may represent threat events specifically associated with anxiety, an outcome for which girls are at heightened risk (Grant et al., 2006; McMahon et al., 2003).

Race/ethnicity is a third fixed individual characteristic that has been examined in a smaller number of studies (i.e., 23 studies; Grant et al., 2006). Most of these studies reported evidence of moderation (Grant et al., 2006). Among those, the most common pattern was a stronger association between stressors and psychological symptoms for White youth relative to youth of color (Baldwin et al., 1993; Barrera et al., 1995; Barrera, Li, & Chassin, 1993; Biafora, Warheit, Vega, & Gil, 1994; Chandy et al., 1996; Costello, Farmer, Angold, Burns, & Erkanli, 1997; Feiring, Coates, & Taska, 2001; Guerra et al., 1995; March et al., 1997).

Moderators such as cognitions, coping, and competence represent relatively malleable individual characteristics relative to age, sex, and race/ethnicity. Variables such as these have more frequently been the focus of theory-based moderator research. For example, in their review, Grant and colleagues found 13 separate studies that examined specific etiological models of psychopathology, based on cognitive theories of depression (Abela & Sullivan, 2003, Chang & Sanna, 2003; Cole & Turner 1993; Davila, Hammen, Burge, Paley, & Daley, 1995; Hammen & Goodman-Brown, 1990; Hankin & Abramson, 2002; Hankin et al., 2001; Hilsman & Garber, 1995; Nolen-Hoeksema et al., 1992; Panak & Garber, 1992; Robinson et al., 1995; Rudolph et al., 2001; Shirk et al., 1998; Southall & Roberts, 2002; Tram & Cole, 2000; Turner & Cole, 1994). Although these studies generally did not examine the same specific cognitions, they provide some of the best examples of theory-driven moderation research. All but three of the studies (Cole & Turner, 1993; Davila et al., 1995; Tram & Cole, 2000) found support for the moderating role of specific depressogenic cognitions. For example, Hammen and Goodman-Brown (1990) and Shirk and colleagues (1998) found that youth high on interpersonal self-schema, but not youth high on achievement self-schema, exhibited heightened depressive symptoms in response to interpersonal stressors.

In addition, age has been examined in conjunction with cognitive factors, which has revealed that development influences appraisal processes in response to stressors. Nolen-Hoeksema et al. (1992) examined stressors, cognitions, and age as predictors of depressive symptoms among youth followed from third to eighth grade. The authors reported that stressors alone emerged as a powerful predictor of depression among younger children; however, among older youth, the interaction of stressors with negative explanatory style emerged as a predictor. Turner and Cole (1994) reported a similar finding in their sample of fourth-, sixth-, and eighth-grade youth. Negative cognitive style interacted with stressors to predict depressive symptoms for older, but not younger youth. The specific, developmentally grounded, and theory-based nature of these studies exemplify the type of research needed to test and further develop specific conceptual models of the etiology of stressors in the development of specific types of psychopathology.

Environment-based contextual variables (e.g., social support, family environment, peer environment, activities/positive events) also have been examined as moderators (Grant et al., 2006). Studies examining environment-based moderators have frequently been concerned with discovering variables that buffer or protect youth from the negative effects of stressors. Unfortunately, in spite of the importance of contextual influences on the relation between stressors and psychopathology in youth, studies in this area have been characterized by variability in

conceptualization and measurement of central moderating constructs, thus limiting the conclusions that may be drawn (Grant et al., 2006).

Mediators Explain the Relation Between Stressors and Psychopathology

Although some variables may serve either a moderating or a mediating function (e.g., cognitive attributions, coping), mediators are conceptually distinct from moderators in that they are activated, set off, or caused by the current stressful experience and serve to, conceptually and statistically, account for the relation between stressors and psychopathology (Baron & Kenny, 1986; Holmbeck, 1997). Whereas moderators are characteristics of the child or of his or her social network prior to the stressor, mediators become characteristics of the child or of his or her social network in response to the stressor. In some cases, the child may possess some of the mediating characteristic prior to exposure, but the characteristic increases (or decreases) substantially in response to the stressor (Grant et al., 2006).

Results of studies testing the hypothesis that mediators explain the relation between stressors and developmental psychopathology provide support for this hypothesis. In contrast with the vast majority of moderator studies (which have tested for moderation in the context of a broader set of analyses), all mediator studies have focused intentionally on testing a mediational model and, as a result, have generally been theory-driven. The most consistent finding across studies is that family-based variables (including parent–child relationships and parenting behaviors) mediate the relation between stressors and psychological symptoms in children and adolescents (Conger et al., 2002). In particular, there is evidence that negative parenting practices mediate the relation between economic stressors and psychological problems in children and adolescents (see Grant et al., 2003 and 2006 for reviews). This finding is consistent with interpersonal models of developmental psychopathology (Hammen & Rudolph, 2003) and suggests that stressors exert their negative impact on youth by disrupting important interpersonal relationships/interactions (see Grant et al., 2003 and 2006 for reviews).

Although consistent support has been found for family-based mediators, most of the studies that examined these variables did not test competing mediational models. Those studies that examined child- (e.g., coping strategies) and environment-based (e.g., daily hassles) mediators found they also accounted for the relation between stressful events and symptoms in young people. Studies are needed to evaluate integrative models to determine how family, child, and environment-based mediators fit together to explain the relation between stressors and psychopathology. In particular, family and child variables are likely to be integrally related. A child's coping repertoire, for example, may be expanded or limited based on his or her family context (Gore & Eckenrode, 1994). It may be that parent behaviors elicit child behaviors (and vice versa) such that the types of parenting behaviors implicated in mediator studies that focused on family variables (e.g., hostile/rejecting parenting, inconsistent discipline) lead to the types of child behaviors/characteristics implicated in the studies focusing on child variables (e.g., low self-esteem, external locus of control, avoidant coping). For example, hostile/rejecting parenting may lead to low self-esteem, which in turn leads to psychological symptoms (Garber, Robinson, & Valentiner, 1997).

Specificity in the Relations Among Stressors, Moderators, Mediators, and Psychopathology

The fourth proposition of Grant and colleagues' (2003) broad conceptual model is that there is specificity in relations among particular stressors, moderators, mediators, and psychological outcomes. According to this proposition, a particular type of stressor (e.g., interpersonal rejection) is linked with a particular type of psychological problem (e.g., depression) through a particular mediating process (e.g., ruminative coping) in the context of a particular moderating variable (e.g., female gender, adolescent age).

In their review of the literature on specificity in the relation between particular stressors and particular psychological outcomes in children and adolescents, McMahon and colleagues (2003) reported that they were unable to find any studies that had examined a "full specificity model" including specific mediating and moderating processes in the relation between particular stressors and particular outcomes. A number of studies examined more than one stressor and more than one outcome, thereby allowing for the examination of specific associations between particular stressors and particular outcomes (McMahon et al., 2003). With a few notable exceptions (e.g., Sandler, Reynolds, Kliewer, & Ramirez, 1992), these studies did not define themselves as "specificity" studies or test a specificity theory (McMahon et al., 2003).

McMahon and colleagues' (2003) review did not reveal a consistent pattern of specific effects except in the area of sexual abuse. Several studies demonstrated that sexual abuse was specifically associated with sexual acting out and with internalizing outcomes, particularly posttraumatic stress disorder. Results from studies examining the relations between other stressors (exposure to violence, physical abuse, neglect, divorce, marital conflict, poverty, illness, and cumulative stress) and psychological outcomes were more consistent with tenets of equifinality and multifinality although there was some suggestion of specific relations between conflict and externalizing outcomes and between loss events and internalizing outcomes. This general lack of consistent effects is likely due to high co-occurrence rates among

psychological problems, for particular types of stressful experiences, or both.

Recent methodological advances in specificity research, such as those proposed by Mesman and Koot (2000) and Weiss, Susser, and Catron (1998), allow investigators to use both within-subjects and between-subjects tests to tease out specific associations among variables that are highly correlated. Such methods promise to increase the sensitivity, sophistication, and rigor of specificity research. In addition, tests of theoretically driven, comprehensive specificity models that include specific associations among particular stressors, outcomes, moderators, and mediators have the potential to refine our understanding of pathways linking stressors and outcomes among children and adolescents.

Relations Among Stressors, Moderators, Mediators, and Psychopathology Are Reciprocal and Dynamic

The final proposition, that relations among stressors, moderators, mediators, and psychopathology are reciprocal and dynamic, broadly encompasses the following specific hypotheses: (1) Each variable in the model influences the other (with some exceptions, e.g., fixed moderators such as age will not be influenced by other variables); (2) The role of specific variables within the model may vary across specific stressors and shift over time (e.g., a mediator that developed in response to a particular stressor may become a fixed pattern of responding and therefore interact as a moderator with subsequent stressors); and (3) Reciprocal and dynamic relations among stressors, moderators, and mediators will predict not only the onset of psychological problems but also the exacerbation of symptoms and movement along a continuum from less to more severe forms of psychopathology (e.g., shifts from depressive symptoms to depressive disorder; Grant et al., 2003).

This proposition has received scant research attention. Longitudinal research that measures stressors and potential mediators, moderators, and psychological outcomes at each of several time points is needed for a full examination of reciprocal and dynamic relations among these variables over time. Extant research has generally focused on the hypothesis that psychopathology predicts additional stressful experiences (Hammen, 1991). Results of Grant and colleagues' (2004) literature review suggest that psychopathology does predict stressful life experiences in young people over time. For example, findings from multiwave prospective research with adolescents showed that greater depressive symptoms at one time predicted increases in stressors, especially interpersonal stressors, at a later time point, even after accounting for the stability of both depression and stressors over time (Hankin, Roesch, Mermelstein, & Flay, 2004). Another recent multiwave investigation by Carter, Garber, Ciesla, and Cole (2006) revealed similar findings with an interesting twist. For adolescent report, a "stress exposure" model best fit the data, in that adolescent reports of stressors predicted later reports of psychological symptoms. By contrast, for mother report, a "stress generation" pattern emerged, such that mother reports of their adolescents' symptoms predicted later stressors for those youth (Carter et al., 2006). These results indicate that at least some children and adolescents are caught in a continuing cycle in which stressful experiences contribute to increases in internalizing and externalizing symptoms, and these symptoms contribute to disrupted interpersonal relationships, failures in achievement tasks, and other types of stressors (Grant et al., 2004).

Additional research is needed to test for reciprocal and dynamic relations among particular stressors, particular moderating and mediating processes, and particular outcomes. Little research has been conducted on reciprocal and dynamic relations among these variables, but at least three studies exemplify the type of research needed. Davila and colleagues (1995) tested the hypothesis that interpersonal stressors function both as predictors of depressive symptoms and as mediators of the relation between initial and later depressive symptoms in a sample of older adolescents. The authors found support for their hypothesis in a series of reciprocal relations, thus illustrating the dynamic relations among stressors, psychopathology, and mediating processes. Nolen-Hoeksema and colleagues (1992) found that stressors predicted a pessimistic explanatory style in youth that was associated with depression but that was unchanged despite the remittance of depressive symptoms. This phenomenon, which the authors labeled a "scar," suggests that pessimistic explanatory style may initially play a mediating role in response to stressors in the prediction of depression but, over time, may become a fixed pattern of responding and eventually function as a moderator in relation to future stressors. Lakdawalla and Hankin (2008) found that the personality trait of neuroticism predicted greater exposure to stressors over time and was associated with elevated cognitive vulnerability. In turn, the interaction of cognitive vulnerability with more stressors predicted increases in depressive symptoms. This finding suggests that moderating variables may also serve as predictors of stressors. Additional studies testing hypotheses such as these are needed to determine the ways in which relations among stressors, mediators, moderators, and psychological problems may be reciprocal and dynamic.

Research on reciprocal and dynamic processes in the relations among stressors, moderators, mediators, and psychopathology represents an especially promising area of inquiry for stress research across the life span. For example, some developmental psychopathologists (Cole & Turner, 1993; Shirk, 2004) have theorized that cognitive mediational processes may be more salient than cognitive moderational processes at younger ages. Cognitive attributions and coping styles are not likely to be well

developed in young children; thus these types of variables are more likely to serve mediational functions in younger samples. Across development, however, these cognitive processes may develop into stable attributional or coping styles that are better conceptualized as moderators (Grant et al., 2003). Thus, from a life-span perspective, it will be useful to examine the ways in which mediators may develop into moderators (or predictors of additional stressors and symptoms) across development (Grant & McMahon, 2004).

It also will be useful to investigate the ways in which stressors experienced at varying points in development may be related to varying types of psychopathology. As the brain develops, the capacity for particular types of cognitive mediation also develops, thereby providing the mediational link between stressors and emerging manifestations of particular types of disorders (Mash & Barkley, 2003). The ways in which development constrains or fosters potential mediating cognitions, the degree to which stressors might operate within a developmental context to further facilitate or inhibit development of particular cognitive processes, and the degree to which developmental influences on cognitive mediation might explain developmental variations in the manifestation of psychopathology, represent interrelated and promising avenues for future research (Grant & McMahon, 2004).

Another promising area of inquiry is investigation of the degree to which uncontrollable stressors experienced in early childhood may set the stage for controllable, self-generated stressors later in life. For example, abuse experienced in childhood may lead to avoidance, which may become a fixed pattern of responding that is predictive of additional stressors and distress. Thus, stressors experienced in childhood may predict both maladaptive coping strategies and psychopathology, which may in turn set the stage for additional stressful experiences at older ages (Gibb, 2002; Hankin, 2005; Magnus, Diener, Fujita, & Payot, 1993; Monroe & Simons, 1991; Simons et al., 1993; Sobelowski, Strelau, & Zawadski, 2001).

SUMMARY, INTEGRATION, AND DIRECTIONS FOR FUTURE RESEARCH

In recent decades, research on the effects of stressors on children and adolescents has followed in the footsteps of research on the effects of stressors on adults, with little concerted effort at collaboration or integration. In the past few years, however, there has been a concerted effort on the part of child and adolescent stress researchers to "catch up" with their adult stress research counterparts. Recent reviews of stress research on children and adolescents (Grant et al., 2003, 2004, 2006; McMahon et al., 2003) have resulted in (1) a working definition of stressors that builds on research with adults and younger samples, (2) a proposed conceptual model applicable across the life span, and (3) a clearer picture of the state of the field, including strong evidence of prospective effects of stressors on psychopathology and evidence that family relationships mediate the effects of economic hardship on child and adolescent mental health. In addition, child and adolescent stress researchers have built on adult research (Brown & Harris, 1989) to develop a narrative interview methodology for young people (Adrian & Hammen, 1993; Goodyer & Altham, 1991; Hammen, 1995, 1997; Rudolph & Hammen, 1999) and have begun to use this methodology to develop a taxonomy of stressors for children and adolescents that will complement existing efforts in the adult literature (Dohrenwend, 2006).

A recommended next step is to further integrate the work conducted on adult and child/adolescent samples. Whereas there is value to examining specific developmental periods and the etiology of specific disorders within certain populations (i.e., certain disorders tend to be exhibited in childhood, whereas others have onset in adulthood), a life-span approach can lead us to consider both continuity and change in the relation between stressors and outcomes from a developmental perspective (Cicchetti & Toth, 1997). With advances in the area of developmental psychopathology, there has been a greater interest in integration of research across the life span. However, few investigators have taken this necessary next step (Ingram & Price, 2001).

There is a need for a conceptual bridge and a common language to facilitate longitudinal investigations of the impact of stressors across the life span. To develop a common language, we recommend continued collaboration between adult and child/adolescent researchers toward the development of a taxonomy of stressors that is comparable across the life span (Grant & McMahon, 2004). To build a conceptual bridge, we recommend that studies of the role of stressors in the development of psychopathology in children, adolescents, and adults build upon a simple, general conceptualization like that proposed by Grant and colleagues (2003). A general model such as this one includes the most consistently described elements of stress research proposed in both the child and adult literatures (e.g., Aneshensel, 1999; Chorpita, 2003; DeBellis, 2001; Fletcher, 2003; Hammen & Rudolph, 2003; Pearlin, 1999; Rubin, Burgess, Kennedy, & Steward, 2003; Sher, 1991; Zuckerman, 1999). Once each of the propositions of the simple, general stress model has been supported or rejected, it will be important to integrate this simple model with a larger ecological model of environmental influences (Grant & McMahon, 2004; Hatch & Dohrenwend, 2007). To understand fully environmental effects on mental health, it will be important to examine the degree to which broader ecological influences (e.g., societal values related to female beauty that might pose threats to adolescent girls; pervasive but subtle forms of racism that might threaten the well-being of youth of color) and minor events (daily hassles) might also pose threats to individuals in our society (Grant & McMahon, 2004). In addition, an examination of positive environmental influences that contribute to positive outcomes,

despite stressors, may contribute to our understanding of development and inform interventions to reduce psychopathology and promote positive mental health.

In conclusion, stressors remain a construct of central importance to the field of developmental psychopathology. Nonetheless, definition and measurement problems have limited incremental progress in child and adolescent stress research, as has the paucity of theoretically driven studies. We believe that the lack of consensus around operationalization of stressors and their role in the etiology of psychopathology requires the following responses: (1) a rigorous, focused definition of stressors; (2) the development of a taxonomy based upon such a definition; (3) incremental research based on a relatively simple generic model; and (4) a developmental approach that integrates theory and research across the life span (Grant & McMahon, 2004). These steps, we hope, will lead us to the next generation of stress research, characterized by consistent measurement, incremental progress, a clearer understanding of the direct role of stressors in the etiology of psychopathology, an enhanced picture of moderating and mediating influences that vulnerabilities and stressors may have on the development of psychopathology, and ultimately a better road map to effective interventions and policy initiatives across the life span.

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27 Physical Health Outcomes of Trauma

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Approximately 50–60% of individuals are likely to be exposed to a traumatic event in their lifetime (Kessler et al., 1995). Events that are potentially traumatic are sufficiently threatening or harmful to most victims to provoke significant stress reactions. Responses to trauma can be manifested as psychosocial, behavioral, and biological changes that can have a critical impact not only on mental health but also on physical health outcomes. Fortunately, the majority of trauma victims recover from their experiences. However, a significant group continues to experience symptoms of distress many years after the event ended. Researchers have found evidence of chronic stress responding and important mental and physical health outcomes decades after traumas occur, such as 10 years after the nuclear accident at Three Mile Island (TMI) (Dew & Bromet, 1993), 20 years after the Chernobyl nuclear disaster (Bromet & Havenaar, 2007), 25 years after a disastrous hotel fire (Lundin & Jansson, 2007), 33 years after the Aberfan landslide (Morgan, Scourfield, Williams, Jasper, & Lewis, 2003), and 36 years after the Vajont valley landslide (Favaro, Zaetta, Colombo, & Santonastaso, 2004).

Given the far-reaching impact of traumatic events, it is important to understand the myriad of health outcomes that can follow in their wake. This chapter will review the definition of traumatic events and discuss the health effects of trauma with a focus on the many different types of physical health outcomes that can occur. Additionally, we will describe some of the potential mechanisms that may explain the onset and/or exacerbation of physical health conditions, and discuss the implications and possible applications of this literature. Given our physical health focus, we refer readers to several comprehensive reviews that are available for discussions of the deleterious mental health effects of traumatic events, such as posttraumatic stress disorder (PTSD), depression, and substance use disorder (APA, 2000; Brewen, Andrews, & Valentine, 2000; Norris, Friedman, & Watson, 2002; Norris, Friedman, & Watson, et al., 2002; van der Velden & Wittman, 2008).

TRAUMATIC EVENTS

The *Diagnostic and Statistical Manual IV-TR* (*DSM-IV-TR*) of the American Psychiatric Association (APA, 2000) defined a traumatic event as one that poses a significant risk of death or serious injury and evokes fear, helplessness, or horror. This definition is in one sense restrictive in that the event must pose significant threat, but in another sense it is inclusive in that any variety of events may be traumatic as long as they are perceived as posing significant threat and they demonstrably produce trauma outcomes. In the time since this definition was formalized, there has been debate in the literature regarding whether or not particular events are sufficient to qualify as a traumatic experience (McHugh & Treisman, 2007). In general, individuals are impacted differentially based on the type of event, whether they were directly or vicariously exposed to the event, the level of event impact, and the community characteristics of the event (Norris et al., 2002; Norris, Friedman, Watson, et al., 2002). Nevertheless, individuals exposed to any major event may experience a variety of symptoms that echo physical and psychological reactions to events that have been clearly classified as traumatic (e.g., combat trauma; APA, 2000). Consequently, the literature on the health effects of traumatic events includes a wide range of potentially traumatic events that have been systematically studied. This breadth in the research has informed the literature on stress reactions and health effects that are specific to certain traumatic events. Additionally, the similarities and differences among the various types of events studied provide confidence in the nature of the effects observed and help to inform future research and clinical applications aimed at mitigating adverse effects. Some of this research will be reviewed below as it pertains to the physical health outcomes that have been observed following exposure to a traumatic event.

PHYSICAL HEALTH OUTCOMES

There are a wide variety of physical health outcomes that have been documented after exposure to a traumatic event. A detailed description would be prohibitive. However, we will discuss specific health effects that fall into the following general categories: injuries and illness as a direct result of exposure, general illness symptoms, seeking and using medical care, and specific medical conditions.

INJURY AND ILLNESS DURING EXPOSURE

Exposure may be related to health outcomes through direct pathways, such as physical trauma or chemical exposure, or through indirect pathways, such as behavioral and biological changes that accompany psychosocial reactions to trauma. Direct effects on health are most evident during a disaster or in its immediate aftermath, and usually take the form of acute injury or illness. For example, victims of motor vehicle accidents often experience neck or back injuries, and emergency workers may come into contact with dangerous debris (Centers for Disease Control and Prevention [CDC], 2002; Dougall, Ursano, Posluszny, Fullerton, & Baum, 2001). Two large-scale disasters in recent US history, the terrorist attacks on 9/11 and Hurricane Katrina, have stimulated numerous research investigations that have broadened our knowledge base concerning the effects of trauma exposure on health. First responders at the World Trade Center (WTC) site on 9/11 were exposed to harmful environmental conditions and several studies have indicated that these workers developed respiratory problems from their direct exposure (CDC, 2002; Mauer, Cummings, & Carlson, 2007). Additionally, New York City Transit workers caught in the dust cloud at the time of the WTC collapse were at greater risk for developing lower respiratory symptoms than workers not exposed to the dust cloud (Tapp, Baron, Driscoll, Mueller, & Wallingford, 2005). Other people surrounding the WTC on 9/11 and the days following were also exposed to high levels of contaminants and were at increased risk for acute and chronic respiratory effects (Lorber et al., 2007). Similarly, first responders to Hurricane Katrina experienced environmental hazards, with many sustaining injuries, such as lacerations and sprains, as well as illnesses, such as upper respiratory conditions and skin rashes (CDC, 2006).

There is evidence to suggest that exposure to environmental contaminants, during a trauma or its immediate aftermath, can continue to have long-term physical health effects. For example, 2–3 years after 9/11, 67% of victims who enrolled in the WTC Health registry reported new or worsening respiratory symptoms (Farfel et al., 2008). Exposure may also be associated with neurological changes. Three years after 9/11, healthy adults with greater exposure had lower gray matter volume in the amygdala, hippocampus, insula, anterior cingulate, and medial prefrontal cortex than did adults with less exposure (Ganzel, Kim, Glover, & Temple, 2008).

Vulnerable populations, such as children, elderly, and pregnant women, may be at an even higher risk for adverse physical health outcomes following injury or exposure to environmental contaminants during trauma. A body of research has emerged describing the changes in birth outcomes among pregnant women exposed to trauma. Pregnant women who have been exposed to trauma were at an increased risk of giving birth to infants with shorter birth lengths (Lederman et al., 2004), lower birth weights (Chang, Chang, Lin, & Kuo, 2002; Lederman et al., 2004; Xiong et al., 2008), smaller head circumferences (Engel, Berkowitz, Wolff, & Yehuda, 2005; Lederman et al., 2004), and shorter or longer gestation times (Engel et al., 2005; Lederman et al., 2004; Xiong et al., 2008). These altered birth outcomes have important implications for infant mortality rates as well as for neurocognitive development and future negative health outcomes (Heron et al., 2009). Birth rates can also be affected. A decrease in the male birth fraction following the Chernobyl nuclear disaster indicated that prenatal exposure to environmental chemicals during the third month of gestation negatively selected male fetuses (Peterka, Peterkova, & Likovsky, 2004).

Negative birth outcomes may be the direct result of chemical contamination or may be mediated through behavioral and biological changes that are associated with posttraumatic stress reactions. Symptoms of posttraumatic stress among pregnant women have been associated with smaller infant head circumferences (Engel et al., 2005). Additionally, pregnant women with PTSD reported engaging in health-damaging behaviors such as smoking, alcohol use, and substance use during pregnancy, having poor prenatal care, and gaining excess weight (Morland et al., 2007). All of this may adversely affect birth outcomes. Rice and Records (2006) demonstrated that abused pregnant women had greater cardiac responses to an orthostatic challenge than did other women of childbearing age, suggesting that trauma during pregnancy, such as physical abuse, may be associated with a vasovagal response profile that could be used to help identify at-risk patients.

In summary, sustaining an injury or having exposure to environmental contaminants during a traumatic event may lead to a number of negative health outcomes for the victims themselves as well as for unborn fetuses. Many victims complain of more general health symptoms following a trauma even if no environmental agent has been identified. Not surprisingly, increases in symptom reporting are related to concomitant increases in medical care use.

SYMPTOM REPORTING AND SEEKING MEDICAL CARE

Trauma victims have been shown to be more likely to seek medical care (Goto, Wilson, Kahana, & Slane, 2002; Smith, Christiansen, Vincent, & Hann, 1999; Stuber, Galea, Boscarino, & Schlesinger, 2006) and to self-diagnose or treat themselves than nonexposed people (Lowe, 1999; Weine et al., 2000). These effects have not been limited to the immediate aftermath of trauma. For example, examination of medical records from general practitioners' clinics revealed that exposure to a community fireworks explosion was associated with increases

in mental health problems during the year that followed, and among victims who sought mental health treatment there was a concomitant increase in doctor visits, gastrointestinal and musculoskeletal problems, and medically unexplained physical systems (den Ouden, Dirkzwager, & Yzermans, 2005). Likewise, exposure to a tornado disaster was a predictor of physical health complaints 1 year later (Polusny et al., 2008), and first responders to an air disaster used more self-initiated health care and reported more psychological distress 8.5 years after the disaster than did nonexposed colleagues (Slottje et al., 2008; Witteveen et al., 2007).

Victims may attribute many different types of symptoms (e.g., fatigue, skin problems, anxiety, dyspnea, and backache) to their trauma experience and seek medical care (Donker, Yzermans, Spreeuwenberg, & van der Zee, 2002). However, physicians may only perceive that a minority of symptom complaints were due to disaster exposure (Donker et al., 2002). Consequently, some research findings have indicated that trauma victims who reported more health problems and sought more health care were less satisfied with the quality of the care that they received than were nonaffected comparison groups (Remennick, 2002).

Furthermore, many traumas affect an entire community, and disruptions in accessing medical care arise that are especially problematic for victims who are undocumented aliens and/or uninsured (Messias & Lacy, 2007), or who have preexisting chronic health conditions for which medications and medical access are needed in order to manage the disease (Rath et al., 2007). Many victims of Hurricane Katrina endured unusual circumstances when they were relocated to trailer parks. Evacuees not only had a hard time obtaining appropriate medical care, they also found themselves living in unhygienic conditions and exposed to dangerous levels of formaldehyde in the building materials of the government-supplied trailers that contributed to physical symptoms such as headaches, stomachaches, and nosebleeds (Madrid et al., 2008). Inadequacies have also been demonstrated in field medical care provided by volunteer organizations. Two years after the 2001 Gujarat earthquake, one-tenth of the injuries were missed, and inappropriate care and lack of follow-up resulted in complications and the need for reoperations among the patients who were treated (Roy, Shah, Patel, & Bagalkote, 2005).

Therefore, victims who experience physical symptoms and seek medical care may not have access to the proper care, or may not receive the level of care that is necessary to tend to their ailments, leading to lingering injuries and medical concerns especially in areas where resources are limited. As discussed below, these findings have important implications for specific medical conditions such as infectious illness, human immunodeficiency virus (HIV) disease and acquired immunodeficiency syndrome (AIDS), rheumatoid arthritis (RA), cardiovascular disease, and diabetes.

SPECIFIC MEDICAL CONDITIONS

Infectious Illness

Infectious illnesses are diseases caused by pathogens (e.g., bacteria, viruses) that are usually transmitted between two or more individuals. Many of these diseases are of acute duration (e.g., cold, flu), but some are chronic conditions that involve significant life threat (e.g., HIV/AIDS, hepatitis C). The immune system is the body's primary defense against infection, and both acute and chronic stressors have been linked with alterations in immune system activity that may increase vulnerability to infection (Segerstrom & Miller, 2004).

Due to logistic issues involved in collecting and processing blood samples, very few studies have examined the relationships between immune system functioning and infectious illness symptoms following trauma exposure. Decreases in immune system functioning after a trauma, especially involving natural killer cells (NK cells; important immune cells involved in the first line of defense against invading pathogens), have been associated with greater reports of illness symptoms, number of colds, number of days ill, presence of allergies, and presence of asthma (Delahanty et al., 1997; Ironson et al., 1997). In contrast, increases in self-reported respiratory illness in a sample of kindergarten students exposed to the 1989 Loma Prieta earthquake were related to previous up-regulation of immune responses from before to after a major life event (starting school; Boyce et al., 1993). Specifically, increases in both $CD4^+/CD8^+$ ratios and lymphocyte response to pokeweed mitogen predicted greater incidence of respiratory illness after the earthquake, even after controlling for respiratory illness incidence prior to the earthquake. Unfortunately, because no immunological measures were collected after the earthquake, it is impossible to know if the immunological up-regulation existed after the earthquake as well (Boyce et al., 1993).

Other researchers have examined the immune system's ability to regulate viral infections that may lay dormant in the body that may be reactivated to produce symptoms in a cyclic fashion (e.g., cold sores). Many people who are infected with the viruses that cause these illnesses never exhibit symptoms, but the virus is still present and may reactivate under times of stress. The immune system is responsible for keeping these viruses latent; therefore, measures of antibody titers are used as indicators of reactivation and immune system impairment and have been shown to increase following exposure to trauma (McKinnon, Weisse, Reynolds, Bowles, & Baum, 1989).

Despite the logistic/measurement difficulties, these findings are consistent with the idea that trauma experiences lead to a reduction in immune system activity that make a victim more vulnerable to infection. However, other variables could be responsible for the observed outcomes. Infection also depends on exposure to the

pathogen. Trauma victims who experience open wounds, crowded conditions, and unsanitary environments will more likely be exposed to pathogens and, as a consequence, will be more susceptible to becoming infected. Additionally, trauma research rarely affords the opportunity to examine prospective relationships among immune system functioning and infection. Therefore, more research needs to be conducted on the exact mechanisms by which infectious illnesses develop following trauma.

HIV/AIDS

HIV preferentially attacks the CD4 T cells in the immune system and can remain latent in the form of proviruses. Progression of HIV disease and the development of AIDS occur when the virus replicates and progressively destroys the CD4 cells. The result is immunosuppression that leads to development of opportunistic infections and cancers and makes patients more vulnerable to other diseases (Frisch, Biggar, Engels, & Goedert, 2001). Following exposure to a traumatic event, patients with HIV are more likely to experience greater progression of HIV disease, as reflected in greater decreases in CD4 number, increases in viral load, disability, and mortality (Leserman et al., 2005; Leserman, Ironson, O'Cleirigh, Fordiani, & Balbin, 2008), and they are also less likely to adhere to the rigorous medication regimen (Whetten, Reif, Whetten, & Murphy-McMillan, 2008). Additionally, patients may have difficulty in obtaining antiretroviral medication in disaster-affected communities. HIV-positive individuals had a hard time obtaining their antiretroviral medications after Hurricane Katrina because there were no open pharmacies and only makeshift clinics available for health care (Clark et al., 2006).

Rheumatoid Arthritis

RA, a degenerative disease of the joints, is an autoimmune condition in which helper T cells produce joint inflammation and degeneration (Abbas & Lichtman, 2006). Because it is caused by the body's own immune system, enhanced immune system functioning (e.g., in response to acute stress) should be associated with increased disease activity, whereas suppression of the immune system (e.g., chronic stress responses) should be associated with improvement in symptoms. This reasoning has been supported in research by Potter and Zautra (1997) in which minor daily stressors were associated with exacerbation of RA, but major life events were associated with decreases in disease activity. However, among a subset of RA patients who were seropositive for the autoantibody rheumatoid factor, stressful life events were not related to disease activity. Among their seronegative counterparts, life events were associated with increases in disease activity and with the onset of the disease (Stewart, Knight, Palmer, & Highton, 1994). This suggests that some RA patients will experience exacerbation of disease symptoms during or immediately following traumatic events. However, exposure to severe trauma may, in some cases, be sufficient to suppress disease activity. One study of RA patients found more disease flares and more disease progression following a hurricane or an earthquake than among patients not exposed to a disaster (Grady, Reisine, Fifield, & Lee, 1991).

Cardiovascular Disease

Cardiovascular diseases form a set of chronic conditions of the heart and blood vessels whose development, progression, and acute clinical manifestation can be influenced by psychological, behavioral, and physiological stress reactions. Stress mainly affects cardiovascular disease through its direct and indirect effects on autonomic nervous system and sympathetic adrenomedullary activity. Increases in blood pressure and heart rate are typically seen following exposure to a traumatic event (Davidson & Baum, 1986), and sustained increases in blood pressure may directly result in new diagnoses of cardiovascular disease (Kannel, 1989). Other stress-related cardiovascular changes, such as platelet aggregation and coronary vasoconstriction, may also contribute to pathophysiological processes, such as atherosclerotic plaque formation and rupture, thrombosis, ischemia, and acute myocardial infarction (Kamarck & Jennings, 1991; Markovitz & Matthews, 1991; Traub & Berk, 1998). Among elderly individuals with established cardiovascular disease, exposure to trauma has been associated with subsequent elevations in blood pressure and hematocrit levels (Kario et al., 1997) as well as with more frequent episodes of potentially fatal arrhythmias as reflected in increases in the number of shocks generated by implanted cardiac defibrillators (Shedd et al., 2004). There also appears to be a relationship between exposure to earthquake trauma and myocardial infarctions (Leor et al., 1996; Suzuki et al. 1997; Tsai, Lung, & Wang, 2004), and PTSD was an independent risk factor for all-cause mortality and cardiovascular mortality among male veterans 30 years after military service (Boscarino, 2008). Holman and colleagues (2008) conducted a prospective examination of changes in cardiovascular health in a national survey sample following 9/11. Physician-diagnosed cardiovascular ailments increased each year following 9/11, with changes in the third year rising from 21.5% to 30.5%. These cardiovascular outcomes were especially pronounced when high levels of acute stress symptoms were reported immediately following 9/11. This was associated with a nearly twofold increase in risk of being diagnosed with hypertension, and a threefold increase in the risk of being diagnosed with heart problems, 1–2 years after 9/11.

Diabetes

Diabetes mellitus is one of the most common neuroendocrine disorders, affecting ~8% of the US population

(CDC, 2008). There are two primary types of diabetes: insulin-dependent or type 1 and insulin-independent or type 2. Both are characterized by high levels of blood glucose and symptoms such as blurred vision, fatigue, and increases in thirst and urination. Glucose is the primary energy source for the body's cells. In type 1 diabetes, the immune system attacks the beta cells in the pancreas, leading to decreased production of insulin, the hormone necessary for glucose to be used by cells (CDC, 2008). In type 2 diabetes, the cells within the body become resistant to the effects of insulin and are no longer able to use glucose. Both types are influenced by family history and genetics, but type 2 diabetes is also heavily influenced by risky lifestyles that include being overweight, lack of physical activity, smoking, having high blood pressure or high cholesterol levels, and having had gestational diabetes during pregnancy (CDC, 2008). Changes in health behaviors that occur following a trauma, such as increases in smoking and drinking, alterations in sleep patterns, and poor nutrition (Clum, Nishith, & Resick, 2001; McNutt, Carlson, Persaud, & Postmus, 2002; Schnurr & Spiro, 1999), in conjunction with increases in circulating glucose levels related to stress (McEwen, 1998), may contribute to the onset or exacerbation of either type of diabetes. A study examining risk factors for diabetes among Native Americans demonstrated that interpersonal traumas that occurred in early life in association with community and family dysfunction predicted prevalence of diabetes (Jiang, Beals, Whitesell, Roubideaux, & Manson, 2008). Additionally, trauma exposure in refugee samples has been associated with greater prevalence of diabetes and hypertension (Kinzie et al., 2008). These relationships appeared to have been mediated by increases in body weight.

DISEASE PATHWAYS

There are many pathways through which trauma may influence susceptibility to, recovery from, and progression of illness and disease. The exact mechanisms for these effects have not been completely elucidated, but research has identified several key response systems. Among these are physiological, behavioral, and psychosocial changes that have interdependent influences on one another creating a milieu ripe for disease processes to occur.

PHYSIOLOGICAL PATHWAYS

The most direct route for traumatic stress to affect illness and disease is through activation or dysregulation of physiological response systems. Numerous acute and chronic biological outcomes have been identified, including changes in immune functioning (Melamed, Shirom, Toker, Berliner, & Shapira, 2004), heightened heart rate and blood pressure (Baum, Gatchel, & Schaeffer, 1983; Kario et al., 1997), sleep disorders (Lamarche & De Koninck, 2007), and general complaints of somatic symptoms (Zatzick, 2003). We have discussed alterations in the autonomic, sympathetic adrenomedullary, and immune systems as important mechanisms contributing to the manifestation or progression of medical conditions such as infectious illnesses, HIV/AIDS, RA, cardiovascular disease, and diabetes. Another important physiological pathway that is demonstrably altered under periods of traumatic stress is the hypothalamic–pituitary–adrenal cortical (HPA) axis (Bevans, Cerbone, & Overstreet, 2008; Ganzel et al., 2007; Yehuda, Giller, Southwick, Lowy, & Mason, 1991). Dysregulation of the HPA axis has been associated with many chronic conditions including PTSD, depression, cardiovascular disease, and diabetes, as well as chronic pain conditions (Chrousos, 1995; Heim, Ehlert, Hanker, & Hellhammer, 1998; Yehuda et al., 1991). Therefore, corticosteroid responses by the HPA axis following trauma may have important implications for a multitude of disease processes.

Alterations in physiological response profiles have been documented years after exposure to a traumatic event and have even occurred in the absence of continued psychological responses. Baum and colleagues (Davidson & Baum, 1986; Davidson, Weiss, O'Keeffe, & Baum, 1991; McKinnon et al., 1989) have conducted a series of longitudinal investigations that have shown sustained increases in stress hormones (i.e., epinephrine, norepinephrine, cortisol), blood pressure, heart rate, and antibody titers to latent viruses (indicating possible immunosuppression) more than 5 years after the TMI nuclear disaster relative to a nonexposed control group. As discussed next, behavioral alterations, including lifestyle factors like diet and physical activity, have also been documented following exposure to trauma, and may have direct or indirect influences on health through effects on these and other physiological response pathways.

BEHAVIORAL PATHWAYS

Traumatic stress can be manifested in behavioral and cognitive changes that affect disease processes by increasing vulnerability to injury or exposure to pathogens, interfering with a person's ability to manage a medical condition, or becoming a pathological condition in its own right. Health-related behaviors observed following exposure to traumatic events include engaging in aggressive and high-risk behaviors (Field, Claassen, & O'Keefe, 2001), changes in sleeping patterns (Hougen, 1988), poor dietary choices (Brunello et al., 2001), lack of physical exercise (Hassett, Moseley, Tate, & Harmer, 2008), and use of legal and illegal substances (Peden, van der Spuy, Smith, & Bautz, 2000; Smith, et al., 1999; Stellman, Stellman, & Sommer, 1988; Sullivan & Evans, 1994). While in most cases these behaviors are the result of coping process aimed at ameliorating the effects of trauma, the behaviors

can continue, resulting in pathological disorders, or can have indirect effects on physiological pathway variables affecting disease processes.

Trauma victims can experience increased likelihood of exposure to injury or disease pathogens by engaging in high-risk behaviors or through decrements in their ability to perform required tasks. Victims of trauma are more likely to engage in high-risk behaviors such as unprotected sexual intercourse and drug use (Chiasson et al., 2005; Evans-Campbell et al., 2006; Wagner et al., 2009). These behaviors can increase the likelihood that a person will be exposed to infection or experience unplanned consequences such as pregnancy. Decrements in the ability to perform a behavioral task have also been documented and are associated with inattention and decreased ability to concentrate (Baum, Gatchel, & Schaeffer, 1983). Performance effects can include lost work time and decreases in worker productivity (Boscarino, Adams, & Figley, 2006; Izutsu, Shibuya, Tsutsumi, Konishi, & Kawamura, 2008). For example, New York City workers evidenced decreased productivity rates at 1 year after 9/11. Symptoms of both PTSD and depression predicted lower work quality, and symptoms of depression predicted more work loss and greater use of medical services (Boscarino et al., 2006). Decrements in performance could have profound impacts on the individual, resulting in dismissal from work or injury and death as a result of inattention and inadequate concentration while engaging in important activities, such as driving a car or operating machinery. Stress-related appetitive behaviors, such as smoking, alcohol, and substance use, may also contribute to the etiology of serious health problems.

Substance use disorders are especially problematic because they can lead to clinically significant functional impairment in addition to influencing disease processes. Trauma victims report increases in use of a variety of substances such as tobacco and smoking, alcohol use and abuse, pharmaceuticals including psychiatric medications, and recreational drugs like cannabis (Boscarino, Galea, Ahern, Resnick, & Vlahov, 2003; Nandi, Galea, Ahern, & Vlahov, 2005; Parslow & Jorm, 2006; Vetter, Rossegger, Rossler, Bisson, & Endrass, 2008; Vlahov et al., 2004). Not surprisingly, use of these substances has been associated with higher levels of traumatic stress and depression (Fu et al., 2007; Pfefferbaum et al., 2002; Vetter et al., 2008; Vlahov et al., 2006). However, there is evidence to suggest that continued substance use after a trauma persists even when symptoms of PTSD and depression decrease (Vlahov et al., 2004). Furthermore, substance use appears to be a risk factor for future symptoms of PTSD, depression, general distress, and decreased quality of life (Adams, Boscarino, & Galea, 2006). Substance abuse is commonly comorbid with PTSD following exposure to trauma (for a review see Jacobsen, Southwick, & Kosten, 2001), and the two conditions together appear to be associated with greater decrements in physical and mental health than substance use alone (Mills, Teesson, Rosa, & Peters, 2006). Behavioral and physiological pathways are important links between trauma and disease and each of these mechanisms may be influenced by psychosocial mechanisms to alter risk for illness and disease.

PSYCHOSOCIAL PATHWAYS

Traumatic events bring about numerous psychosocial effects (Lopez-Ibor, 2006) that can impact health through the physiological and behavioral pathways discussed above. Individuals who experience a traumatic event often show psychological symptoms including bereavement (Gard & Ruzek, 2006), anxiety (Grinage, 2003), lower self-esteem (Bunce, Larsen, & Peterson, 1995), acute stress and dissociation (Johansen, Wahl, Eilertsen, Hanestad, & Weisaeth, 2006), intrusive and unwanted thoughts (Dougall, Craig, & Baum, 1999), PTSD (Fullerton et al., 2001), depression (Deimling, Bowman, Sterns, Wagner, & Kahana, 2006), panic disorder (Pfefferbaum, Stuber, Galea, & Fairbrother, 2006), withdrawal (Wastell, 2002), family conflict (Norris et al., 2002; Norris, Friedman, Watson, et al., 2002), and thoughts of blame or guilt (Koss & Figueredo, 2004). In addition, social effects include withdrawal from social support networks (Bunce et al., 1995), loss of resources (Dekel & Hobfoll, 2007), and issues in reintegration into society (Daggett, Bakas, & Habermann, 2009), including bias or prejudice toward the individual as a result of the event (Whetten et al., 2008).

The mental health effects of trauma have been reviewed extensively elsewhere (Brewen, Andrews, & Valentine, 2000; Norris et al., 2002; Norris, Friedman, Watson, et al., 2002; van der Velden & Wittman, 2008). Mental health outcomes are important in their own right, but also have adverse effects on physical health. Symptoms of depression or posttraumatic stress may persist or be so severe that they decrease a person's ability to function, resulting in clinically significant psychiatric disorders. Additionally, any of these psychosocial symptoms can be associated with alterations in physiological response profiles and behavioral patterns, both of which can promote the development, maintenance, or progression of disease.

Particularly relevant to the experience of traumatic events is the risk of psychiatric disorders such as PTSD. PTSD is the most common disorder experienced following exposure to a traumatic event (O'Donnell, Creamer, Pattison, & Atkin, 2004). The incidence of full-blown PTSD in the general community is estimated to be 1–14% (APA, 2000). It is characterized by responses to trauma involving intense fear, hopelessness, or horror. Individuals experiencing this disorder exhibit the following clinically significant symptoms: reexperiencing the event in some way, avoiding stimuli associated with the event, emotional numbing, and increased arousal during normal activities (APA, 2000).

A number of negative health-related outcomes have been associated with PTSD, including lower quality of life

and more frequent reports of a variety of medical conditions (Olatunji, Cisler, & Tolin, 2007; Schnurr & Jankowski, 1999). Additionally, many of the health effects appear to be independent of exposure to the event itself (Schnurr & Jankowski, 1999). For example, a study with female Veterans Affairs primary care patients demonstrated that PTSD was an important mediator of the effects of trauma on future mental and physical health outcomes, accounting for any relationships between exposure and health outcomes (Lang et al., 2008). Additionally, having PTSD was a risk factor for all-cause and cardiac mortality in male veterans 30 years after service (Boscarino, 2008). A history of trauma exposure and prior diagnoses of PTSD are potent risk factors for subsequent diagnoses of PTSD and symptoms of diseases such as diabetes and arthritis (Norman et al., 2006; Ursano et al., 1999). Similarly, trauma victims may experience major life events subsequent to trauma exposure. These events may be related to the initial trauma (e.g., dislocation, property damage, bereavement) or may be more independent (e.g., work-related events, interpersonal stressors), but any of them may potentiate the physical health effects of trauma (Adams & Boscarino, 2006; Schnurr & Jankowski, 1999).

In summary, traumatic events can have profound effects on physical health and well-being that can range from general symptom reporting to severe, life-threatening diseases. The mechanisms through which disease is promoted involve physiological, behavioral, and psychosocial processes. The pathway to disease may be readily apparent (as in substance abuse or PTSD) or it may be more subtle (as when physiological responding continues even though psychosocial mechanisms have evidenced adaptation), and many responses may work in concert to explain relationships between trauma exposure and physical health outcomes.

CONCLUSIONS AND FUTURE DIRECTIONS

The literature reviewed above suggests that for many individuals exposure to trauma may be associated with new health problems, with the exacerbation of preexisting medical conditions, and with increased use of health care. Several important lessons learned from these findings can be used to inform future research and trauma prevention and recovery efforts. These involve the role of health care providers in the identification of trauma and in the delivery of care, the need to identify and rectify unintentional hazards associated with emergency preparedness and trauma recovery efforts, and the necessity for systematic investigation of interventions designed either to promote recovery or to prevent deleterious effects following trauma.

Physicians are important gatekeepers for detection of posttraumatic syndromes and health outcomes. Individuals increase their use of medical services following trauma (e.g., Stuber et al., 2006), and health care providers are commonly the first person to whom trauma victims disclose their trauma experiences (Leibowitz, Jeffreys, Copeland, & Noel, 2007). Therefore, health care providers are in a unique position to help identify traumatic stress reactions and, as recommended by Ursano and Engel (2008), should regularly screen for potentially traumatic events and posttraumatic stress reactions. However, health care providers practicing in a trauma-stricken community may be faced with their own burdens as victims themselves, or as secondary victims exposed vicariously to other victims' accounts, and may be without proper medical resources (Ben-Ezra, Palgi, & Essar, 2008; Calderon-Abbo, Kronenberg, Many, & Ososfsky, 2008; Tomczyk et al., 2008). Therefore, the health care needs of medical providers are another area rich for research and intervention.

There are many disaster-relief programs and providers who volunteer their services to come to the aid of trauma victims. While these services are needed, establishing a community infrastructure that can support continuing care after the volunteers and organizations pull out of the disaster site is important for maintaining health and wellness (Kutcher & Chehil, 2008). As was demonstrated with victims of Hurricane Katrina and other traumatic events, access to medical care is often limited from the beginning (e.g., Madrid et al., 2008; Roy et al., 2005). "Training the trainer" programs have been advocated as one effective method for strengthening local community resources so that disaster-relief operations can be sustained after volunteer organizations have left (Gelkopf, Ryan, Cotton, & Berger, 2008).

Disaster preparedness training and planning is a primary way in which the adverse effects of traumatic events can be averted or at least minimized. Individuals can learn important ways to behave during a traumatic event, such as following evacuation routes or seeking suitable shelters. Indeed, previous disaster training and experience was the best predictor of optimal disaster behavior and resilience following a factory explosion (Weisaeth, 1989). Disaster planning should also involve securing medical items such as proper medications, adequate stores of foods appropriate for medically based diets, and face masks to prevent inhalation of irritants or cold air (Mori et al., 2007). Research is being directed at prophylactically training military personnel in methods of resilience so as to minimize or eliminate the effects of combat exposure (Novotney, 2009). Success of these programs will help to develop interventions that can be disseminated to other populations who are at-risk for trauma exposure.

Nevertheless, most trauma victims have no way of predicting when trauma exposure may occur so little can be done beforehand. However, interventions can be distributed after a trauma in order to promote resilience and recovery. For example, a community survey of New York City residents indicated that having attended one to three brief worksite interventions following 9/11

was associated with positive outcomes (e.g., reductions in alcohol problems and symptoms of PTSD, depression, and anxiety) up to 2 years afterward (Boscarino, Adams, Foa, & Landrigan, 2006). Unfortunately, the literature on debriefing occurring in the immediate aftermath of a trauma is mixed, with some researchers finding benefits and others finding harm caused by the debriefing (Bryant, Harvey, Dang, Sackville, & Basten, 1998; Litz, Gray, Bryant, & Adler, 2002). Additionally, participation in trauma-related research may also increase awareness of somatic sensations, increase health worries, and decrease reassurability by physicians (Verschuur, Spinhoven, van Emmerik, & Rosendaal, 2008). Research is focusing on systematic evaluations following traumas that identify victims who are at risk for pathological response profiles and customize intervention efforts based on duration and type of symptoms (e.g., Ruggiero et al., 2006).

Although the evidence for physical health effects of trauma exposure appears to be strong, more research is needed that systematically investigates the mechanisms through which adverse health effects occur. The trauma literature is riddled with cross-sectional studies that help to identify potentially important pathways but do not provide necessary information on the prospective relationships among trauma, physical health outcomes, and the mediating physiological, behavioral, and psychosocial pathways. In part, this problem reflects the logistic barriers that trauma researchers face. We rarely know when a trauma will occur and the expense of following even those populations of individuals who are highly at-risk with the expectation that they eventually will be traumatized is prohibitive. This calls for resourceful approaches, such as described by Holman and colleagues (2008), who used an ongoing national survey as a platform for their 9/11 research.

In addition to longitudinal investigations, trauma researchers need to incorporate behavioral, physiological, and health assessments into their research designs. Out of the vast number of studies conducted with trauma victims, relatively few incorporated measures of these important disease pathways or outcomes. Self-reported behavioral and health variables are relatively easy to add to surveys, and researchers should especially attend to these measures. Measurement of physiological parameters and performance on behavioral tasks may be less feasible, but can at times be accomplished as evidenced in some of the research we have reviewed. Longitudinal, mechanism-focused will help to elucidate targets for improved interventions for ameliorating the detrimental effects of trauma. Through such efforts, trauma research has the potential to help millions of future victims to avoid or recover more quickly from the harmful physical health effects of trauma.

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28 Stress and the Heart: Psychosocial Stress and Coronary Heart Disease

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INTRODUCTION

The study of psychological stress and coronary artery disease (CAD) is one of the most well-established areas in health psychology and behavioral medicine. Yet, despite extensive research, there are still doubts in the mainstream medical community regarding the importance of psychological stress processes in cardiovascular disorders and other organic conditions (Angell, 1985; Freedland, Miller, & Sheps, 2006). This skepticism persists in the face of a considerable amount of evidence supporting a causal relationship between stress-related psychosocial factors and cardiac disease (see reviews by Dimsdale, 2008; Krantz & McCeney, 2002; Strike & Steptoe, 2003, 2004, 2005). Indeed, the divergence of opinion between psychosocial and biomedical researchers resulted in a "Great Debate" at an annual meeting of the American Psychosomatic Society and has received substantial attention in subsequent publications (Freedland et al., 2006; Krantz & McCeney, 2002). It has even been suggested that those of us in the psychosocial research community need to "see our work as our critics see it" and examine our evidence and assumptions more carefully (Freedland et al., 2006).

Much of the confusion regarding the stress–heart disease relationship is related to difficulties in definition and measurement in stress research. Investigators are often committed to certain definitions and/or particular measures (Freedland et al., 2006) and may not stay current with recent developments in the stress field. Adding to the problem is the complexity in the development of CAD, a chronic disease that differs in the processes and symptoms that are manifest at each stage of development. CAD progresses over decades as the coronary arteries that supply blood to the heart begin to accumulate plaque (see Figure 28.1). Early stages of CAD are typically asymptomatic. As CAD progresses, it may become symptomatic, with manifestations such as myocardial infarction (MI) and sudden cardiac death (SCD; see Figure 28.1).

Research on the effects of stress in CAD often differentiates between acute and chronic stress. This differentiation is important because CAD progresses over long periods of time, while MI and SCD occur suddenly and are often unpredictable. Thus, chronic stress may be more relevant to long-term CAD progression, whereas acute stress may be more relevant to transient symptomatic manifestations. With respect to acute stress, the concept of a "trigger" is often used to refer to acute precipitating factors for a symptomatic CAD event. Differentiation between the effects of chronic and acute stress is extremely important and is one of the major concepts that will be covered in this chapter.

Several decades of research indicate that psychosocial variables, including mental stress and personal and social-contextual factors that are related to stress, can influence the progression of CAD at various points in the disease process. The purpose of this chapter is to provide a selective, rather than comprehensive, discussion of the relationship between stress and the stages of CAD (illustrated in Figure 28.2), namely, risk factors, intermediate markers, and fatal and nonfatal cardiac events. Several recent reviews provide a comprehensive examination of the mechanisms connecting stress to these markers of CAD (Bhattacharyya & Steptoe, 2007; Fuster, Badimon, Chesebro, & Fallon, 1996; Rozanski, Blumenthal, Davidson, Saab, & Kubzansky, 2005; Strike & Steptoe, 2005). This chapter will begin by providing an overview and explanation of the progression of CAD. Next the general implications of psychosocial stress for disease risk and exacerbation will be addressed. In addition, this chapter will highlight the relationship between stress and markers of the specific stages of disease, including risk factors (smoking, obesity, cholesterol, high blood pressure), intermediate markers of disease (endothelial function and inflammation, platelet aggregation), and cardiac events (myocardial ischemia, MI, arrhythmias). Finally, a summary and evaluation of the evidence will address the state of the research today.

MARKERS OF CAD RISK AND PROGRESSION

Taken together, cardiovascular diseases are the leading cause of death in North America and in all industrialized nations (Lloyd-Jones et al., 2009). CAD refers to a set of clinical cardiovascular conditions that are the product of a long-term accumulation of plaque in the arteries. Atherosclerotic lesions begin early in life

and can be present in adolescents and young adults (Krantz, Whittaker, & Sheps, in press; Ross, 1999). If the accumulations persist over time, then clinical atherosclerosis develops (Figure 28.1). When clinical atherosclerosis becomes severe, blood flow is compromised and tissues in the heart, brain, and extremities may not receive the amount of oxygen necessary for proper function. If this lack of oxygen, or ischemia, persists, then infarction (permanent tissue damage) may occur. In the coronary arteries, atherosclerosis is particularly dangerous. Myocardial ischemia can be a frequent occurrence for individuals with CAD and is often accompanied by chest pain, called angina pectoris. It also can lead to MI, which involves death of heart tissue and can induce SCD (Ross, 1999). Clinically significant disturbances in heart rhythm, called malignant arrhythmias, are another mechanism by which atherosclerosis can lead to SCD (Krantz et al., in press; Verrier, Nearing, & Kwaku, 2005; Ziegelstein, 2007).

The development of atherosclerosis involves biochemical, immune, inflammatory, and hemodynamic processes in combination with behavioral risk factors (Krantz & McCeney, 2002; Ross, 1999). Clinical manifestations of CAD, such as MI and SCD, often constitute the final stages of this atherosclerotic process in the coronary arteries. Other consequences of CAD may develop over time as the heart and cardiovascular system compensate for reduced blood flow associated with atherosclerosis. When CAD persists, this compensatory process can lead to heart failure, which is a permanent reduction in the heart's ability to pump the necessary amount of blood required by the body. In individuals with CAD, cardiac events such as MI and SCD can be triggered by a variety of factors, including physical, psychological, and emotional stressors (Mittleman et al., 1995; Verrier & Mittleman, 1996). The concept of "triggering" and its association with acute stress will be discussed in a later section of this chapter.

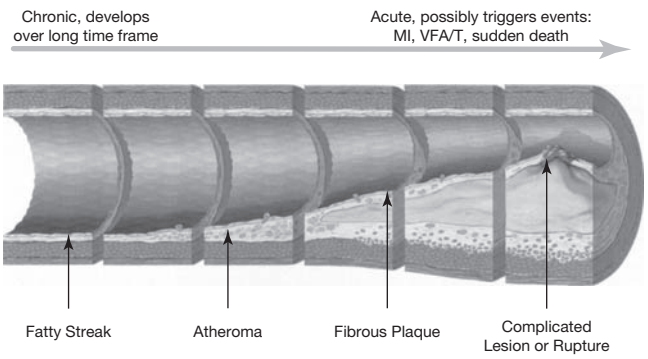

Figure 28.1 ■ *Plaque accumulation in the arteries resulting in clinical atherosclerosis.*

PATHOPHYSIOLOGY OF DISEASE AND THE RELATIONSHIP BETWEEN BEHAVIOR AND STRESS

The concept of stress is pivotal when discussing the relationship between psychosocial factors and CAD. Stress has known hemodynamic, endocrine, and immunologic concomitants that provide a basis through which it plausibly affects the development, progression, and occurrence of cardiac events in patients with CAD (Dimsdale, 2008; Holmes, Krantz, Rogers, Gottdiener, & Contrada, 2006). It is important to note that most of the physiologic changes associated with stress are a normal part of the human organism reacting to its environment and are not necessarily signs of disease risk or presence. However, when stress responses are present in exaggerated strength or duration, they become more likely to be associated with health risk and disease.

The occurrence of exaggerated or prolonged stress responses and their impact on health has received a great deal of attention in recent years, as evidenced by the other chapters in this volume. It is therefore not surprising that stress-induced hemodynamic, endocrine, and immunologic changes are central to research linking psychosocial factors to the etiology and development of CAD. Evidence shows that stressors, such as exercise, mental stress, and sexual activity, can induce myocardial ischemia, MI, or malignant arrhythmias (Kop et al., 2004; Lampert et al., 2002; Mittleman et al., 1995; Verrier & Mittleman, 1996). The link between stress and these clinical CAD events is likely mediated, in part, by stress-induced hemodynamic, endocrine, and immunologic changes. However, it is important to note that because of the multifaceted nature of both psychosocial stress and CAD, there are likely to be several additional pathways that link the two phenomena (Krantz, Glass, Contrada, & Miller, 1981). In addition to the direct effects of stress on physiology, including the above-mentioned hemodynamic, endocrine, and immunologic changes, stress may influence cardiac risk indirectly, by promoting and maintaining health-impairing habits, such as smoking and overeating, or by undermining healthy habits, such as regular physical exercise and sleep. A third pathway linking stress to cardiac outcomes involves an individual's reactions to signs and symptoms of illness, such as delay in seek medical care, nonadherence to medication prescriptions, and adoption of certain sick-role behaviors (Christopoulos, 2001; Mechanic & Volkart, 1961) that may undermine disease management.

As illustrated in Figure 28.2, the natural history of CAD progresses from a set of risk factors to a set of clinically manifested cardiac events in susceptible individuals. The following sections of this chapter address the influence of psychosocial stress on each set of disease markers presented in Figure 28.2. First, evidence will be examined that links stress to both behavioral (exercise,

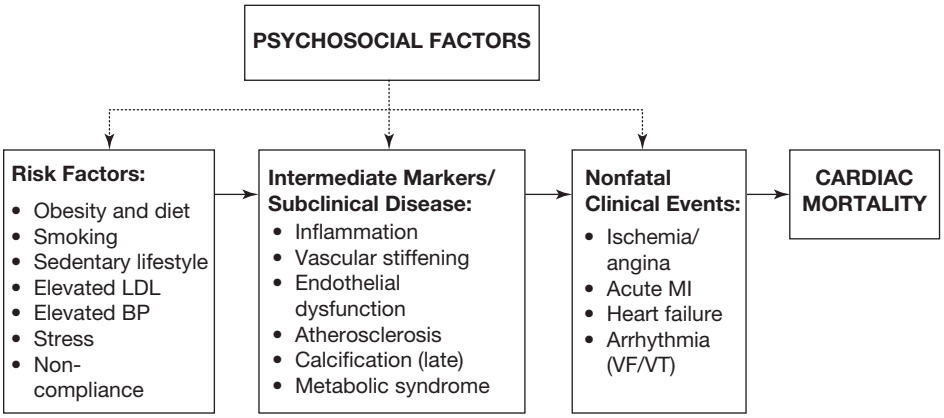

Figure 28.2 ■ *Stages of coronary artery disease progression*: Progressive Pathology, Multiple Causes, and Varied Disease Manifestations. Adapted from APA Address by Karen Matthews, 2005.

eating, smoking) and biological risk factors (cholesterol and blood pressure). The next section will discuss the relationship between stress and intermediate disease markers (endothelial function and inflammation, platelet aggregation). Finally, the evidence linking psychosocial stress to clinical events (myocardial ischemia, MI, malignant arrhythmias) will be addressed.

DOES STRESS INFLUENCE STANDARD RISK FACTORS FOR HEART DISEASE?

BEHAVIORAL RISK FACTORS

Eating and Obesity

Eating and obesity are potent modifiable risk factors for CAD. High intake of saturated fats and abdominal obesity are well-established links to the development of CAD in healthy populations (Castelli, 1990; Despres, 2006). Stress, both acute and chronic, contributes to disordered eating and obesity. Acutely stressful time periods can differentially impact eating, either contributing to increased or decreased food intake compared to nonstressful periods (Bjorntorp, 2001; Halford, 2001; McCann, Warnick, & Knopp, 1990; Ng & Jeffery, 2003; Takeda et al., 2004; Walcott-McQuigg, 1995). Furthermore, chronic stress is related to weight gain, especially abdominal obesity, which is particularly dangerous to cardiac health (Bjorntorp, 1996, 2001; Kyrou, Chrousos, & Tsigos, 2006; Takeda et al., 2004).

One of the reasons obesity is detrimental to cardiovascular health because it is often associated with the development of Type II diabetes mellitus (Despres, 2006; Lee & Aronne, 2007). Diabetes has been shown to increase the risk for CAD in healthy patients and to increase risk for cardiac events in patients with established CAD (Haffner, Lehto, Ronnemaa, Pyorala, & Laakso, 1998). Diabetes is also associated with disruption in platelet coagulation, dysregulated low-density lipoprotein (LDL) to high-density lipoprotein (HDL) cholesterol ratios, and impaired endothelial function, all of which increase the risk for CAD events (e.g., thrombotic events, infarcts) (Feng & Tofler, 1995; Verges, 2005).

Smoking

Smoking is related to CAD development and prognosis. Smoking has been shown to have negative effects on vascular health by impairing vasomotor function and contributing to atherosclerosis (Li, Srinivasan, & Berenson, 2006). There is substantial evidence that stress promotes both initiation and maintenance of smoking behavior. Chronic life stress is related to an increased prevalence of smoking in young adolescents (Baer, McLaughlin, Burnside, Pokorny, & Garmezy, 1987). In addition, exposure to a major stressor, such as a natural disaster, increases tobacco use in adults (Parslow & Jorm, 2006). Clinical studies also suggest a causal relationship between chronic stress disorders and smoking (Fu et al., 2007; Leonard et al., 2001). Though people tend to think of smoking as a way of coping with or reducing stress, smoking may actually promote or increase stress levels in smokers, most likely due to the stress of nicotine withdrawal a smoker experiences between cigarettes (Parrott, 1995). This response results in a vicious cycle of cigarette use particularly detrimental to cardiovascular health.

Lack of Exercise

Exercising has definite health benefits, whereas the lack of regular exercise constitutes a risk factor for cardiac disease (Twisk, Snel, Kemper, & van Mechelen, 1999). Individuals who lead sedentary lives have twice the risk of developing CAD. Even mild physical activity has been shown to be beneficial for individuals with preexisting conditions. Exercise can decrease symptoms of angina and attenuate the severity of exercise-induced ischemia (Miller, Balady, & Fletcher, 1997). In addition, exercise promotes psychological well-being (Miller et al., 1997), which may buffer cardiovascular reactivity to stress (Tsatsoulis & Fountoulakis, 2006). Moderate exercise can

lower resting blood pressure and heart rate, promote an anti-inflammatory environment in the body, and increase muscle sensitivity to glucocorticoids, reducing circulating levels of these hormones (Hamer, 2006).

Exercise is also important as an intervention in patients with CAD. Blumenthal et al. (2005) conducted a study in which patients with preexisting CAD were randomized to one of three conditions: stress management, exercise training, and usual care. At the end of a 16-week period, patients were tested for autonomic function (heart rate variability and baroreceptor sensitivity), endothelial dysfunction (brachial artery flow-mediated dilation), and mental stress and exercise-induced ischemia. Results indicated improvements in all three of these areas in the exercise and stress management groups compared to the usual care group (Blumenthal et al., 2005).

BIOLOGICAL RISK FACTORS

Serum Cholesterol

High cholesterol is a risk factor for CAD because it contributes to the formation of atherosclerotic plaques. LDL cholesterol is particularly deleterious because it adheres to the arterial wall. HDL cholesterol lowers the risk of heart attack by carrying LDL away from the artery walls and back to the liver from which it can be removed from the body. As such, the best measure of CAD risk reflects the relative proportions of LDL and HDL cholesterol (Wilson, 1994). Cholesterol may reflect psychosocial stress, but the evidence is still inconclusive. For example, clinical research suggests that posttraumatic stress disorder (PTSD) may be related to high total cholesterol. However, depression and certain personality disorders, which are also consistently associated with chronic stress, have been found to be associated with low cholesterol (Jakovljevic, Reiner, & Milicic, 2007).

Other studies have demonstrated an association between work stress (a form of chronic stress) and cholesterol. One Swedish study showed that workers exposed to highly controlled and socially isolated work environments had higher serum lipids than those who felt they received social support at work (Bernin, Theorell, & Sandberg, 2001). Another study, conducted in peri-menopausal women, also suggested that greater job strain was related to an unhealthy lipid profile (Evolahti, Hultcrantz, & Collins, 2009). Despite recent research efforts, evidence on the nature of the relationship between cholesterol and stress-related psychological constructs remains equivocal.

Blood Pressure

High blood pressure is a key risk factor for CAD. Hypertension is a risk factor for CAD as well as for stroke and kidney disease. Elevated blood pressure causes strain on the vasculature, resulting in an increase in shear stress and thereby promoting atherosclerotic plaque formation. Chronically elevated blood pressure reflects an increase in total vascular resistance, which compromises the arteries' ability to respond to changes in blood flow demands. There is evidence to suggest that highly stressful events may promote the subsequent development of hypertension. For example, the siege of Leningrad appears to have produced hypertension even 20 years later in the individuals exposed to that trauma (Sparen et al., 2004). A recent systematic review of 82 studies determined that chronic stress, and not acute stress, leads to an increased risk for hypertension (Sparrenberger et al., 2009). Further studies comparing the effects of acute and chronic stress on hypertension risk are necessary. It seems likely that in susceptible individuals, stress-induced hypertension results from neurohormonal factors that promote vascular hypertrophy (Zimmerman & Frohlich, 1990).

Section Summary

Stress appears to promote behaviors that increase risk for CAD. Stress also may play a role in the development of biological risk factors, such as cholesterol and blood pressure levels. These risk factors, in turn, exert deleterious effects on elements of the cardiovascular system, such as endothelial function and cardiac output, which are involved in atherogenesis and clinical cardiac events. As will be discussed below, psychological stress also exerts a direct influence on these processes. It is also likely that stress interacts with risk factors in producing structural and hemodynamic processes associated with CAD.

DOES STRESS INFLUENCE INTERMEDIATE/ SUBCLINICAL MARKERS OF CAD?

Intermediate markers of disease are often used in cardiovascular research to evaluate disease risk and progression. These markers reflect the progression of disease in terms of different mechanisms by which CAD develops. Identifying these markers enables researchers to pinpoint areas for the development of interventions to reduce CAD risk. In the psychosocial field, identification of CAD markers that are associated with stress strengthens the claim that stress has a role in the mechanism of CAD development and provides clues as to how stress reduction interventions might improve cardiovascular risk profiles.

Platelet Aggregation

It was previously thought that platelet aggregation was only involved in the later stages of atherosclerosis, but recent evidence suggests that it has a role in plaque formation even in the early stages (see review by Brydon, Magid, & Steptoe, 2006). Evidence suggests that psychosocial stress can influence hemostasis and thrombosis, which are clotting processes that may lead to cardiac events.

Acute stress has traditionally demonstrated inconsistent results in triggering platelet aggregation and coagulation. However, newer methods of measuring platelet activation have shown more encouraging results. For example, Steptoe et al. (2003) used a novel measurement of platelet-leukocyte aggregation in response to standard stress tasks (Stroop and mirror tracing tasks) in healthy men. Blood samples were taken at baseline, immediately posttask, and then 30 and 75 minutes posttask. The stressors produced significant increases in platelet-leukocyte aggregation (Steptoe et al., 2003). Therefore, acute stress was shown to alter platelet aggregation, such that greater clotting would be expected.

In another study, a group of accountants were followed during a period of high work demand (i.e., end of the fiscal year) and a period of low work demand. During the period of high work demand, agonist-stimulated platelet aggregation was increased (Frimerman, Miller, Laniado, & Keren, 1997). In cardiac patients, the same rise in platelet-leukocyte aggregation is observed as in healthy individuals, but the effect is more prolonged (Strike et al., 2004). Platelet activation has also been correlated with hostility in cardiac patients, but not in healthy controls, offering a possible mechanism through which hostility confers cardiac risk (Markovitz, 1998).

Results from enduring psychosocial factors including chronic stress have traditionally been more consistent. Individuals with depression, hostility, or work stress have a more activated platelet profile (Brydon et al., 2006). Feelings of low control (a marker of stress) are associated with high levels of fibrinogen, a blood clotting factor that predicts cardiovascular diseases (Brunner et al., 1996). In addition, men with low socioeconomic status (SES), which may be considered a chronic stressor, have elevated levels of platelet-leukocyte aggregation at rest. However, the response of platelet-leukocyte aggregation at peak stress is the same between low- and high-SES individuals (Steptoe et al., 2003).

Endothelial Function

The endothelium is the lining on the inside of blood vessels. Through interaction with various chemical messengers (e.g., cytokines) the endothelium controls vascular dilation and constriction. Some of the cytokines that control vasodilation and constriction also contribute to the creation of a proinflammatory state in the vascular system. These proinflammatory cytokines make vascular constriction and dilation more difficult and affect blood flow through the vessel. Atherosclerotic plaque impairs the endothelial function of blood vessels and increases the risk of ischemia in the surrounding tissues.

Stress influences the vasomotor responses of the arteries. A landmark study by Yeung et al. (1991) demonstrated that patients referred for chest pain and other symptoms demonstrated differences in artery constriction after mental stress based on the degree of artery stenosis (amount of plaque built up in the artery). Artery segments with significant stenosis showed 24% constriction, those segments classified as irregular had 9% constriction, and smooth segments showed no significant difference (Yeung et al., 1991). Other studies have corroborated these finding. For example, a study in healthy individuals showed impairment in endothelial function up to an hour and a half after mental stress (Ghiadoni et al., 2000). In addition, chronic stress is thought to be a mechanism through which depression, low SES, work stress, and lack of social support negatively impact endothelial function (see reviews by Strike & Steptoe, 2004; Vanhoutte, 1997).

Inflammation and Atherosclerosis

Research suggests that the immune system plays an important role in CAD. There is substantial evidence linking the etiology and progression of CAD to disease processes that involve inflammatory activity (a key aspect of the immune system) (Ross, 1999). The response to injury hypothesis suggests that many of the CAD risk factors cause some type of endothelial dysfunction resulting in injury to the lining of the blood vessels. In response to this injury, the immune system and, in particular, inflammatory processes become activated. Over time, the continued activation of the immune response leads to the progression of atherosclerotic lesions. Various markers of inflammation, such as C-reactive protein (CRP) and interleukin-6 (IL-6), have been used to predict CAD events in at-risk populations prospectively (Ridker, Rifai, Stampfer, & Hennekens, 2000). Research has shown that proinflammatory cytokines are released in response to mental stress (Bierhaus, Humpert, & Nawroth, 2006). Therefore, one of the mechanisms through which psychosocial stress may contribute to the development of atherosclerosis is the immune/inflammatory response (Black & Garbutt, 2002; Brydon et al., 2006; Ellins et al., 2008).

Inflammatory processes provide a link between psychosocial factors, such as depression, low SES, and coronary disease. Inflammatory markers, such as CRP and IL-6, are elevated in depressed patients (Appels, Bar, Bar, Bruggeman, & de Baets, 2000; Maes, 1999). CRP is also higher in low-SES versus high-SES populations (Owen, Poulton, Hay, Mohamed-Ali, & Steptoe, 2003). One recent study suggests that CRP is not a causal mechanism for CAD but rather provides information about underlying immune and inflammatory responses (Nordestgaard & Zacho, 2009). Elevated levels of these inflammatory markers have been linked to the progression of CAD and CAD events, which suggests a possible mechanism for the relationship between depression and coronary heart disease (Licinio & Wong, 1999; Lippi, Montagnana, Favaloro, & Franchini, 2009).

Section Summary

Although there are inconsistencies in the research, results generally point toward an association between

psychosocial stress and intermediate and subclinical markers of disease both in healthy populations and in populations with or at-risk for CAD. This link can be strengthened by more methodologically rigorous studies that examine a specific rather than general relationship between CAD markers and psychosocial stress. Moreover, the research can be improved by more stringent measurement or definition of psychosocial constructs, such as depression, work stress, and low SES. Having stronger evidence regarding intermediate markers of disease is important in understanding and intervening in the CAD process before clinical disease develops. Knowledge concerning the role of stress in influencing these markers increases the ability to intervene effectively to control and potentially even reverse the disease process.

DOES STRESS INFLUENCE THE OCCURRENCE OF FATAL/NONFATAL CLINICAL EVENTS IN CAD?

ACUTE STRESS AS A TRIGGER FOR MYOCARDIAL ISCHEMIA AND MI

Epidemiological Studies

There is a considerable amount of evidence that supports the notion that acute stress triggers cardiac events. Cardiac events such as ischemia do not occur randomly in daily life but are likely to be preceded by episodes of physical or mental stress (Krantz, Kop, Santiago, & Gottdiener, 1996; Muller, Ludmer et al., 1987). Acute MI has also been shown to be triggered by transient mental stress, such as an instance of anger (Mittleman et al., 1995). These results have been supported in controlled observational studies that used a case-crossover design to determine whether episodes of anger triggered an MI by comparing to a control period on a day when there were no events (Muller, Abela, Nesto, & Tofler, 1994). At least three studies have found that risk of daily life myocardial ischemia was elevated during periods of daily life mental stress (Barry et al., 1988; Gabbay et al., 1996; Gullette et al., 1997). Instances of intense emotion such as anger have also been shown to lead to a twofold increase in the probability of MI in the 2 hours following the emotional experience in a group of individuals with prior MI (Mittleman et al., 1995).

The daily stressors discussed so far may be considered relatively mild. However, there are also a number of epidemiological studies that examined the effects of more severe stressors on cardiac events. Studies of natural disasters show consistent associations with increases in ischemia and MI. For example, during the 1994 Northridge earthquake, which measured 6.5 on the Richter scale, acute MI admissions in critical care units increased by a factor of 2.4 in the week after the earthquake compared to the week before the disaster. The earthquake resulted in a 35% increase in mortality due to CAD (Leor & Kloner, 1996; Leor, Poole, & Kloner, 1996). Self-reports obtained within 1 hour of the event seemed to suggest that this finding was attributable to psychosocial stress and not to physical exertion related to the earthquake.

Furthermore, the evidence from nonnatural (i.e., man-made) disasters, such as war, is generally consistent with the psychosocial hypothesis. For example, during the initial air strikes of the 1991 Gulf War, there were increases in MI and SCD in the Tel Aviv area (Meisel et al., 1991). These associations remained significant when controlling for rates of acute MI and SCD during the same week in the previous year.

Laboratory Studies

Though the evidence from studies of natural and man-made disasters is substantial, epidemiological research does not provide the control necessary to conclude that there is a causal relationship between stress and cardiac events. Therefore, laboratory studies using more rigorous methodology have been devised to test the hypothesis that stress triggers cardiac events. In particular, laboratory research has employed structured mental stress tests to provoke myocardial ischemia in patients with pre-existing CAD. These studies have also used a variety of techniques (e.g., radionuclide or cardiac ultrasound imaging, ST-segment depression) to detect the presence and severity of mental stress-induced ischemia. A recent systematic review has estimated that mental stress can provoke ischemia in 30–50% of patients with CAD (Strike & Steptoe, 2003).

Mental stress has been shown to be a trigger for cardiac events in a subset of CAD patients who are susceptible (Gabbay et al., 1996). Laboratory studies have provided ample evidence that mental stress can induce myocardial ischemia (see review by Strike & Steptoe, 2003). This result is consistent across a variety of stressor tasks and ischemia measurements, although some measures produce more consistent associations. For example, stressors such as public speaking or the mirror-trace task may be more effective at producing mental stress ischemia than stressors like mental arithmetic (Blumenthal et al., 1995; Jain et al., 2001). An interesting finding regarding mental stress-induced ischemia is that it generally occurs without the typical chest pain or pain radiating down the arm that is associated with exercise-induced ischemia (Deanfield et al. 1984; Modena et al., 1989). Therefore, episodes of ischemia may occur in response to stressors during daily life without the patient's knowledge.

Mechanisms underlying the association of stress and ischemia may be related to increased vascular resistance provoked by mental stress, which then leads to a reduction of blood flow to the heart and ischemia (Goldberg et al., 1996; Jain et al., 1998). In addition, endothelial dysfunction during mental stress causes coronary constriction (Kop et al., 2001; Lacy et al., 1995; Yeung et al., 1991), which reduces blood flow and increases the risk for an

ischemic event. Increases in circulating catecholamines, shown to occur in response to stressors, might also explain the association between mental stress and ischemia given their possible role in reducing ejection fraction (see review by Strike & Steptoe, 2003). However, the literature on catecholamines as a mechanism for mental stress-induced ischemia is inconsistent. Although studies have shown a relationship between increased catecholamines and ischemia (Yoshida et al., 1999), there is also evidence that an increase in catecholamine levels is not related to mental stress-induced ischemia (Goldberg et al., 1996).

The occurrence of mental stress-induced ischemia is also of prognostic value in patients with CAD. One prospective study of 126 patients with stable angina who underwent mental stress and exercise stress testing showed that mental stress ischemia was associated with a threefold increased risk of subsequent clinical events (e.g., cardiac death, MI) over a follow-up of 3.2 years (Jiang et al., 1996). This association remained significant after controlling for a variety of biological risk factors.

Acute Stress and Emotional Triggers of Malignant Arrhythmias

The autonomic nervous system changes that are produced by mental stress may predispose patients with CAD to lethal arrhythmias through effects on cardiac neural transmission (Dakak, Quyyumi, Eisenhofer, Goldstein, & Cannon, 1995). Most of the research concerning the effects of stress on the development of arrhythmias seeks to understand such arrhythmic triggers. A landmark study by Verrier and Lown (1984) showed that stress provokes arrhythmia in dogs and that dogs with an occluded coronary artery that were exposed to a stressor had a lower threshold for experiencing a stress-induced arrhythmia (Verrier & Lown, 1984).

Epidemiologic studies in humans suggest that acute stress and intense emotions such as anger can act as potent triggers of MI and SCD (see review by Dimsdale, 2008; Holmes et al., 2006; Strike & Steptoe, 2005). Emerging evidence from laboratory and ambulatory monitoring studies demonstrates that mental stress and negative emotions are associated with the onset of malignant arrhythmias and elevation in markers of arrhythmic vulnerability. For example, Lampert and colleagues (2000) found that mental stress affected ventricular tachycardia (VT), a dangerous arrhythmia that originates in the ventricles. Mental stress changed the duration and termination of VT and also created ischemia. The 10 patients tested in that study underwent the mental arithmetic and anger recall stressors. VT speed increased in five patients and VT was more difficult to terminate in five patients during mental stress, with four patients requiring defibrillator therapy (Lampert, Jain, Burg, Batsford, & McPherson, 2000). These findings suggest that acute mental stress may facilitate lethal ventricular arrhythmias and may be a mechanism linking stress and CAD.

Natural (i.e., earthquake) and man-made (i.e., war) stressors may trigger arrhythmias in certain populations. Regarding man-made disasters, there is evidence of that an increase in malignant arrhythmias occurred in NYC during the aftermath of the 9/11 terrorist attacks (Shedd et al., 2004; Steinberg et al., 2004). However, subsequent, better controlled research failed to replicate these findings (Chi, Poole, Kandefer, & Kloner, 2003; Chi, Speakman, Poole, Kandefer, & Kloner, 2003). This type of research is limited by difficulties inherent in controlling all of the relevant variables, and so the true relationship between man-made disasters and CAD outcomes remains unclear.

Similarly, the epidemiologic evidence for the effects of natural disasters on arrhythmias is complex and often suggests that factors other than mental stress may account for the observed associations. For example, a study was conducted using data collected from 12 patients who were undergoing ambulatory Holter monitoring at the time of the 1999 earthquake in Taiwan. The researchers observed an increase in sympathetic activity in the minutes after the earthquake (Lin et al., 2001). However, the psychosocial effects might have been due to or exacerbated by the fact that the earthquake was in the early hours of the morning. Autonomic nervous system activity shows a diurnal pattern, with greater activity shown in the morning versus the afternoon and evening (Feng & Tofler, 1995; Muller, Tofler, Willich, & Stone, 1987). One study of an earthquake that happened later in the day (5 pm) showed no relationship between the quake and any CAD events (Brown, 1999).

Clinical laboratory studies shed further light on the ability of acute stress to trigger arrhythmias. For example, one study examined daily life triggers of arrhythmias, measured by the number of therapeutic shocks administered to terminate malignant arrhythmias in patients with implantable cardioverter-defibrillators (ICDs). Patients were 1.83 times more likely to report experiencing high levels of anger in the 15 minutes preceding the shock compared to a control period 1 week later (Lampert et al., 2002). In addition, individuals with trait anger might be particularly susceptible to the triggering effects of acute anger (Stopper et al., 2007). Burg et al. (2004) found that patients with high trait anger had more frequent acute anger episodes that were then followed by ICD discharge. Similar results were found in patients with high trait anxiety when shocks were preceded by an acute anxiety episode (Burg, Lampert, Joska, Batsford, & Jain, 2004).

Our research group recently conducted a study of the effects of acute stress on arrhythmic vulnerability in ICD patients with CAD and known vulnerability to arrhythmias (Kop et al., 2004). T-wave alternans, a beat-to-beat alteration in the slope of the ECG T wave, is a marker of vulnerability to malignant arrhythmias. Patients with ICDs and matched controls were subjected to laboratory-induced anger and distress through the anger

recall and mental arithmetic tasks. After correcting for heart rate increases, the T-wave alternans effect was more pronounced with mental stress compared to exercise in this group of patients (Kop et al., 2004). Furthermore, ICD patients showed a higher level of stress-induced T-wave alternans than matched healthy controls. These results were replicated in another recent study demonstrating an association between anger, anger-induced increases in catecholamines, and increased T-wave alternans (Lampert et al., 2007). These studies further support a link between stress and malignant arrhythmias. In addition, the data are consistent with human and animal research that demonstrates that emotional arousal can induce ventricular arrhythmias and exacerbate latent arrhythmic vulnerability (Coumel & Leenhardt, 1991; Verrier & Mittleman, 1996; Verrier et al., 2005).

CHRONIC STRESS, MYOCARDIAL ISCHEMIA, AND MI

Epidemiologic Studies

Prospective epidemiologic studies have observed that exposure to chronic stress is predictive of subsequent CAD. For example, the largest such study, INTERHEART, examined almost 30,000 people in more than 50 countries and demonstrated that higher scores on a simple measure of chronic stress more than doubled the risk of MI (Yusuf et al., 2004). A further analysis of the same data used a case-control comparison of psychosocial factors in individuals who suffered MI versus those who did not. Individuals who suffered an MI reported more work stress, financial stress, and stressful life events in the year prior to their MI. This effect held across gender, countries, and ethnic groups, emphasizing the importance of psychosocial stress in the disease process within various groups (Rosengren et al., 2004).

Work Stress

Estimates have placed the prevalence of individuals experiencing work stress between 10% and 40%, with approximately 30% of these individuals suffering from severe chronic psychosocial stress (Peter & Siegrist, 2000). Work stress in behavioral research often refers to one of two models (Strike & Steptoe, 2004). The first is the job strain model, which is the idea of a job that places high psychological demands on the worker but offers little control over these demands (Karasek, 1979). A typical example would be an overworked secretary. The second model is the effort-reward imbalance model and refers to the notion that work stress increases when the effort put into a job is not reinforced by enough reward (Siegrist, 1996).

Recent reviews have concluded that there is support for the notion of an association between work stress and the development of CAD, although there are some inconsistencies. For example, results from the Whitehall II study demonstrated that self-reports of low control at work in civil servants predict CAD development in a dose-response manner (Bosma et al., 1997). However, there are also longitudinal studies that counter these findings. In particular, one study found that job strain was not related to prevalence or severity of CAD or cardiac events during the follow-up period (Hlatky et al., 1995).

A review of 13 prospective studies found that all but three showed moderate to high associations between work stress and CAD with a relative risk of more than 1.5 (Kuper, Marmot, & Hemingway, 2002). For example, work stress has been associated with MI in men (Bosma, Peter, Siegrist, & Marmot, 1998). In addition, recent evidence has shown that the effort-reward imbalance model seems to have more predictive utility of the two work stress models (Head et al., 2007). Kivimaki and colleagues (2002) compared the two models and found that high job strain had an odds ratio of 2.2 for cardiac-related death, whereas effort-reward imbalance had an odds ratio of 2.4 (Kivimaki et al., 2002).

Marital Stress

It has been suggested that work stress is less potent in women than in men and that women might be more susceptible to a different type of chronic stress, namely, marital stress. Marital stress predicts depression in women and is associated with a variety of negative psychosocial factors (Strike & Steptoe, 2004). Marital stress has been associated with poorer prognosis in women with preexisting CAD (Balog et al., 2003; Orth-Gomer et al., 2000). This CAD risk is particularly increased in women with marital stress and depression, low SES, and low social support (Orth-Gomer et al., 2000). In addition, women with both marital and work stress have five times higher risk for CAD than women with neither type of chronic stress (Orth-Gomer, Moser, Blom, Wamala, & Schenck-Gustafsson, 1997).

A related concept that has received attention is that of caregiver stress (Haley, Roth, Howard, & Safford, 2010). Results from the Nurses Health Study indicated that women who had to care for an ill spouse for 9 or more hours per week had a significantly higher risk for new CAD. This was independent of a variety of covariates, including age, smoking, and hypertension (Lee, Colditz, Berkman, & Kawachi, 2003). However, other studies have not consistently replicated these results (Haley et al., 2010, see review by Strike & Steptoe, 2004).

Socioeconomic Status

Heart disease is inversely related to SES, with those of low SES more likely to suffer from CAD. This relationship is only partially accounted for by factors associated with the lower SES condition, such as poor access

to health care, poor nutrition, poor social support, and an increased prevalence of behavioral risk factors for CAD (Krantz, Sheps, Carney, & Natelson, 2000). Chronic stress also seems to link SES with CAD. For example, one study showed that living alone led to a nearly doubled risk of recurrent MI. Also, single CAD patients as well as patients with low SES (measured by household income) were at increased risk for cardiac-related death over a 5-year follow-up period (Williams et al., 1992).

Stress-induced physiological reactivity has been proposed to account for some of the association between psychosocial stress and cardiac events. A recent study has suggested that individuals from a lower SES have impaired cardiovascular recovery from stress tasks (Steptoe et al., 2002). The authors suggested that this delay in recovery may reflect chronically elevated stress levels, known as high allostatic load, in low-SES individuals (Kubzansky, Kawachi, & Sparrow, 1999; Steptoe et al., 2002). This finding confirms evidence from a Taiwanese sample proposing that individuals from a lower social position have more difficulty recovering from stressful life events (Glei, Goldman, Chuang, & Weinstein, 2007).

STRESS REACTIVITY AND CAD

An important concept to consider in this context is "stress reactivity." Stress reactivity refers to the stable predisposition of some individuals to have particularly volatile cardiovascular responses to stressful stimuli, such as greater heart rate or blood pressure increases than would normally be expected (Krantz & Manuck, 1984). Mental stress produces changes in blood pressure and heart rate in most individuals. These hemodynamic changes usually represent an adaptive process that increases cardiac output and peripheral blood flow, thereby preparing the organism for vigorous muscle activity ("fight-or-flight"). However, if the magnitude of these changes is very large and metabolically inappropriate (e.g., the threat is psychological rather than physical), pathological processes may be induced. For example, an increase in shear stress on blood vessels produced in response to mental stress could contribute to the formation of atherosclerotic plaque (Treiber et al., 2003).

In the past two decades, research has suggested that individuals displaying especially pronounced response to stressors are predisposed to develop CAD (Chida, Hamer, & Steptoe, 2008). There is evidence that individuals who have high levels of stress reactivity may have greater long-term risk of developing hypertension (Cinciripini, 1986). Even more compelling evidence is the fact that certain stress reduction programs have demonstrated substantial reductions in blood pressure (Blumenthal et al., 2005). Other research in stress reactivity suggests that men with exaggerated blood pressure responses during mental stress are more susceptible to carotid atherosclerosis (Jennings et al., 2004; Kamarck et al., 1997). Furthermore, a longitudinal study of 2,816 healthy women showed that increased blood pressure reactivity to a video game stress task predicted risk of coronary calcification 13 years later (Matthews, Zhu, Tucker, & Whooley, 2006).

Research in both animals and humans on the relationship between allostatic load and cardiovascular markers has suggested that a dysregulated HPA axis promotes inappropriate heart rate and blood pressure responses to stress (Al'Absi et al., 1997). In a study investigating the association between chronic stress and job strain, participants with high levels of job strain experienced elevated blood pressure responses to a laboratory task that was perceived as uncontrollable (Steptoe, Cropley, & Joekes, 1999). This change in blood pressure persisted even after the task had ended. This effect was not found with a similar controllable task. The researchers suggested the failure to recover from stress was a manifestation of allostatic load in these chronically stressed individuals (Steptoe et al., 1999).

After the development of atherosclerosis, hemodynamic reactivity to mental stress can be predictive of cardiac vulnerability. Individuals with preexisting CAD who have high blood pressure responses to acute stress are more likely to have mental stress-induced ischemia (Blumenthal et al., 1995; Goldberg et al., 1996; Krantz et al., 1991) and show worsened prognosis (Krantz et al., 1999; Manuck, Olsson, Hjemdahl, & Rehnqvist, 1992). A striking example comes from a study that followed a group of men for 23 years after administration of a cold pressor task that involves holding the arm under ice water. It was found that the magnitude of diastolic blood pressure changes to this task predicted future heart disease (Keys et al., 1971). However, a similar study conducted more recently failed to replicate this finding (Coresh, Klag, Mead, Liang, & Whelton, 1992). The authors speculated that the increased risk found in Keys et al. (1971) may have been due to preexisting atherosclerosis in that sample, which increased the blood pressure elevations to stress. There are also questions about the relevance of the cold pressor task to psychosocially induced reactivity.

Studies have found that heightened hemodynamic activity is associated with susceptibility to mental stress-induced ischemia as reflected in left ventricular dysfunction (Blumenthal et al., 1995; Goldberg et al., 1996). These hemodynamic responses are modified by a number of factors. First, the hemodynamic responses to mental stress in depressed individuals may be blunted (York et al., 2007). Also, individuals with more advanced heart disease, such as heart failure, may have blood pressure reactivity responses that are unrelated to mental stress-induced ischemia (Holmes et al., 2007). Finally, there has been some research to suggest that stress reactivity might be more pronounced in postmenopausal women than in premenopausal women and men and thus may be a mechanism through which estrogen deficiency contributes to CAD risk (Bairey Merz et al., 1998).

PSYCHOSOCIAL TRAITS ASSOCIATED WITH CHRONIC STRESS AND CAD

Evidence suggests that psychosocial traits that influence responses to stress, including emotional conditions such as depression and personality traits such as hostility, are associated with both chronic stress and CAD. Depression is predictive both of CAD in healthy individuals and of symptomatic events after a diagnosis of CAD (see review by Strike & Steptoe, 2004). Depression may contribute to CAD risk and development through several pathways. There is evidence to suggest that depression produces inflammation, which may lead to atherosclerosis and CAD. Depression could also be a manifestation of chronic stress in the individual's life. In addition, depression promotes unhealthy behavior, such as smoking and overeating.

Trait anger and hostility have also been associated with increased risk for symptomatic CAD manifestations (see review by Strike & Steptoe, 2004). Prospective studies have found that anger increases the risk for these events two- to threefold (Kawachi, Sparrow, Spiro, Vokonas, & Weiss, 1996). Anger may also be a factor in inducing hypertension and thus increasing underlying risk for CAD (Williams, Nieto, Sanford, & Tyroler, 2001). This work is a major area of study for health psychology researchers and much has been published in regards to these factors (Lesperance & Frasure-Smith, 2000; Razzini et al., 2008; Smith, Glazer, Ruiz, & Gallo, 2004).

Section Summary

There is a substantial amount of evidence linking stress and CAD events in epidemiological studies, laboratory studies, and everyday life. The relationships are complex, with certain stressors showing greater potency in particular populations or for specific types of cardiac events. The different ways in which stress is conceptualized and measured, combined with the variety of CAD endpoints used within the literature, might cause the associations between stress and CAD events to appear inconsistent. There is a great deal of evidence relating stress to CAD, but future research should focus on the inconsistencies in the literature in an attempt to address the criticisms of the field.

SUMMARY AND EVALUATION OF THE EVIDENCE

The goal of this chapter has been to provide a selective overview of research evidence linking acute and chronic stress to the development of CAD and to identify gaps in the literature in need of further investigation. In the studies reviewed, different psychosocial constructs are defined as "stress," and many assessment instruments are employed in different populations. As portrayed in Figure 28.2, evidence suggests that stress can impact the CAD disease process at different points in its development. The numerous effects of stress at various points in the disease process and the multiple measures used in research make this area of investigation complex and also contribute to inconsistencies in the literature. In addition to problems of definition and measurement of stress, many of the relationships linking stress to CAD may be bidirectional or even multidirectional.

There are several gaps in the literature linking stress to the development of CAD that should be addressed by additional, tightly controlled studies. For example, risk factors and subclinical markers of disease are often inconclusively linked to measures of stress. These inconsistencies may be related to the inadequacy of older measurement techniques for assessing certain subclinical markers such as endothelial dysfunction or subclinical atherosclerosis (Brydon et al., 2006). Physiological changes caused by mental stress may interact with biological risk factors for CAD, thereby contributing to the advancement of intermediate disease markers, such as atherosclerosis. Mental stress may also act directly on these intermediate disease markers, resulting in a complex multidirectional relationship between stress and CAD.

Another area in need of further investigation is assessment of the effects of stress-reduction methods to reduce CAD risk and progression. To date, this research has been at best inconsistent. Several clinical trials assessing whether stress-reduction methods are effective in reducing CAD progression have been implemented with encouraging results (Blumenthal et al., 1997, 2005; Linden, Stossel, & Maurice, 1996). However, there have also been inconclusive results in intervention trials designed to improve CAD risk and outcomes by treating psychosocial variables, especially depression (Berkman et al., 2003). These inconsistent results highlight the difficulties of studying psychosocial factors and point out areas where additional research is needed.

That being said, studies like INTERHEART and others are raising awareness about the importance of psychosocial factors in the development of heart disease. Newer, more rigorous methodological techniques need to be developed and utilized to allow psychosocial researchers to delineate the many pathways linking stress and heart disease. This next generation of research should provide the evidence necessary to claim a causal relationship between stress and heart disease.

NOTES

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29 Stress and Cardiometabolic Syndrome

Larry Brooks, Philip McCabe, and Neil Schneiderman

INTRODUCTION

Selye (1956) used the term *stress* to represent the effects of anything that threatens homeostasis. The perceived threat to an organism is referred to as the *stressor* and the response to the stressor is called the *stress response*. Although stress responses evolved as adaptive processes, Selye observed that prolonged stress responses may have adverse consequences resulting in disease. In physiological terms, stressors are sometimes defined as stimuli that activate the sympathetic nervous system (SNS) and the hypothalamic–pituitary–adrenocortical (HPAC) axis, whose effects support an organism's efforts to deal with threat (Maier & Watkins, 1998). Psychosocial stressors associated with increases in SNS and HPAC activity have been shown to lead to the development of cardiovascular disease (CVD; Schneiderman, 1983) and, in turn, lead to exaggerated vascular responses to SNS stimuli, which, if continued, may lead to further endothelial injury (Strawn et al., 1991).

Prolonged stress activities of the SNS and HPAC axis can lead to insulin resistance (Schneiderman & Skyler, 1996). Insulin resistance, in turn, has been related to inflammatory markers such as interleukin-6 (IL-6) and C-reactive protein (CRP; Klaus et al., 2009). These inflammatory cytokines are known to impair endothelial function. Stress can also lead to overeating in both animals (Lemieux & Coe, 1995) and humans (Rodin & Wing, 1988), thereby further stimulating the HPAC and SNS axis (Björntorp, 1992) as well as causing obesity. Visceral obesity is related to insulin resistance and corticosteroid activity as well as to elevated cytokines IL-6 and tumor necrosis factor alpha (TNFα; Orban, Remaley, Sampson, Trajanoski, & Chrousos, 1999). It should be noted that IL-6 is a major adipocyte-signaling molecule. Between 25% and 30% of IL-6 is released from visceral fat stores, subsequent to SNS activation (Pradhan et al., 2001). Thus, there is an important interaction between stress and obesity in the development of CVD. Stress hormones, obesity, insulin metabolism, and the release of inflammatory cytokines, all appear to play an important role in the development of CVD.

During the past two decades, there has been worldwide recognition of an obesity epidemic that is associated with an increased prevalence of Type 2 diabetes, cardiometabolic syndrome (CMS), and CVD. The CMS consists of a cluster of symptoms that includes insulin resistance, glucose intolerance, central obesity, hypertension, and dyslipidemia. This syndrome is associated with an approximately threefold increase in the risk of Type 2 diabetes (Lorenzo et al., 2003), a twofold increased risk of CVD events and mortality (Malik et al., 2004), and a 40% increased risk of all-cause mortality (Hu et al., 2004). Given the strong relationships between stress, stress hormones, and CMS variables, those relationships will serve as the focus of this chapter

CARDIOMETABOLIC SYNDROME

The CMS consists of multiple, correlated risk factors of metabolic origin that are involved in the development of atherosclerotic CVD. These consist of dyslipidemic factors, including elevated triglycerides and apolipoprotein B, small LDL particles, and low HDL cholesterol concentrations. The syndrome also includes elevated blood pressure, elevated plasma glucose, insulin resistance, obesity, prothrombotic variables, and proinflammatory processes.

Specific diagnostic criteria for CMS have been established by several organizations. Two of the most commonly referenced include the World Health Organization (WHO, 1999) and the National Cholesterol Education Program Adult Treatment Panel III (Expert Panel on Detection and Evaluation, and Treatment of High Blood Cholesterol in Adults, 2001). The WHO diagnosis of CMS requires the presence of insulin resistance or impaired glucose regulation and at least two risk factors, including obesity, hypertension, dyslipidemia, and microalbuminuria. Similarly, the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) diagnosis includes the presence of at least three risk factors (obesity, hypertension, dyslipidemia, raised fasting glucose) but does not include a measure of insulin resistance. However, insulin resistance and elevated blood glucose are closely related (Klaus et al., 2009). Shen et al. (2006) examined the factor structure of variables

implicated in CMS, using confirmatory factor analysis on data from normal healthy adult participants in the Miami Community Health Study. In a hierarchical 4-factor model, including insulin resistance, obesity, lipids, and blood pressure, with CMS as the overarching factor, the proposed factor structure was well supported (comparative fit index = 0.97) and similar between men and women and across multiple ethnic groups.

Estimations of the prevalence of CMS vary across countries, gender, and ethnicity. Findings from the third National Health and Nutrition Examination Survey (NHANES III) in the United States indicated that the overall age-adjusted prevalence of CMS was 24% between 1988 and 1994 (Ford et al., 2002). Mexican Americans had the highest prevalence (32%), and White Americans had a more modest prevalence (24%). The age-adjusted prevalence was similar between genders (~24%), but there were gender differences within ethnic groups. Among Mexican Americans and African Americans, women had a significantly higher prevalence than men. Applying the ATP III criteria to a later NHANES study conducted between 1999 and 2002, approximately 35% of Americans met criteria for CMS (Ford, 2005a).

The CMS is now viewed as a precursor to CVD and Type 2 diabetes (Rader, 2007). In addition, the risk factors for CVD and the criteria for CMS share considerable overlap. The primary traditional risk factors for CVD are elevated LDL cholesterol, cigarette smoking, hypertension, low HDL cholesterol, family history of early CVD, and age (ATP III, 2001). The presence of CMS increases the risk of mortality after adjusting for these traditional cardiovascular risk factors (Lakka et al., 2002). Although CVD is generally recognized as an inflammatory disorder with an oxidative stress component, similar hypotheses have been developed for Type 2 diabetes (Eriksson, 2007; Meigs et al., 2007; Shoelson et al., 2006). Obesity has been characterized as a low-grade inflammatory state, and it has been hypothesized that oxidative events in the pancreas and adipose tissue contribute to the dysregulation of the adipokine- and insulin-signaling pathways. The CMS has come to be viewed as a precursor to Type 2 diabetes and CVD. Further highlighting the overlap between these disorders, both Type 2 diabetes and CMS convey a twofold risk for CAD mortality (Malik et al., 2004).

FREE FATTY ACIDS

All cells contain fatty acids, as they are used to form the phospholipids bilayers of cell membranes. Fatty acids are more relevant to energy homeostasis and one of the body's main sources of fuel. In a homeostatic intracellular environment, the quantity of fatty acids that each cell contains equals its reserve for the phospholipid bilayer plus whatever fatty acids are needed to undergo oxidation to meet the metabolic needs of the cell. Adipose tissue is the primary storage site of free fatty acids (FFAs), which are combined with glycerol to be stored in the form of triglycerides.

Lipolysis is the process by which stored triglycerides are broken down into FFAs, which are released into the circulation to provide energy. A primary target for the FFAs is muscle tissue, which use them for energy. If there are more FFAs released than the muscle requires, then the liver absorbs the FFAs and converts them into triglycerides. These triglycerides are then sent back to the fat cells for further storage. Obesity causes increased influx of FFAs into nonadipose tissue and is characterized by elevated plasma FFAs (Campbell, Carlson, & Nurjhan, 1994). In obese states, adipocytes expand and proliferate to accommodate increased lipid-storage needs. Despite these structural changes in the adipose tissue, increased lipid-storage demands eventually result in a state where the adipose tissue can no longer store all of the plasma lipids. Consequently, there are elevations in circulating FFAs, which then enter nonadipose tissues and are sequestered. Although not all types of adipose tissue are equally pernicious, in CMS and related diseases, visceral fat is especially implicated. Its increased lipolytic activity and proximity to the portal blood supply significantly affects hepatic function and systemic metabolic activity.

In several of the tissues that experience significant elevations in triglyceride content, there can be pathogenic responses, including insulin resistance (Defronzo, 2004; Shaffer, 2003). The accumulation of surplus lipid in nonadipose tissue leads to cell dysfunction or death and is termed *lipotoxicity* (Schaffer, 2003). In the skeletal muscle tissue, increased triglycerides are correlated with insulin resistance. In the liver, increased triglyceride storage is related to insulin resistance. In addition, increased circulating FFAs are utilized by the liver for synthesis of very low-density lipoproteins. Furthermore, insulin suppresses hepatic glucose production, but insulin resistance prevents insulin from doing so. As a consequence, hepatic glucose production increases in an insulin-resistant state. In pancreatic β cells, increased islet lipid exposure has been associated with impaired insulin secretion (Yu et al., 2002; Zhou & Grill, 1994) and β-cell apoptosis in primary rat pancreatic β-cell culture (Shimabukuro et al., 1998). Thus, obesity contributes to CMS by leading to excess circulating FFAs, which have effects on insulin resistance in muscle, impaired suppression of hepatic glucose production, and impaired insulin secretion by islets.

Lipolysis affects insulin resistance by increasing circulating FFAs and free glycerol, which inhibit the responsiveness of fat and liver cells to insulin. FFAs promote insulin resistance by altering the insulin transduction signal via inhibition of several key components of the receptor system, which facilitates insulin's action of promoting cellular-glucose uptake (Griffin et al., 1999). Specifically, increased FFAs lead to a serine kinase cascade that ultimately inhibits insulin receptor substrate-1

tyrosine phosphorylation and reduced GLUT4 glucose transporter translocation to the cell membrane. FFAs also induced reactive oxygen species (ROS) formation in human vascular endothelial cells (Chinen et al., 2007).

In summary, as adipose tissue expands, it becomes insulin resistant. Because insulin is antilipolytic, increased insulin resistance leads to greater lipolysis and higher circulating FFAs. This leads to higher circulating FFAs, resulting in the peripheral tissues oxidizing the FFAs. Over time, this may produce insults to the tissues, as they cannot sustain oxidizing FFAs over prolonged periods. The clinical presentation of the downstream effects of obesity includes key criteria of CMS: dyslipidemia, increased waist circumference, increased weight, insulin resistance, and glucose dysregulation.

ADIPOSE TISSUE AND INFLAMMATION

Adipose tissue resides at the crossroads of metabolic and immune activity linked to CMS, diabetes mellitus, and atherosclerosis (Greenberg & Obin, 2006; Rajala & Scherer, 2003). Research has revealed that adipose tissue secretes numerous chemical messengers, such that it has been characterized by some as an endocrine organ (Gimeno & Klaman, 2005; Schaffler, Binart, Scholmerich, & Buchler, 2005). Dysregulation of adipokine release has been correlated with atherosclerosis and CMS. Adipose tissue responds to inputs from the SNS, parasympathetic nervous system, and HPAC axis. Lastly, central obesity resulting from expansion of abdominal adipose-tissue depots plays a key role in insulin resistance, CMS, Type 2 diabetes, and CVD. As a consequence, adipose tissue has received much recent attention in efforts to discover the mechanisms by which stress and stress responses influence disease progression.

White adipose tissue produces large quantities of cytokines, including IL-6, TNFα, plasminogen activator inhibitor 1 α (PAI-1), and monocyte chemoattractant protein 1 (CMP-1). IL-6 induces the acute-phase response, including production of CRP (Bataille & Klein, 1992; Heinrich, Castell, & Andus, 1990). TNF-α promotes lipolysis (Zhang, Halblieb, Ahmad, Manganiello, & Greenberg, 2002), induces insulin resistance (Hotamisligil et al., 1993) and adhesion molecule expression (Ouchi, Kihara, Arita, et al., 1999), and is correlated with insulin resistance (Kern, Ranganathan, Li, Wood, & Ranganathan, 2001). PAI-1 is a known risk factor for thrombosis, and plasma PAI-1 levels correlate with visceral adiposity (Gimeno & Klaman, 2005). MCP-1 is a chemokine that attracts circulating monocytes and is implicated in the process of macrophages infiltrating into adipose tissue. For example, plasma levels of IL-6 are correlated with adiposity (Cottam, Mattar, Barinas-Mitchell et al., 2004), as adipose tissue has been shown to produce up to 30% of plasma IL-6 (Mohamed-Ali et al., 1997). However, recent research has demonstrated that most of the proinflammatory cytokine production in white adipose tissue results from macrophage infiltration. As obesity increases, elevated numbers of macrophages are found in the white adipose tissue, particularly in the visceral fat. Through endocrine and paracrine mechanisms, the proinflammatory cytokines released by macrophages have systemic effects as well as more local effects on adipocyte function.

Beyond proinflammatory cytokines, such as IL-6, TNF-α, and MCP-1, adipose tissue secretes dozens of adipokines, including leptin, adiponectin, resistin, and visfatin. Several of these are specific to adipose tissues, including leptin and adiponectin, which have been the targets of extensive research (Beltowski, 2006; Greenberg & Obin, 2006; Rajala & Scherer, 2003). Leptin and adiponectin influence disease processes through different mechanisms than macrophage-associated proinflammatory cytokine release. Leptin has been described as having several potentially pathogenic properties, including causing oxidative stress, modulating endocannabinoid production, and increasing plasma CRP (Beltowski, 2006). Its primary role is to convey satiety signals from adipose tissue to the central nervous system (Yang & Barouch, 2007). Congenital absence of leptin or a leptin-receptor deficiency leads to obesity, and leptin replacement therapy resolves many of the metabolic problems associated with leptin deficiency (Clement et al., 1999; Farooqi et al., 1999; Montague et al., 1997). Plasma leptin increases as adiposity increases; however, in obese individuals, leptin often fails to effectively transmit a satiety signal sufficient to curb continued excess energy intake. It is hypothesized that the central nervous system becomes leptin resistant as plasma leptin levels increase, thus explaining leptin's inability to induce weight loss in overweight individuals (Yang & Barouch, 2007).

Adiponectin is an adipokine with potentially antiatherogenic properties (Greenberg & Obin, 2006). It increases insulin sensitivity and increases FFA oxidation. Plasma adiponectin is lower in patients with coronary artery disease (Hotta et al., 2000). It inhibits lipopolysaccharide (LPS)-induced NF-κB activation and IL-6 production in adipocytes (Ajuwon & Spurlock, 2005); it also inhibits TNF-α–induced expression of adhesion molecules (Ouchi, Kihara, Arita et al., 1999) and prevents macrophages from becoming foam cells (Ouchi, Kihara, Arita et al., 2001).

Adipose tissue is composed of multiple types of cells, including adipocytes, macrophages, preadipocytes, and fibroblasts (Gimeno & Klaman, 2005). Macrophages accumulate in adipose tissue as adiposity increases, and some researchers claim that obesity is categorized by a chronic state of low-grade inflammation (Wellen & Hotamisligil, 2005; Yudkin, Kumari, Humphries, & Mohamed-Ali, 2000). There appear to be paracrine effects with the other cells comprising adipose tissue, such that secretion from one cell type affects cytokine release from the other (Gimeno & Klaman, 2005).

As obesity increases, the pattern of secretion of adipokines changes, such that plasma levels of antiinflammatory adiponectin decrease, whereas proinflammatory adipokines IL-6, TNF-α, leptin, resistin, and MCP-1 increase. This process affects CMS because certain proinflammatory cytokines have been associated with increased insulin resistance. Insulin has been shown to exert antiinflammatory effects in the mononuclear cells of obese subjects infused with insulin. Insulin infusion resulted in decreased NF-κB levels, decreased proinflammatory protein PAI-1, MCP-1, cellular adhesion molecule concentrations, and decreased ROS (Dandona et al., 2001).

In summary, two separate but related roles of adipose tissue influence the development of CMS. As obesity increases and adipose tissue begins to experience difficulty storing excess energy circulating levels of lipids arise. One long-term consequence of increased plasma FFAs is insulin resistance in skeletal muscle and liver tissues via inhibition of insulin-signal transduction. This prevents insulin from inhibiting hormone-sensitive lipase's lipolytic effects, thus triggering further release of FFAs. In addition, macrophages increasingly infiltrate the adipose tissue of obese individuals, resulting in more proinflammatory cytokines released by adipose tissue. Beyond systemic effects of proinflammatory cytokines from these macrophages, they affect other cells locally within the adipose tissue, exerting effects on adipocytes, which further contributes to increased circulating FFAs.

OXIDATIVE STRESS, CMS, SOCIAL CONDITION, AND ADIPOSE TISSUE

In addition to inflammation, much research has focused on the role of oxidative stress in the pathogenesis of CMS and related disorders (Eriksson, 2007; Stocker & Keaney, 2004). In human subjects, markers of lipid peroxidation have been shown to correlate with body mass index, waist circumference, and plasma adiponectin (Furukawa et al., 2004). Research implicates NADPH oxidase (Talior, Tennenbaum, Kuroki, & Eldar-Finkelman, 2005) and the endoplasmic reticulum (Ozcan et al., 2004) as the key sites of ROS formation. Induction of oxidative stress in 3T3-L1 adipocytes impairs GLUT4 translocation to the plasma membrane (Rudich et al., 1998) and incubation with an antioxidant attenuates the impairment in insulin-stimulated glucose uptake (Rudich, Tirosh, Potashnik, Khamaisi, & Bashan, 1999).

In addition to increasing insulin resistance, oxidative stress in adipose tissue also leads to increased secretion of IL-6, and incubation with an antioxidant agent reduces both ROS and IL-6 production in parallel (Lin et al., 2005). Elevated levels of fatty acids in cultured adipocytes result in NADPH oxidase-mediated oxidative stress and downstream alterations in the productions of adipokines, including IL-6, MCP-1, PAI-1, and adiponectin (Furukawa et al., 2004). In obese mice, an NADPH oxidase inhibitor decreases ROS production and attenuates alterations in adipokine production. In sum, oxidative stress in adipose tissue leads to pro-atherogenic and CMS-related changes in adipokine production, including proinflammatory cytokine production.

Previous findings from our laboratory have suggested that the individually caged Watanabe rabbits may experience significantly more oxidative stress than do animals in other social conditions (i.e., housing with a cage mate or stranger). In the individually caged animals, there was a strong correlation between plasma-oxidized LDL and disease in the aortic arch (Brooks et al., 2005). Moreover, NADPH oxidase activity has been shown to be elevated in the aortic homogenates of individually caged animals (Nation et al., 2008). Furthermore, weight is correlated with disease in these rabbits. Analysis of animal behavior shows that individually caged animals engage in less active behaviors than do paired animals, and current research in our laboratory is exploring whether sedentary behavior leads to weight gain, triggering downstream oxidative stress and subsequent disease progression.

SNS AND CMS

There are several direct and indirect pathways by which SNS activity may affect CMS. As previously noted, pathogenic alterations in inflammation and lipolysis may play a role in CMS disease progression. Adrenergic receptors are present in adipose tissue (Lafontan & Berlan, 1993). Activity of the SNS is associated with both lipolysis and release of inflammatory adipokines. More specifically, SNS stress hormones, epinephrine and norepinephrine, induce lipolysis (Aitchison, Clegg, & Vernon, 1982; Morimoto, Kameda, Tsujita, & Okuda, 2001; Nakamura, 2006), cause IL-6 release from adipose tissue (Keller, Keller, Robinson, & Pedersen, 2004), and promote insulin resistance (Schneiderman & Skyler, 1996). Deleterious effects of the SNS on components of CMS are exacerbated by obesity. In addition to SNS innervation of adipose tissue, there is evidence that adipose tissue also is innervated by the parasympathetic nervous system. Following a vagotomy of parasympathetic inputs to specific fat pads, there were reductions in insulin-mediated FFA uptake (Kreier et al., 2002).

In a review by Black (2006), the author notes that acute and chronic stress responses have immune components that include inflammation. Of particular interest is the role that IL-6 plays in stimulating the acute-phase immune response, and the capacity of psychosocial stressors to activate the acute-phase response: IL-6 secretion occurs to a significant extent in endothelial cells, the liver, and adipocytes. As inflammation is considered by many to be central to CVD and relevant to CMS, disease states may be exacerbated by repeated episodes of the acute-phase response due to chronic stress, in part mediated by

IL-6 production. In obese individuals with elevated macrophage infiltration of adipose tissue, repeated stressors likely result in increased production of adipose tissue-based proinflammatory cytokines.

Further evidence of the link between SNS activation and inflammation-driven disease comes from a series of studies in cynomolgous monkeys fed a high-fat diet, in which an unstable social environment led to development of atherosclerosis in dominant monkeys (Kaplan, Manuck, Clarkson, Lusso, & Taub, 1982). It was found that animals with greater cardiac reactivity to threat of capture showed cardiac hypertrophy and increased coronary-artery lesion area (Manuck, Kaplan, & Clarkson, 1983). In a subsequent study, the administration of a β blocker led to a lowering of heart rate and blood pressure, as well as an attenuation of the amount of atherosclerosis, indicating an SNS role in lesion progression (Kaplan, Manuck, Adams, & Clarkson, 1987). It was hypothesized that chronic SNS overactivation exacerbates atherosclerotic lesion development through a variety of mechanisms, including increased hemodynamic strain, inflammation, and endothelial dysfunction (Manuck et al., 1991).

HPAC AXIS

Cushing's syndrome, a disorder in which there is excess release of the glucocorticoid cortisol, results in a redistribution of fat from peripheral sites to the abdomen. This body-fat distribution resembles the central obesity often found in CMS. The reasons for this change in body-fat distribution are poorly understood; it may result from cortisol's role in preferentially directing FFAs to central fat. Treatment of Cushing's Syndrome by removal of the source of the excess cortisol results in a reversal of central obesity. As a consequence, researchers have become intrigued by the relationship between cortisol and central obesity.

Seeking to validate hypotheses regarding the causal role of glucocorticoids in promoting central obesity, numerous *in vitro* and *in vivo* studies have been conducted that examine the effects of cortisol on inflammatory and metabolic activity. Cortisol stimulates lipogenesis in adipose tissue in human subjects (Ottosson et al., 1994). In primary culture of human adipose tissue, cortisol inhibits its basal lipolysis as well as reduces forskolin-induced lipolysis (Ottosson, Lonnroth, Bjorntorp, & Eden, 2000). However, other studies have demonstrated that excess corticosteroids induce lipolysis, hyperinsulinemia, and insulin resistance (Binnert et al., 2004; Gravholt et al., 2002). In mouse islet cells, glucocorticoids inhibit insulin secretion (Lambillote et al., 1997). Glucocorticoids have also been shown to differentially affect tissue adipocytes and myocytes, such that glucocorticoids increase insulin-stimulated glucose uptake in human subcutaneous adipocytes, but decrease insulin-stimulated glucose uptake in muscle cells (Gathercole et al., 2007). Effects of HPAC-axis dysregulation may be mediated by higher density of glucocorticoids receptors on abdominal versus subcutaneous fat. Higher doses of adrenocorticotrophin (ACTH) result in higher cortisol responses in obese subjects (Marin et al., 1992; Pasquali, Cantobelli, Casimirri et al., 1993). In human subjects, cortisol infusion increased both fasting and postprandial glucose levels by upregulating hepatic glucose supply and by reducing glucose uptake by muscles (Dinneen et al., 1993).

Animal models have been developed to test the theory that excess cortisol is linked to symptoms of the CMS. An enzyme, 11-β-hydroxysteroid dehydrogenase Type 1 (11βHSD1), which is expressed in adipose tissue and liver, changes inactive cortisone into cortisol (Tomlinson, Walker, Bujalska et al., 2004). Mice genetically modified to overexpress 11-β-hydroxysteroid dehydrogenase Type 1 have higher levels of cortisol and develop increased central obesity as well as other symptoms of CMS (Masuzaki, Paterson, Shinyama et al., 2001). Inhibition of 11βHSD1 reduces lipolytic activity in human subjects (Tomlinson et al., 2007). Conversely, 11-β-hydroxysteroid dehydrogenase Type 2 (11βHSD2) inactivates glucocorticoids. A transgenic mouse model with increased levels of 11βHSD2 in adipose tissues was developed by Kershaw et al. (2005). In these transgenic mice, there was less weight gain, reductions in leptin and resistin, improvements in insulin sensitivity and glucose tolerance, and increased adiponectin levels. Results from studies of these two transgenic models suggest that excess activation of glucocorticoids is associated with numerous symptoms of CMS.

Additional studies using the cholesterol-fed cynomologous monkey have revealed that subordination stress in female monkeys is associated with hypercortisolism, ovarian dysfunction, and increased coronary artery atherosclerosis (Shively et al., 1989). Unlike the atherogenic effect of social dominance in male monkeys described earlier, which only occurred under unstable social circumstances, the impact of social subordination on atherosclerosis in female monkeys occurred regardless of the stability of the housing condition. In addition to increased atherosclerosis, subordinate female monkeys also show an increase in the number of anovulatory cycles, luteal-phase deficiencies, and adrenal weight. These findings are consistent with the triad of hypercortisolism, ovarian dysfunction, and CVD that is often observed in humans.

PSYCHOSOCIAL STRESSORS AND CMS

Several studies have found a relationship between stress levels and CVD or CMS (Prescott et al., 2007). Epidemiological studies have shown a link between obesity in men and negative social and occupational factors, including divorce and low socioeconomic status (SES; Rosmond, Lapidus, & Bjorntorp, 1996). There is an inverse

relationship between SES and CVD. SES is typically measured by income, education, or occupation, and lower SES individuals engage in poorer health behaviors, including smoking, less physical activity, and smoking.

In the Whitehall II study, subjects from 20 civil service departments in London were studied over a period of 14 years. Surveys and clinical exams were examined at multiple time points. A dose–response relationship was found between general obesity and work stress, such that increasing amount of work stress was correlated with elevated obesity (Brunner, Chandola, & Marmot, 2007). In addition, employees with chronic work stress were found to be more than twice as likely to have CMS than those without chronic work stress (Chandola, Brunner, & Marmot, 2006). Furthermore, there was a social effect on CMS such that subjects in lower employment grades had more than twice the risk of having CMS. There was also a relationship between metabolic syndrome and harmful health behaviors, such as smoking, heavy alcohol consumption, poor diet, and physical inactivity. It is noteworthy that elevated cortisol levels are found in men who experience higher work stress and of lower SES (Strike & Steptoe, 2004).

ENDOCANNABINOID SYSTEM AND OBESITY

Several reviews have highlighted the burgeoning research on the link between endocannabinoids and energy homeostasis (Osei-Hyiaman, Harvey-White, Batkai, & Kunos, 2006; Pagotto et al., 2006). Anecdotally, cannabinoids have long been linked to food consumption, as in the case of *cannabis sativa*, whose consumption has been suggested to spur appetite. Identification of cannabinoid receptors CB-1 and CB-2 led to increased research on the receptors' ligands, both endogenous and exogenous. A cannabinoid antagonist, Rimonabant, was shown to decrease sucrose and ethanol intake in rats (Freedland et al., 2001). Several studies have shown that treatment with Rimonabant decreases body weight in obese subjects and improves CMS profile (Pi-Sunyer et al., 2006; Scheen et al., 2006; Van Gaal et al., 2005). In overweight and obese nondiabetic human subjects, 1-year treatment with Rimonabant (5 and 20 mg) decreased waist circumference, weight, leptin, and blood pressure, while improving the lipid profile and glycemic control, as compared to placebo (Hollander, 2007). At the higher dose of Rimonabant, reductions in CMS prevalence occurred when compared to placebo. More recent efforts have sought to elucidate the mechanisms by which cannabinoids affect food ingestion.

Cannabinoids have both central and peripheral effects. Centrally, cannabinoid receptors are found in the hypothalamus and have been shown to be involved in central control of appetite (Moldrich & Wenger, 2000). It is noteworthy that cannabinoids modulate corticotrophin-releasing hormone (CRH) levels (Cota et al., 2003), with potential downstream effects on the HPAC axis. In addition, elevated CRH levels in $CB1^{-/-}$ mice indicate an inhibitory role of the endocannabinoid system on the HPAC axis.

Peripherally, endocannabinoid receptors have been identified in numerous tissues, including pancreatic islet cells (Nakata & Yada, 2007) and adipocytes (Cota et al., 2003; Roche et al., 2006). Adipocytes have also been found to be a source of endocannabinoids (Gonthier et al., 2007). As noted previously, a CB-1 receptor antagonist decreases obesity (Hollander, 2007). Increased obesity is associated with downregulation of CB-1 receptors in adipocytes (Bluher et al., 2006; Engeli et al., 2005) as well as fasting insulin (Bluher et al., 2006). Several papers have documented a relationship between leptin and endocannabinoids (Hollander, 2007; Hwan-Jo et al., 2005; Malcher-Lopes et al., 2006). It is interesting that endocannabinoids are orexigenic (appetite-inducing) hormones, whereas leptin is an anorexigenic (appetite-suppressing) hormone. Leptin suppresses the appetite-stimulating properties of cannabinoids by reducing endocannabinoid synthesis (Hwan-Jo et al., 2005; Malcher-Lopes et al., 2006). Plasma endocannabinoids are positively correlated with triglyceride and insulin levels and negatively correlated with adiponectin and HDL levels (Cote et al., 2007). Rimonabant increases adiponectin gene expression in obese rats (Bensaid et al., 2003), but the mechanism is unclear. Moreover, CB-1 activation upregulates lipoprotein lipase activity, resulting in increased lipid storage (Cota et al., 2003). Endocannabinoids promote glucose uptake in human adipocytes, though to a lesser extent than insulin (Pagano et al., 2007).

Preliminary evidence suggests a linkage between the endocannabinoid system and the body's various stress response systems. In rats, treatment with a tricyclic antidepressant upregulated CB1-receptor density in the hippocampus and hypothalamus and also decreased stress-induced corticosterone secretion. Treatment with a CB1-receptor antagonist immediately prior to a swim stressor abolished the effect of the antidepressant on stress-induced corticosterone secretion (Hill et al., 2006). CB1-receptor knockout mice ($CB1^{-/-}$) had higher basal and stress-induced levels of plasma ACTH and corticosterone than wild-type mice (Barna, Zelena, Arszovski, & Ledent, 2004). In a separate study, mice exposed to restraint stress showed small, nonsignificant increases in corticosterone, but when the mice were pretreated with a CB1 antagonist, they showed significant increases in corticosterone in a dose-dependent manner (Patel et al., 2004). Pretreatment with several drugs that facilitate endocannabinoid signaling resulted in restraint stress-induced corticosterone secretion. $CB1^{-/-}$ had an altered circadian corticosterone profile with higher levels at the beginning of dark than wild-type mice (Cote et al., 2007). In addition, $CB1^{-/-}$ mouse-derived pituitary cells had an elevated HPAC response to CRH and forskolin than wild-type mice. Increased CRH mRNA was found in the paraventricular nucleus, and glucocorticoid receptors were downregulated in the hippocampus. The authors conclude that the absence of CB1 receptors causes dysregulation of

the HPAC axis, thus providing evidence of a role for the endocannabinoid system in modulating the HPAC axis.

STRESS AND OBESITY

In addition to the SNS and HPAC axis, researchers have identified several other pathways involved in how stress contributes to obesity (Adam & Epel, 2007; Kuo et al., 2007). Links have been demonstrated between stress and opioid release (Binder et al., 2004). In addition, palatable food has been associated with opioid release in rodents, thus providing a mechanism whereby stress and eating can become coping responses to stressful situations. Much of the research has focused on the interaction of glucocorticoids, leptin, neuropeptide Y (NPY), and insulin. It is important to note that not all individuals, or animals, respond to stress with food intake, as weight loss in response to stress often occurs in a large percentage of individuals. As mentioned earlier, one pathway from stress to weight gain is that chronic HPAC-axis activation leads to elevated cortisol production that drives accumulation of visceral fat (Björntarp, 1992). Increases in visceral fat mass lead to dysregulated adipokine release, including release of leptin, which feeds back to the central nervous system and affect food intake.

Neuropeptides affected by this pathway include NPY, which is implicated in promoting intake of palatable—and often high-fat, high-calorie—food (Kuo et al., 2007). In an elegant series of experiments, cold and aggression stressors were demonstrated to induce NPY release from sympathetic nerves in rodents; however, certain stressors, including restraint stress and water avoidance, did not induce NPY release (Kuo et al., 2007). Stressors that did not increase plasma NPY did not increase abdominal fat, but mice that underwent cold and aggression stressors did show abdominal fat growth. When cold and aggression stressors were combined with a high-fat and high-sugar diet, NPY and NPY2 receptor genes were upregulated in abdominal adipose tissue. NPY was found to increase fat growth when administered directly; when an NPY2 receptor antagonist was administered, adipose tissue weight and volume decreased in lean and obese mice. NPY appeared to increase vascularization of the adipose tissue. The authors then fed a high-fat, high-sugar diet to mice for 3 months and administered daily cold stressors to one group. All mice became obese, but the group that received the cold stressor presented with symptoms of CMS, including liver and skeletal muscle steatosis; impaired glucose tolerance, hyperlipidemia, and hypertension; and elevated plasma leptin, insulin, and resistin. Mice receiving the cold stressor but treated with an NPY2 receptor antagonist did not present with CMS symptoms. Lastly, the authors induced an NPY2-receptor knockout model that reduced NPY receptors only in cell types hypothesized to be involved in the NPY response. After 1 week, NPY2-receptor expression decreased by 80% and within 2 weeks reduced stress-induced fat gain by 50%. Studies have also shown that NPY reduces insulin secretion in pancreatic islet cells, and conversely, those islet cells from NPY-deficient mice show increased insulin secretion (Imai et al., 2007).

The addiction literature has provided a framework for understanding potential links between increased stress and elevated food intake. There is evidence that the intake of palatable food stimulates similar brain centers that addictive drugs stimulate (Wang & Volkow, 2001). Further discussion of the stress–eating relationship may be found in chapter 2 by Dallman and Hellhammer and chapter 21 by O'Connor and Conner in this volume.

PSYCHOSOCIAL INTERVENTIONS

Investigators have sought to implement the findings from basic science research on obesity, CMS, and stress to reduce the prevalence of CMS by lifestyle interventions. In humans, these efforts have focused primarily on changing diet and exercise patterns. In animals, it has been shown that manipulation of the social environment in rabbits with dyslipidemia influences the progression of atherosclerosis such that stable social conditions can slow disease progression (McCabe et al., 2002).

Two randomized controlled trials have demonstrated that a program focusing on improving diet and exercise behaviors can reduce Type 2 diabetes mellitus risk (Diabetes Prevention Program Research Group, 2002; Tuomilehto et al., 2001). Subjects were defined at-risk on the basis of plasma glucose, glucose tolerance, or weight. In both cases, the lifestyle intervention reduced the risk of diabetes by 58% when compared to the control group. In the Diabetes Prevention Program (DPP) study, the lifestyle intervention was more effective in reducing diabetes incidence than a pharmacological intervention with metformin (31% reduction) as compared to placebo. The programs resulted in reductions in body weight and improvements in glycemic control. Although the studies focused on reducing diabetes, secondary analyses of the DPP data showed that the lifestyle intervention positively affected several criteria of CMS, including reduced obesity, HDL, triglycerides, hypertension, fasting glucose, and glucose tolerance. Several smaller studies also have demonstrated the health benefits of a lifestyle intervention by reducing mortality in men with impaired glucose tolerance in Sweden (Eriksson & Lindgarde, 1991), reducing incidence of Type 2 diabetes in China (Pan et al., 1997), and reducing incidence of diabetes in India (Ramachandran et al., 2006).

CONCLUSIONS

Since the WHO, NCEP, and other organizations released their definitions of CMS, the syndrome has received a lot

of attention in the scientific literature. A great deal has been learned about relationships between the variables that comprise the syndrome as well as its prevalence, incidence, and risk of leading to disorders such as Type 2 diabetes and CVD. Although it is clear that the CMS is strongly predictive of CVD and Type 2 diabetes, it is less clear whether the syndrome per se is more predictive than the sum of the individual risk factors that it comprises (Ford, 2005b; Ford, Li, & Sattar, 2008). Nevertheless, because of the strong correlation among the constituent variables and the causal pathways that need to be investigated, CMS is an important organizing principle for understanding the pathogenesis of CVD. Similarly, the centrality of the HPAC and SNS axes in influencing obesity, insulin resistance, and other components of the CMS underscore the usefulness of studying the biological pathways involved in relating stress to CVD.

In previous stress research, the relationships between stressors and disease have characteristically focused largely on the relationship between the stress response and disease outcomes (e.g., Selye, 1956). The studies reviewed in this chapter suggest that investigations relating to stressors and CVD also need to focus on lifestyle factors such as diet and exercise because variables such as obesity and insulin metabolism are known to interact with stress hormones and can lead to the release of proinflammatory cytokines that can promote endothelial dysfunction. It is interesting that, in the stress model of atherosclerosis in cynomolgous monkeys (Kaplan et al., 1982), pronounced atherosclerosis in dominant male animals occurred in monkeys given a high-fat diet. When one compares the magnitude of the atherosclerosis observed in that study with a comparable study that did not use an atherogenic diet (Kaplan et al., 1983), it is clear that atherosclerosis occurred only in animals subjected to the high-fat diet. Thus, it would appear to be important to look at the relationships between the variables that make up the CMS in attempting to understand the relationship between environmental stressors and CVD.

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30 Stress and the Cancers

Andrew Baum, Lara A. Trevino, and Angela Liegey Dougall

Stress and cancer are linked in so many ways that it is difficult to understand why it took so long for these connections to become serious research and clinical targets. To some extent, this may be due to the speed of development of ways of studying and measuring stress. These developments and the theoretical elaboration of processes and pathways linking stress and disease have allowed increasingly sophisticated models of prevention, patient care, and the like. At the same time the dizzying array of real or potential relationships dilutes one's focus and may produce a problem "seeing the forest for the trees." For example, a primary focus in research on stress and cancer has been on whether stress contributes to the etiology or progression of cancer. This has led to a series of derivative hypotheses and models describing stress and potential ways in which stress causes or affects different cancers in different populations. Assumptions based on these models and hypotheses have led to attempts to reduce stress in at-risk or ill people, with attendant squabbles about the value of stress-management interventions. Lost in all of this is the undeniable fact that cancer is an enormously disruptive, potentially life-threatening event that causes stress de novo, exacerbates pre-existing stress, and makes coping with these ongoing stressors more difficult.

At least some of the obstacles to understanding how stress and cancer are linked lie in the nature of stress. Because stress affects every organ system in the body and appears to have effects ranging from the molecular to organismic and societal levels, there are many pathways that could be important. In addition, several key questions remain unanswered. Are there general, nonspecific aspects of stress that play key readying and metabolic roles as well as situation-specific changes motivated by these responses? Are there real differences between acute and chronic stress other than how long they last? How do these differences or similarities speak to issues such as resilience, biobehavioral responses, and consequences?

The nature of cancer itself also poses barriers to understanding how stress may impact its initiation and progression. Carcinogenesis is a complex process that is as yet only poorly understood. Multiple determinants have been identified for many cancers, but there are also undoubtedly many contributing factors that have yet to be uncovered. Much remains to be learned about distinctive and shared aspects of the etiological processes that culminate in different forms of cancer. The natural history of most major forms of cancer, marked by slow progression and change over time, poses obstacles to prospective/longitudinal research. The diagnosis of cancer can be traumatic for patients, and very few find themselves well prepared to cope with such news. The treatments associated with cancer, such as radiation and chemotherapy, are a physical strain on the body, leading to sometimes unbearable side effects that make coping with treatment exceedingly difficult for the patient and often for family members as well. And even following successful treatment, fear of recurrence typically forms a lingering source of stress that is difficult to separate out from stress stemming from earlier pre- and postdiagnostic phases.

This chapter will briefly review what we know about stress and cancer, with an emphasis not only on causal pathways but also on the broader impact of the disease. We provide an overview of how stress may influence cancer at the various stages of induction, progression, and survival. Additionally, we review how reduction of stress may improve long-term health outcomes in cancer patients through psychological interventions. We conclude by discussing the effects of stress syndromes on the survival of cancer patients.

STRESS AND HEALTH

Generally speaking, stress affects health and illness in several different ways (Figure 30.1). Early conceptions of types of pathways by which stress affects the development or progression of disease broke these influences down into direct physiological effects, indirect, behaviorally induced physiological effects, and influences involving behavioral reactions to possible illness. Perhaps greatest attention has been given to the notion that stress directly causes biological changes that can affect pathophysiology. These diverse effects include sympathetic nervous system (SNS) and hypothalamic–pituitary–adrenocortical (HPA) activation and concomitant increases in circulating levels of the hormones epinephrine (E), norepinephrine (NE), and cortisol (C) which, in turn, affect other bodily systems.

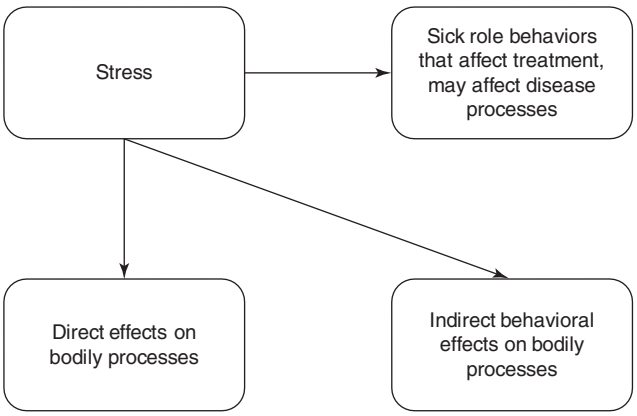

Figure 30.1 ■ Stress tends to affect health in any of the three general ways: direct effects on physiological process, behavioral changes that affect physiology in initially healthy individuals, or changes in behavior when people recognize the possibility that they may be ill.

For example, stress can increase the viscosity of blood by affecting platelet adherence or the number of cells in circulation. It can also reduce defense against infection by affecting the number and/or activity of key immune cells. Many pathways linking stress with cancer are based on these direct effects, represented by hypothesized relationships between stress, oxidative damage, genomic instability, and immunosurveillance (for a detailed review, see Baum, Lorduy, & Jenkins, chapter 7).

Alternatively, stress can affect behaviors that in turn have bodily effects that can alter vulnerability to disease processes. Perhaps the most common example of this pathway is the impact of stress on tobacco use. Smoking has a broad range of physiological effects, including increases in SNS activity, heart rate, and metabolic activity, that have deleterious influences on cell mutation, atherosclerosis, and inflammation. Since stress appears to increase tobacco use among smokers, it undoubtedly exerts indirect effects on health generated in this manner. Other examples include alcohol and drug abuse (see Grunberg, Berger, & Hamilton, chapter 22).

A third pathway in this scheme involves behaviors among individuals who are already ill. Stress may influence health through its effect on actions and inactions following discovery of disease, including delay in reporting symptoms, adherence problems, and poor survivor surveillance. These behaviors can undermine what might otherwise be effective treatment (see Garrido, Hash-Converse, Leventhal, & Leventhal, chapter 35).

STRESS AND CANCER

The effects of stress can operate at any number of points in the disease process. Diseases and syndromes often undergo several stages in their development. Increasingly, diseases like cancer and heart disease are characterized as a continuum of dysfunction and disability. There are many ways to describe these continua; perhaps the most obvious is to base it on time since diagnosis or stage of disease. Coronary heart disease begins with the development of atherosclerosis and this produces subsequent changes in the coronary arteries that may increase risk for cardiac events (see Bekkouche, Holmes, Whittaker, & Krantz, chapter 28). Similarly, there are several different points in cancer pathophysiology that can be readily noted, and several stages of treatment that can also be identified (see Figure 30.2). For cancer, the predisease development phase is often called induction and is primarily concerned with tumorigenesis. Once tumors have formed, the effects of stress may now influence promotion or growth of the tumor. Different treatment approaches are warranted at these different stages.

To some extent, these stages are arbitrary and differences among them may be related to medical discovery and capability. Regardless, these steps help us to think of cancer in more "bite-sized" pieces, allowing formulation of testable hypotheses about induction or development, in which disease processes have just begun and are largely invisible to medical detection. Included in this period would be induction of mutations needed to produce malignancy, efforts by cellular and subcellular processes to eliminate these mutations, and the growth of nascent tumors. At some point in this process, altered cells develop the capacity to metastasize, to spread to remote areas of the body, and to become malignant. Some of the principal methods of defense are applied by the immune system at this point, and treatment becomes more difficult. If the cancer can be treated and eliminated, the individual enters a disease-free status where all elements of the cancer are undetectable. For some, tumor growth may recur, influenced in part by risk factors associated with already having had cancer.

STRESS AND CANCER INDUCTION

There are plausible pathways that explain how stress may affect tumor induction. There is also considerable anecdotal and "circumstantial" evidence for this. However, despite the appeal of this hypothesized relationship, the extent to which stress can act as a cause of cancer has not been convincingly demonstrated in human populations. Evidence from animal research and growing literatures on stress and immune defense in humans have fueled interest research on this dynamic. However, limitations in our ability to detect early events in etiology and progression, as well as methodological constraints imposed by the long recruitment period for most cancers (and the lack of "intermediate" outcomes or biomarkers), make studying causes of cancer challenging. In contrast, for developing heart disease, atherosclerotic processes, changes in heart wall motion, and hypertrophy of heart muscle offer early evidence of disease. They are causal, intermediate

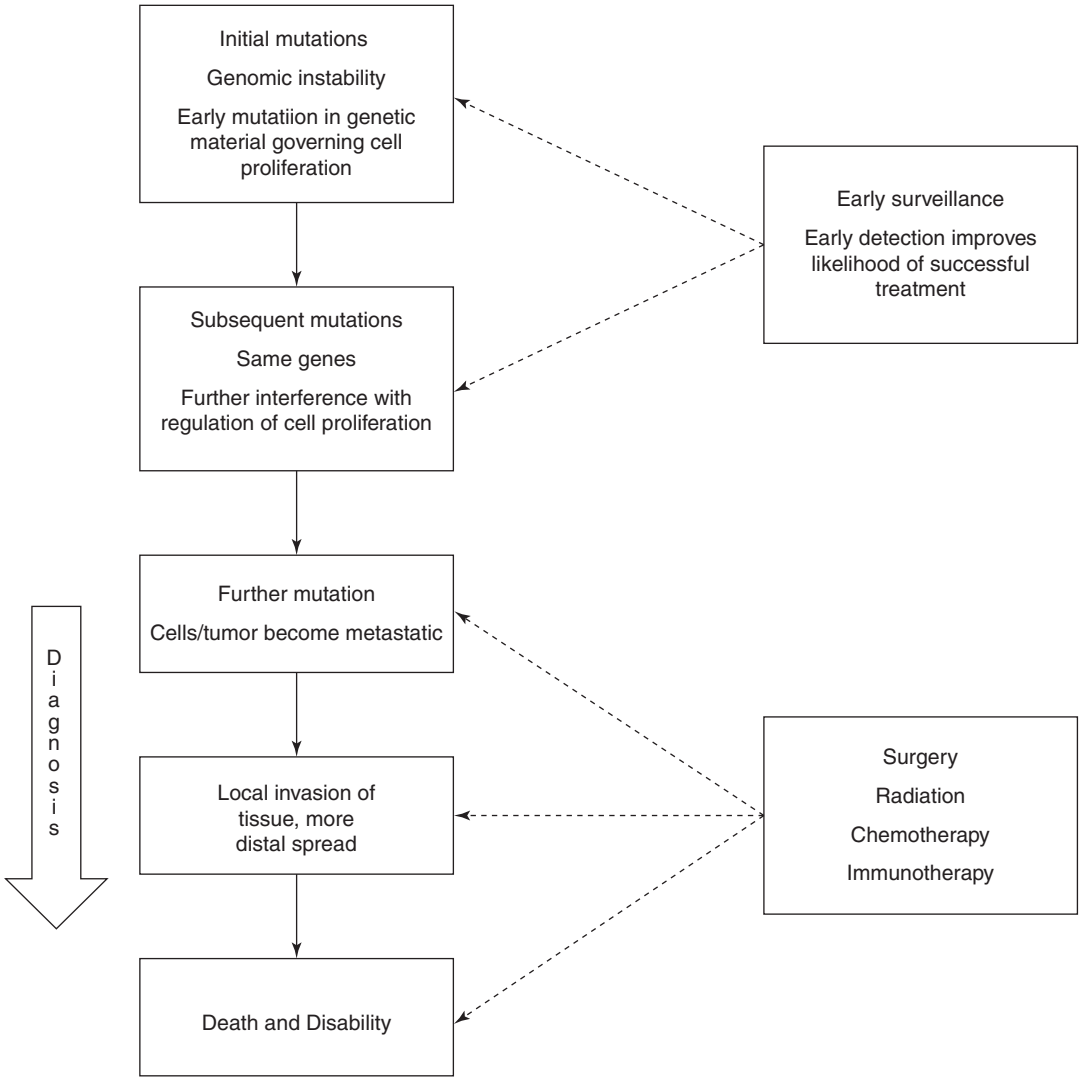

Figure 30.2 ■ Cancer begins with initial mutations and genomic instability, leading to subsequent mutations and tumor development. This may be followed by further mutation and metastasis. These changes afford varying opportunities for detection, diagnosis, and treatment.

markers of the likelihood of significant events like heart attack and sudden death. There are fewer such markers for cancer in its earliest stages.

Our ability to study the processes linking stress with nascent cancer has improved as a function of increasing elaboration of key elements and development of more sophisticated methods for detection of biological changes in the process. We know a good deal about how cancer develops as a genetic event and have been able to develop high-precision estimates of levels and patterns of risk. However, the nature of both stress and cancer dictates that stress as a cause may be better understood by portraying it as one of a few key processes that affect the likelihood of repeated mutation and altered proliferation, control of tumor growth, and defense against metastatic development.

The complexity of stress is one major complication (Antoni et al., 2006). There are many different variables that need to be addressed. Heritable characteristics can play a large role in the development of cancer. Family history is a major risk factor for some cancers, and only some of the effects of family history are accounted for by known heritable mutations. The rest may derive from social factors, shared environments, and so on. Additionally, there are other psychological and social variables that play into the development of cancer, such as health behaviors (e.g., tobacco use), gender, age, coping, and personality. As a result, the study of stress and cancer has traditionally been limited to animal studies. Although this has afforded greater opportunity for experimental control of key factors, these studies have used a variety of measures and approaches, which makes

interpretation more difficult. Different cancer models have been used, types of stressors have varied, timing of stressors in relation to cancer induction has not been systematically controlled, and the frequency and duration of stressors, as well as measurements of tumors, have been inconsistent.

Animal studies of cancer have emphasized effects on tumor incidence and growth, rather than the changes that occur to cause neoplasms to develop into vascularized tumors. This, again, is mainly due to methodological limitations that do not allow for measurements of cancer in early stages of development. Generally, there are four key variables in the design of studies of stress and cancer: models of tumor development or method of induction, differences in stressors, timing of stressor/tumor event, and the frequency and duration of stressors.

VARIABILITY OF CANCER MODELS USED

One can initiate tumor growth in several ways, and the cancer models that have been used in animal research have produced different rates of tumor growth or incidence. Chemical-induced cancer models, such as 7,12-dimethylbenz-(*a*)-anthracene (DMBA) and methylcholanthrene (MCA), have shown differences in weight, count, and prevalence of neoplasms across models. Newberry, Frankie, Beatty, Maloney, and Gilchrist (1972) injected female Sprague-Dawley rats with DMBA after which a stressor (electric footshocks) was administered periodically over 18 hours a day for several days. Shocked animals had significantly lower body weights, but, unexpectedly, had *fewer* tumors compared with the control animals, and their adrenal glands weighed more compared with the controls. In contrast, in an early study using a different stress protocol, Kaliss and Fuller (1968) had injected animals with MCA and found an *increase* in prevalence of tumors in stressed animals compared with controls. Within chemically induced tumor models, there are different results in terms of how stress affects cancer development that may reflect the timing of the stressor and method of tumor induction.

Inconsistencies are even more likely when comparing across different cancers. Viral-induced tumor models, such as Maloney murine sarcoma virus (MSV) and mammary tumor virus (MTV)-induced models, have produced contrasting stress-related changes in tumors. Riley (1975) found an *increase* in prevalence of tumors following exposure to MTV in female mice following housing stressors. Amkraut and Solomon (1972), on the other hand, found *decreases* in size of tumors following stressors using the MSV model.

Transplantation and cellular models, such as Walker 256 carcinosarcoma cells and ascites cells, also have mixed results in terms of tumor size, weight, and prevalence. Some studies that have used Walker 256 carcinosarcoma cells as the model of cancer have found *decreases* in size and weight following various different stressors (e.g., Ader & Friedman, 1965; Visintainer, Volpicelli, & Seligman, 1982). However, Dechambre and Gosse (1973) found an *increase* in tumor weight following housing change using a similar model. In contrast, also using similar models, Marsh, Miller, and Lamson (1959), Matthes (1963), and Sklar and Anisman (1979) had found *decreases* across measures of tumor weight, size, and latency following different stressors.

Research using cancer cell lines offers opportunities similar to those of graft-based or chemically induced tumors, with perhaps a bit more experimental control and validity regarding the identification of mediating processes. For example, using ovarian cancer cells, Sood and his colleagues have found that stress-related increases in E, NE, and C affect a range of tumor outcomes, including vascularization of the tumor (e.g., Sood et al., 2006), and production of cyclic adenosine monophosphate and vascular endothelial growth factor (Lutgendorf et al., 2003). As a result, these investigators were able to draw conclusions regarding the effects of sympathetic and HPA hormones on specific pathways that are important for tumor growth (Thaker et al., 2006).

TYPES OF STRESSORS

There are also many different stressors used in this research, which poses further interpretive difficulties. The more common stressors have included restraint, electric shock, social isolation, rotation stress, cold temperature, food deprivation, audiogenic stress, and novel environments. With some of these stressors, there is an inherent risk for tissue injury. For example, cold temperatures (–2°C to –20°C) may cause ulcerations on cutaneous areas (Yan, Lin, & Huang, 1989). These ulcerations may contribute to confounded conclusions about stress as a cause of cancer. The body's response to these ulcerations can include processes directed at repair of the lesions that can produce inflammation and that promote tumor growth. Stressors that cause tissue damage therefore may confound other influences and produce a compelling alternative explanation for some data. Some physical manipulations cause activation of additional physiological systems, such as nociceptive pathways, that make it difficult to determine if the end results were due to a physical stress response, and not due to activation of these additional physiological systems. Similarly, during food deprivation there may be changes in metabolic functioning that could affect tumor growth. Social isolation appears less problematic as a stressor; there is no risk of injury to the subject, the stress response that is elicited is comparable with the other stress models, and this stressor is most comparable with psychosocial stressors experienced by humans.

TIMING OF STRESSORS IN RELATION TO CANCER INDUCTION

One of the more troublesome issues characterizing some of this work is the timing of stressor exposure and tumor induction. Similar problems characterize psychoneuroimmunlogic studies and are associated with rebound effects following stressor exposure. The timing of stressors in relation to the induction of the cancer model appears to play a significant role in the outcome of tumor development (Aarstad & Seljelid, 1992). For example, Amkraut and Solomon (1972) exposed one group of animals to electric shocks 3 days prior to tumor induction (MSV injection), and another group began receiving the stressor on the day of MSV injections and continued until 2 days after induction. Stress prior to tumor induction *decreased* size and count of tumors, whereas stress during tumor induction *increased* tumor count. When stressors were administered 3 days in advance and stopped on the day of tumor induction, immunosuppression that may have influenced tumors would have occurred primarily prior to induction, and immune functioning was rebounding at the time when the tumors were introduced. The group exposed to stress at the same time as the tumor injections experienced a decline in immune function associated with stress and a related increase in number of tumors. Other studies suggest the effects of stressors are gradually reduced as animals adapt to their effects.

FREQUENCY AND DURATION OF STRESSORS AND STRESS RECOVERY

The frequency and duration of stressors can also affect tumor growth (Antoni et al., 2006). Chronic stressors are present throughout the course of a study, whereas intermittent stressors are presented on a variable schedule throughout the duration of the study (in human studies these distinctions are probably less meaningful). Chronic stressors used in this line of research have consisted of social isolation or being housed in cold temperatures. Social isolation is administered by housing animals either in groups or individually after weaning. Following cancer induction, some of the subjects are moved from group to individual housing, and some of the subjects are moved from individual to group housing. Steplewski, Goldman, and Vogel (1987) used this paradigm to demonstrate the effects of social isolation on tumor growth. They injected rats with either DBMA or adenocarcinoma cells, reporting an increase in tumor weight among the animals that were switched from group to individual housing. These differences held for both cancer models (DBMA and adenocarcinoma). They also found that females in that group had significantly lower tumor weights than did their male counterparts.

Chronic stressors have also been paired with intermittent stressors that are more representative of what humans may experience. Using the social isolation paradigm, Kerr, Wilkinson, Emerman, and Weinberg (1999) used transplanted androgen receptor Shionogi Carcinoma 115 (AR SC115) cells and injected them into DD/S strain male and female mice. Animals were subjected to acute daily stress (five different novelty environments for 15 minutes a day/5 days a week). Stressed males in the group to individual (GI) condition had significantly faster tumor growth rates than did animals in the individual to group condition (IG). Conversely, females in the IG condition showed faster tumor growth rates than did animals in the GI condition. In the nonstressed females, there were no differences among groups.

Steplewski, Vogel, Ehya, Poropatich, and Smith (1985) used the social isolation paradigm with intermittent electric shock in rats that were injected with adenocarcinoma cells. They found that after the stress period, the stressed subjects' tumors were almost twice as large as the control subjects. However, after the 12-day recovery period, the tumors in the control subjects had nearly doubled in size compared with stressed subjects. This suggests that while the physical stress *response* may play a role in tumor *induction*, the physical *recovery* from stress may play a role in *inhibition* of tumor growth.

COMMENT

All of the issues discussed above limit what we can conclude about the role of stress in causing cancer. The methods used to induce tumors are highly variable and have questionable external validity, the timing of the stressors and inductions affect outcomes, and the general issues involved in detecting initial events or early growth of tumors all conspire to make research inconsistent and inconclusive. This runs counter to anecdotal observation, which clearly favors a link, as both physicians and patients often report the impression that stress is related to cancer and other diseases. Further, there are a number of putative mechanisms by which stress *could* have such effects on cancer. The data for progression of cancer are little easier to interpret, but still raise many questions, the answers to some of which must await further advances.

STRESS AS A FACTOR IN SURVIVAL/PROGRESSION

In the animal studies described earlier, it is clear that some form(s) of association link stress and early stages of cancer induction and development. Perhaps more readily studied in humans, progression of disease has also received research attention. Does stress affect the speed or nature of growth once tumors have been established? Clearly, there is no clear demarcation point at which the cancer is "established" and it starts to grow. In all likelihood, these are simultaneous developments. Similarly, it is likely that the same or similar processes contribute to both initiation

and progression of tumor growth. Again, limitations of access and measurement are major obstacles to the study progression, including the lack of a clear transition from induction to later stages, differences in treatment, and the influences of age, socioeconomic status, social support, and environmental context. However, the need for extremely large samples in order to find sufficient numbers of cases, which hampers research on cancer induction, is negated by the ability to study diagnosed cases, in which the presence of cancer is readily established. Thus, even if the impact of stress on both induction and promotion of the disease is identical, the different measurement contexts probably make it more likely that evidence of effects in progression will be found.

So, what is the evidence? Research has approached this question in several different ways, initially in animal populations and subsequently by correlating measures such as life events (e.g., Holmes & Rahe, 1967; Rahe, 1987) with measures of disease recurrence or disease-free survival. Many studies have found that animals that are exposed to stress exhibit faster tumor growth, more extensive spread of tumors, and curtailed survival (e.g., Ben-Eliyahu, Yirmiya, Liebeskind, Taylor, & Gale, 1991; Sklar & Anisman, 1979). In humans, there are studies linking the occurrence of stressful life events with more rapid progression of disease (e.g., Forsen, 1991; Jensen, 1991; Ramirez, Craig, Watson, Fentiman, North, & Rubens, 1989). However, there are also studies reporting evidence of the opposite, with more stress predicting *slower* progression or *longer* survival (e.g., Derogatis, Abeloff, & Melisaratos, 1979; Fawzy et al., 1993; Levy, Herberman, Lippman, D'Angelo, & Lee, 1991; Levy, Herberman, Whiteside, Sanzo, Lee, & Kirkwood, 1990). Still other studies found no differences in progression as a function of stress (e.g., Barraclough, Pinder, Cruddas, Osmond, Taylor, & Perry, 1992; Hislop, Waxler, Coldman, Elwood, & Kan, 1987; Malcarne, compas, Epping-Jordan, & Howell, 1995). More recent research has confirmed this, with inconsistent findings characterizing attempts to link stress management with various manifestations of recurrence, relapse, or remission (e.g., Coyne, Stefanek, & Palmer, 2007; Kraemer, Kuchler, & Spiegel, 2009).

There are not many ways presently available to study the effects of stress on posttreatment survival. Issues derived from imprecise timing of disease-related events, that is, from not knowing when tumors formed, are not as serious for these studies as they are for investigations of cancer induction, particularly when all participants start the study "disease-free." However, different treatments may obscure some effects; some treatments may be more or less effective with a particular tumor or may be more or less sensitive to biological modifiers like stress. Another problem encountered when studying response to treatment or progression is that the participants may have had variable screening histories. People who engage in screening have an enhanced chance of detecting disease early in its development, and this can make the tumor more "treatable" or more sensitive to treatments. It is difficult to measure the age of tumors or to predict which will be more aggressive.

The point is that these kinds of studies are extremely difficult and rely on variations and "manipulations" that occur outside the researchers' control, and that a major reason for the equivocal effects in the literature may be the compromises that must be made in order to study stress and cancer. Potential strategies that may control for a large portion of this noise include identification and use of valid markers for mechanisms and experimental study of stress management in group or in one-on-one therapy sessions of cancer patients or survivors. Either of these approaches will be useful, although testing whether stress reduction is associated with longer survival or less recurrence offers a compelling look at the impact of stress on cancer outcomes.

One line of evidence suggesting ties between stress and cancer progression is based on a putative mediator of such a connection. One of the characteristics of stress responses that we have noted is that it is driven by the SNS and HPA axis. Specifically, adrenergic receptors and HPA effects on tumor growth and immune function may play an important role. Molomut, Lazere, and Smith (1963) exposed mice that had been injected with MCA to high-frequency sound. There was a delay in tumor induction only in the animals exposed to the sound stressor, though their survival rate was similar to that of the other groups. This means that stress may have an inhibiting effect on the induction of tumors, but that the recovery of body from the stress response may actually have increased tumor growth.

Sood et al. (2006) looked at the effects of C, E, and NE on the development of ovarian cancer. Most ovarian cancer cells contain β-adrenergic receptors, and the effect of propranolol, a β-adrenergic antagonist, was studied in an in vivo model consisting of the exposure of three lines of ovarian cancer cells (EG, SKOV3, and 222) to differing levels of C, E, and NE. They found that E and NE increased the cancer cell invasiveness potential approximately 1.7- and 3-folds, respectively. In addition, only the SKOV3 cell line showed an increase in invasiveness potential in response to C. The response to C and E or C and NE was similar to that to exposure to E or NE.

The ovarian cancer cell lines were then injected into female nude mice amidst exposure to saline, isoproterenol (a β-agonist), or isoproterenol and propanolol. The isoproterenol group had significantly larger tumors than did the saline group, which served as a control. One interesting finding was that the isoproterenol and propanolol group showed significantly less tumor growth than the isoproterenol group. Though not significantly different, the isoproterenol and propanolol group also weighed less than the saline group. This is consistent with findings reported by Flint and her colleagues (summarized by Baum et al., chapter 7) and these findings indicate that the stress hormones may play a larger role in the

development and growth of tumors than had been previously thought.

There are some limitations to this study. The in vivo model that was used eliminated the presence of other hormones, such as estrogen and progesterone, that may play additional roles in the development of ovarian cancer. The in vitro model artificially mimicked the stress response, which may not fully demonstrate the effects the stress hormones normally have on the body. However, this work offers the best evidence we have of direct effects of stress on cancer, and adds to findings implicating stress-related changes in cell cycling and genomic stability.

ADDITIONAL CONCERNS AND ALTERNATIVE STRATEGIES

Surprisingly, problems associated with fairly common variables have also plagued this literature. Sex is a limiting factor, and in some cases, a variable not considered in animal models of stress and cancer. For example, some of the studies that used mammary gland tumor models were conducted in male rodents (Rowse, Weinberg, Bellward, & Emerman, 1992; Strange, Kerr, Andrews, Emerman, & Weinberg, 2000). Though males may develop breast cancer, women are the dominant group that will develop this disease; so, ultimately the results of these studies are not fully applicable to the human population that this cancer mostly affects. Nonetheless, studies that did use both male and female subjects found differing effects of stress on tumor growth between the two genders (Wilkinson, Emerman, & Weinberg, 1999). Stress seemed to enhance the effect of tumor growth in males, and suppress or inhibit tumor growth in females. These findings support the suggestion that sex-specific hormones (i.e., estrogen, progesterone vs. testosterone) may play a role in the development of cancer in different genders. However, there are limitations to these studies as well. The studies that did find gender differences in terms of cancer development following stress did so in adult populations, not in older populations. Age itself is a risk factor for developing cancer and, therefore, the effects of stress on tumor growth and development across age groups warrant further study.

We have suggested that the relationships between stress and cancer are difficult to characterize and explain due to the complexities of the disease, its slow development, and the vagaries of studying uncontrolled phenomena. It is difficult to demonstrate the direct impact stress may have on cancer development in human populations due to the number and variability of stressors individuals may have over their lifetimes. In addition to the inability to control or measure many of these stressors, it is also difficult to reliably measure the effects of these stressors on biological processes that lead to the development and growth of cancer. Several studies have attempted to demonstrate the direct effects of stress on cancer development but have done so with clear methodological concerns. First, within these studies, there has been a lack of uniformity in the stress measures that were used. For example, some studies have used self-report measures of stress, whereas others have used biological measures, such as cortisol or measures of immune function, to demonstrate stress within the individual. Though both of these types of measures are acceptable to use, it is difficult to come to a clear consensus on results when comparing across studies using different measurement approaches. Second, to fully demonstrate an effect of stress on cancer, a well-controlled, large sample is needed, which has been attempted on a limited basis and with varying degrees of success. For these and other reasons, tracking and correlating stress events, stress responses, and cancer markers has yielded mixed results and provides often weak tests of hypothesized relationships.

Another way to understand the relationship between stress and cancer growth is to evaluate how stress management and reduction of stress impact prognosis in existing cancer patients. Turner-Cobb, Sephton, Koopman, Blake-Mortimer, and Spiegel (2000) found that increased social support promoted by their intervention was negatively correlated with mean cortisol levels in metastatic breast cancer patients. Reducing cortisol or other aspects of the biological stress response can have an impact on immune function, which in turn affects cancer prognosis. For example, Carlson, Speca, Patel, and Goodey (2003) found that improvements in quality of life (QOL), stress symptoms, and sleep were associated with increased T-cell production of interleukin-4 in breast and prostate cancer patients following a mindfulness-based intervention. McGregor et al. (2004) showed that a cognitive-behavioral stress-management intervention with positive psychological effects (increased benefit-finding) improved lymphocyte proliferation compared with what was seen in controls. Studies of cancer progression have the advantage of offering a compressed time period while patients are undergoing treatment in which there is an opportunity to measure stress and disease-related changes. Additionally, fewer subjects are needed for these studies, and to some degree, stressors can be controlled for or at least documented. However, these studies are subject to retrospective bias and there is no guarantee that the mechanisms governing progression resemble those involved in initial development.

EFFECTS OF PSYCHOLOGICAL INTERVENTIONS ON LONG-TERM HEALTH OUTCOMES

A growing body of literature has developed an array of psychological interventions targeted to reduce perceived stress levels in cancer patients to improve their QOL. Many of these interventions are geared toward a particular cancer, taking into account specific considerations of that population. For example, oral cancer patients are encouraged to discontinue the use of tobacco products to improve their prognosis. Smoking cessation can be

stressful, and may have an impact on QOL. Interventions targeted toward this population may need to include smoking cessation and coping techniques as a way to reduce stress and improve QOL. For a review of the types of interventions used, see Nezu, Nezu, & Xanthopoulos, chapter 34).

However, some of these interventions do not translate into results when applied to different cancer populations. For example, a psychological intervention geared toward breast cancer patients, where the population is largely made up of women, did not show similar results in prostate cancer patients. Additionally, each of these interventions may measure different health outcomes, either short term or long term, to determine the success of their intervention. These could include short-term outcomes such as reducing depression, stress, pain, anxiety, or fatigue, or increasing coping, social support, or optimism. The long-term outcomes to determine success of an intervention have ranged from the patient entering remission, delayed recurrence, or prolonging life in metastatic cancer populations. With these differences in health outcomes and variability in the psychological treatments themselves, it is difficult to determine whether and how the interventions reduce stress and thereby cause favorable changes in cancer progression and prognosis. The sections that follow attempt to summarize these studies.

QUALITY OF LIFE

Some psychological interventions have been designed to improve QOL in cancer populations. Carlson et al. (2003) used a mindfulness-based intervention to improve QOL in breast and prostate cancer patients. Following the intervention, there was a significant increase in global QOL compared with pre-intervention measurements. This study also found a reduction in depression, anxiety, emotional irritability, and cognitive disorganization. Additionally, measurements of immune function were taken; however, the intervention did not improve lymphocyte production as hypothesized. Heinrich and Schag (1985) targeted cancer patients and their spouses in their study. The intervention consisted of a stress and activity management program that involved educating patients and their spouses about cancer and teaching stress-management skills. This intervention did not improve the QOL measurements of depression, anxiety, or stress for the patients or the spouses. Patients and their spouses reported knowing more about cancer than the control group, but it did not seem to have an effect on other psychological variables. The lack of support for hypotheses could have been due to the fact that the sample was drawn from a mixed cancer population. Because each cancer was different in terms of treatment and QOL concerns, this may have introduced too much variance within the study with regard to factors influencing treatment effects.

Speca, Carlson, Goodey, and Angen (2000) examined the effects of a mindfulness-based intervention on stress and QOL in a heterogeneous cancer sample. They found that the intervention reduced mood disturbances and stress among both male and female cancer patients. Although not an intervention study per se, Penedo et al. (2003) looked at perceived stress-management skills as a factor in the effects of dispositional optimism on positive mood in prostate cancer patients. They found that dispositional optimism and positive mood were positively correlated, and this relationship was mediated by patients' assessments of their stress-management skills. This suggests that the ability to utilize stress-reduction techniques may be an important factor in intervention research.

Many different intervention approaches have been developed for group and individual support, for different cancers, for different stages of treatment, and so on. Books and reviews have appeared on this and related topics (Baum & Andersen, 2001; Coyne et al., 2007). Overwhelmingly, these studies suggest intervention benefits for QOL. However, each study has used different intervention procedures and different measures to determine improvements in QOL. Due to these variations across studies, it is difficult to clearly determine what form the intervention should take and what areas of improved QOL might be expected. It is also difficult to know whether these interventions should be applied in other cancer populations.

SURVIVAL

Increasing survival in terminal cancer patients by reducing stress or increasing acceptance of mortality has been somewhat difficult to demonstrate. One reason for this difficulty is the variation in short-term health outcomes in these studies. Some have targeted reducing stress, others reducing depression and anxiety, and still other studies have focused on increased coping among these populations. Even with these targeted, short-term health outcomes, there have been mixed results on how they translate to survival in these terminal populations. For example, Spiegel, Bloom, Kraemer, and Gotthell (1989) found that reducing anxiety, depression, and pain and increasing coping in metastatic breast cancer patients translated into an improvement in survival. On average, those who participated in the intervention lived 18 months longer than those in the control group. Additionally, Fawzy et al. (1993) found improved survival outcomes in melanoma patients when stress and depression were reduced and coping was increased. Richardson, Shelton, Krallo, and Levine (1990) targeted patient adherence in lymphoma and leukemia patients and found that their survival improved independent of adherence to treatment. Kuchler (1999) and Ratcliffe, Dawson, and Walker (1995) showed improvement in survival outcomes in gastrointestinal and non-Hodgkin's

lymphoma patients, respectively; what short-term health outcomes may have been affected by their interventions was unreported. It is important to note, though, that Ratcliffe et al. (1995) only found a marginally significant difference in survival outcomes.

In contrast, however, there are several studies that have found no effect on survival even though patients showed improvement in short-term health outcomes. For example, in a mixed cancer population, Linn, Linn, and Harris (1982) found improvements in depression, self-esteem, life satisfaction, locus of control, and alienation; this did not translate into improvement in survival. Similarly, Edelmann, Lemon, Bell, and Kidman (1999) and Goodwin et al. (2001) found improvement in distress among metastatic breast cancer patients; this, too, did not result in improved survival. Cunningham et al. (1998) also showed psychological improvements in metastatic breast cancer patients, with improvements in anxious preoccupation and feelings of helplessness, but did not find an effect of the intervention for survival outcomes. Oddly, Ilnyckyj, Farber, Cheang, and Weinerman (1994) did not find any psychological improvements in the treatment group, in addition to finding no effect on survival outcomes.

There are several possible reasons for the differences in the survival outcomes. Though most of the previously mentioned studies targeted similar cancer populations, there were differences in therapy focus. For example, Linn et al. (1982) used individual existential psychotherapy, whereas as Spiegel et al. (1989) used supportive/expressive group therapy. Additionally, the sample sizes of these studies were different. Many studies that found improved survival outcomes had smaller sample sizes compared with those reporting no improvement in survival outcomes. It is possible that the significant effects observed with smaller samples may be due to reduced variability as opposed to a true and meaningful treatment effect on survival outcomes.

The duration of the interventions has varied greatly as well. Spiegel et al.'s (1989) intervention required weekly meetings for 1 year, whereas other studies had shorter durations of intervention. However, one of the main complaints about the Spiegel et al. and Fawzy et al. studies was the fact that neither had planned on survival as an outcome. Coyne et al. (2007) reviewed several studies of psychological interventions in cancer populations and argued that even though these studies had an effect on psychological variables, survival was not a variable that was targeted a priori, subjecting the findings to problems associated with post hoc subgroup analyses. In contrast, Spiegel (2002) argued that the differences in survival results could be have been due to medical advancements in treatment. In his 2002 review, he pointed out that breast cancer treatment in 1989 was vastly different from treatment in 1999, and therefore the lack of survival effects other researchers have obtained could be simply due to advancements in medicine. Several of the studies cited by Coyne et al. (2007) as examples of where psychological interventions did not improve survival outcomes used mixed cancer populations. It would stand to reason that, with the differences in treatment and specific concerns associated with each cancer, it would be difficult to find a psychological intervention that would equally suit each of these populations. It would also stand to reason that, due to the mixed cancer populations, it would be difficult to show an effect of a psychological intervention on survival outcomes. Based on our current understanding of biological processes and mechanisms associated with stress hormones and immune function, it is difficult to disregard the idea that improving psychological well-being in cancer patients would improve physical health and ultimately survival.

STRESS CAUSED BY CANCER

Cancer is a stressful disease. It raises the specter of premature death, causes organs and organ systems to malfunction, and can produce unpleasant symptoms as well as considerable pain and suffering. Its treatments are also very aversive. Depending on the type, stage, and aggressiveness of a tumor, its location, and a number of other factors, surgical, medical, radiation, and/or immune therapies may be applied, often with substantial disfigurement, collateral tissue damage, and adverse side effects. For those who survive and join the growing ranks of people who have overcome this disease, a lifetime of surveillance and prevention awaits, punctuated by the fear that their cancer will come back. All of these features of cancer and cancer care are sources of stress and nearly all cancer patients and survivors experience some discomfort as a result.

STRESS SYNDROMES AND CANCER

ACUTE STRESS DISORDER

Acute stress disorder (ASD) is a syndrome that reflects distress experienced just after exposure to a traumatic or stressful situation, whether it is transient or not. Most people experience some distress in the wake of a major stressor, and this may take the form of intrusive and avoidant thoughts and behaviors and/or a series of emotional changes that reflect cognitive processing of and coping with the newly introduced threats. Interest in this construct reflects a need to conceptualize and treat peritraumatic stress and to identify people at risk for chronic difficulties. However, evidence of ASD among newly diagnosed cancer patients is still relatively scarce and does not generally permit careful prospective analysis of ASD and more chronic stress syndromes. Although there is evidence that people experience stress soon after learning that they have cancer (e.g., Brain, Williams, Iredale, France, & Gray, 2006), there is little systematic evidence

of acute syndromes or the emergence of post traumatic stress disorder (PTSD). Nonetheless, stress experienced after diagnosis does appear to contribute to adjustment and life quality (e.g., Golden-Krentz et al., 2005).

The potential importance of immediate stress effects was highlighted in a recent study of people with head and neck or lung cancer (Kangas, Henry, & Bryant, 2005). Patients were seen within a month of their cancer diagnosis, allowing diagnosis of ASD, and about 60% of them exhibited frank or subsyndromal ASD within that month. Follow-up data collection several months later included measurement of PTSD. More than half (53%) of the participants with ASD in the first month after diagnosis developed PTSD 6 months after diagnosis, compared with only 11% of those who did not exhibit ASD (Kangas et al., 2005). Findings from a second follow-up indicated that PTSD decreased 12 months after diagnosis and was less common than other anxiety and mood disorders (Kangas et al., 2005). These data suggested continuity and possible shared causes of ASD and PTSD in this population and point to an important marker for identifying patients who are likely to have more chronic difficulties.

POSTTRAUMATIC STRESS DISORDER

Posttraumatic stress disorder (PTSD) is a now relatively mature diagnostic category that was derived from several different literatures that featured stressful, life-threatening victimization, and disordered or discomforting reactions to these events. Much of the data describing PTSD are from studies of combat veterans (the Vietnam War was a watershed event for the diagnosis and treatment of PTSD) and disaster victims and, despite recent reformulation that extends PTSD to situations marked by serious or life-threatening illness, the focus of PTSD research has not concentrated on medical illness. However, research in this general area is growing and much of it has focused on cancer patients and survivors.

Several issues have characterized the study of PTSD secondary to cancer, including general questions about rates of PTSD in cancer-related populations. For example, considerable attention has been paid to people who know that they are at high risk for cancer. Research has suggested that knowledge of one's risk is stressful and contributes to chronic burdens that characterize people's lives. Apparently, a number of people at risk experience symptoms of PTSD, related either to parental cancer (a key indicator of one's risk) or high-risk surveillance and worry (e.g., Hamann, Somers, Smith, Inslicht, & Baum, 2005; Mosher & Danoff-Burg, 2005). For example, in a sample of 31 women with maternal breast cancer histories, about 20% appeared to meet criteria for PTSD (Mosher & Danoff-Burg, 2005). The apparent importance of maternal cancer in this sample is interesting in light of findings in research on genetic testing for cancer risk suggesting that the procedures involved in risk testing are not generally associated with ASD, PTSD, or significant increases in stress (e.g., Gritz et al., 2005; Hamman et al., 2005; Murkami et al., 2004; Smith et al., 2006). Further, distress associated with notification that one carries a mutation associated with increased risk of cancer appears to be transient and mild (Gritz et al., 2005; Smith et al., 2006). Some studies have detected relatively low rates of PTSD in high-risk samples (e.g., Lindberg & Wellisch, 2004) and the evidence does not consistently support hypotheses that high risk is associated with PTSD.

Studies of patients and survivors also suggest relatively low levels of PTSD. The distinctions between studies of patients and survivors, while more than semantic, are primarily a matter of when measures are collected vis à vis where a patient is in treatment. The "boundary" between patient and survivor is somewhat arbitrary, not always clear, and not always utilized. One can use a number of cutoffs for defining the beginning of survivorship but the relationships among these criteria and implications of the distinction for understanding cancer and stress are not known.

Regardless of whether one uses time-since-treatment criteria, frequency of care, or other ways of determining where treatment "ends" and survivorship begins, the available evidence regarding PTSD among patients/survivors is mixed. There are several reasons for this, perhaps the most important of which is that the preponderance of studies of PTSD has been done in breast cancer samples. Breast cancer, particularly primary breast cancer, has a relatively good prognosis. One can argue that in order for people to experience the threat to life that is characteristic of traumatic stress, the prognosis must be poor. Diagnosis of breast cancer is serious and stressful to be sure, but this stress may be mild compared with that experienced after diagnosis of cancers with poorer prognoses (e.g., Kadan-Lottick, Vanderwerker, Block, Zhang, & Prigerson, 2005). In support of this, several studies suggest that more severe cancers with poorer prognoses are associated with greater rates of PTSD than is primary breast cancer (e.g., Butler, Koopman, Lassen, & Spiegel, 1999; Smith, Redd, DuHamel, Johnson Vickberg, & Ricketts, 1999).

Estimates vary, but generally suggest that no more than 5% of breast cancer patients or survivors exhibit syndromal PTSD. Many studies evaluate PTSD among women years after their diagnosis and treatment, and others have assessed participants at intermediate time points along the way. Studies of survivors a year or more after treatment report evidence of distress and PTSD symptoms, but relatively low rates of PTSD (Andrykowski, Cordova, Studts, & Miller, 1998; Palmer, Kagee, Coyne, & DeMichele, 2004). Studies evaluating shorter posttreatment or postdiagnostic intervals also yield evidence of distress but low rates of PTSD (e.g., Green et al., 1998; Tjemslad, Soreide, & Malt, 1998a, 1998b). In this population, therefore, evidence favors caution as research has uncovered indications of distress but low rates of PTSD, calling into question the extent to which primary breast cancer represents a traumatic stressor (e.g., Green

et al., 1998). Perceived life threat, rather than disease stage, appears to predict distress and QOL (Laubmeier, Zakowski, & Bair, 2004).

It is useful to note that, despite the relatively low rates of PTSD in breast cancer survivors, the persistence of symptoms such as intrusive thoughts, hyperarousal, and avoidance suggests long-term psychological consequences among survivors (e.g., Kornblith et al., 2003). Among high-risk women who had a parent with cancer or who had cancer themselves, their brush with cancer remains a significant source of threat for many years (e.g., Hamann et al., 2005). Among hematologic cancer survivors, fear of cancer recurrence persisted for many years and was related to PTSD symptom experience (Black & White, 2005).

CONCLUSIONS AND FUTURE DIRECTIONS

The relationship between stress and cancer is not well characterized. Due to the variability in methodology among studies, it is difficult to draw many definitive conclusions from current research. Stress can affect the incidence and growth of cancer, but the direction of these effects and their importance in humans remains unclear. The type of tumor, the timing of the stressor, and other methodological factors, to some degree, dictate how stress will affect the development and growth of cancer. In addition, some of these studies were designed prior to recent advances in knowledge of how the immune system works and of the role of inflammation in the development of cancer (Gottfried, Molomut, & Patti, 1961).

There are further limitations in this literature. First, at best, the available studies only explain how stress affects tumors after they have already developed. Though this may be applicable to current cancer patient populations in terms of prognosis, it does not illuminate how stress may impact the development of neoplasms into vascularized tumors. Future directions should include cancer models that are more applicable to human populations, as well as stressors that are less invasive than some of the previous stressors used, such as skin wounds or spinal cord transection. Additional future directions should incorporate developing technologies for identifying the formation of neoplasms, and should evaluate the effect of stress on treatment of cancer.

Demonstrating direct effects of stress on cancer has proved difficult due to the slow growing nature of cancer, the inability to control stressors over the course of one's lifetime, and other factors. Therefore, an alternative approach is to study the effects of stress management in cancer progression. Many of these studies have focused on improving QOL by reducing stress, anxiety, or depression, strengthening coping skills, and enhancing knowledge about the disease. Though these studies have brought about improvements in these short-term outcomes, it has been difficult to show how these variables improve long-term survival and recurrence. Because of several methodological concerns there is a lack of consensus regarding the prospects for improving prognoses among cancer patients, and a debate as to whether reducing stress in cancer patients translates into long-term health outcomes, such as survival and recurrence. Future research directions should include improving methodologies as discussed by Coyne et al. (2007), as well as tailoring the interventions that work to specific cancer populations. Additional research should also include measures of pathways that may mediate the effects of stress, such as stress hormones and markers of immune function.

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31 Stress and Susceptibility to Infectious Disease

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INTRODUCTION

Since Pasteur's classic studies in the mid-nineteenth century, it has been recognized that exposure to an infectious agent is an absolute prerequisite for developing an infectious disease. The etiology of infectious diseases may thus seem entirely determined by the pathogen. However, exposure to an infectious agent does not necessarily result in infectious disease, as host defenses play a critical role. Accumulating evidence indicates that such defenses can be powerfully affected by psychological factors. An exhaustive review of studies of stress and infectious disease in humans concluded that substantial evidence then existed for a relationship between stress and increased risk of infectious disease, as found by analyzing illness behaviors such as symptom reporting and medical care seeking, but cautioned that hard evidence of effects on infectious pathology was then scant. Additional recommendations for future research in that review included increased focus on differential effects of shorter- and longer-term stressors on disease susceptibility, experimental studies manipulating the independent variable (stress), and investigations of possible biological mechanisms underlying associations between stress and infectious disease in viral exposure studies (Cohen & Williamson, 1991). As will be highlighted in this chapter, research in more recent years has addressed these suggestions.

INFECTIOUS DISEASES: PATHOGENESIS AND HOST DEFENSE MECHANISMS

The development and resolution of infectious diseases are the result of complex interactions between pathogen and host that can only be touched on here (see review). The term *pathogen* refers to any microorganism that can cause disease, including viruses, bacteria, and fungi. Invading pathogens typically colonize in particular host organs or tissues causing functional impairment and/or tissue injury. The host has the ability to defend itself against pathogens in three basic ways. The first line of defense consists of intact skin and mucus membranes. In addition to serving as a passive barrier, active processes here also help prevent infection. Cilia in the respiratory tract, for example, carry particles to the throat where they can be expelled through coughing or sneezing. Secretions here eliminate many pathogens, as is the case for gastric acid in the stomach and lysozyme in saliva and tears. A second evolutionarily ancient line of defense is provided by nonspecific activities of white blood cells. For example, phagocytic processes of white blood cells, such as neutrophils and macrophages, engulf and kill pathogens at the site of infection. Secretions of toxic substances (e.g., oxidizing agents) by white blood cells also contribute to the elimination of pathogens. Natural killer (NK) cells can eliminate intracellular pathogens (e.g., viruses) by killing the host cell in which they reside. In distinction from the general defense mechanisms involved in the first and second line of defense, the third line of defense is highly specific and is primed by prior exposure to the particular pathogen. Specific immunity depends on antigen-specific B cells and T cells, which bear receptor sites that fit with the molecular shape of an invader. When activated, these cells proliferate to create a population of cells with the same antigen specificity. It may take several days before a full antibody (B cell) or cytotoxicity (T cell) defense is mounted. It is important to note that the symptoms associated with infectious diseases (e.g., fever, runny nose, cough) may be a direct effect of the tissue damages caused by pathogens, but they are often indirect effects of the immune defenses highlighted previously. In rare instances, activation of bodily defenses can be fatal to the host (e.g., in septic shock).

ASSESSING INFECTIOUS DISEASES

Infectious illness is generally accompanied by the experience of various symptoms, including sore throat, sneezing, headaches, and stomachaches. Such self-reported symptoms have often been used in the literature as an indicator of infectious disease. However, the validity of this approach, as well as the utility of relying on clinical signs of infection (e.g., fever), have been questioned. Individuals can be infected, as confirmed by bioassay for the presence of a pathogen, without experiencing symptoms or demonstrating a clinical syndrome. Conversely,

some individuals may report symptoms without actually being infected. Stress can not only increase awareness of bodily sensations but can also decrease awareness of bodily sensations in some instances. Research has also shown that women, for as yet unknown reasons, report more infectious symptoms during the perimenstrual period compared to midcycle. Because of the questionable reliability of self-reported symptoms, investigators may attempt to verify possible cases of infections, either by clinical examinations or by assay for a particular pathogen. Clinical verification requires that a trained health care worker find observable signs of an infection, for example, herpes lesions, fever, or presence of mucus in nose, sinuses, and lungs. This approach sometimes requires the aid of technology, such as x-rays, but often still relies to a considerable degree on patients' initial symptom reports. Biological verification involves assay of the presence or replication of an infectious agent in tissue or in body fluids. It is, however, often difficult to demonstrate the presence of an unknown pathogen, given the large number of possible infectious agents. The expensive and time-consuming attempt to verify diseases caused by an unknown pathogen has been reported to succeed only about 15–28% of the time. Biological verification is thus most suitable for experimental challenge studies where one is interested in detecting the presence of a known particular pathogen.

ASSOCIATIONS BETWEEN STRESS AND INFECTIOUS DISEASE

As depicted in Figure 31.1, there are at least five basic ways through which stress may affect infectious disease. First, stress may alter exposure to pathogens. For instance, one method of coping with stress is seeking social support. This implies contact with others who may be carriers of pathogens, thereby increasing the risks of being contaminated with a virus. Stress may also alter the first line of defense, for example, causing changes in the nasal mucosa that allow deeper tissues to be exposed to pathogens. Second, a substantive literature has explored the effects of stress on immune defenses. The central nervous system can influence the immune system through direct innervation (e.g., sympathetic nerve fibers) of the primary (bone marrow and thymus) and secondary lymphoid tissues (spleen and lymph nodes). The brain can also influence the immune system indirectly through release of neuroendocrine mediators. Examples of such indirect pathways from the brain to the immune system include the hypothalamic–pituitary–adrenal (HPA) axis and the hypothalamic–pituitary–ovarian (HPO) axis. It is interesting that the pathway from the brain to the immune system is bidirectional, and activation of the immune system has been shown to influence the firing rate of neurons in the ventromedial nucleus of the hypothalamus. Third, in another indirect pathway from psychological processes to immune function, behavioral changes that may take place when an individual feels stressed (e.g., consumption of alcohol, poor diet, and less physical activity) may affect the immune system. Stress may also cause changes in sleep patterns and sleep quality, which can result in immune dysregulation (e.g., reduced NK-cell mobilization after exposure to a stressor). Fourth, stress may play a role in accentuating the clinical syndrome of infectious disease. For example, about one third of individuals who are infected with rhinovirus do not normally manifest symptoms of the disease, and it is possible that some of the hormones

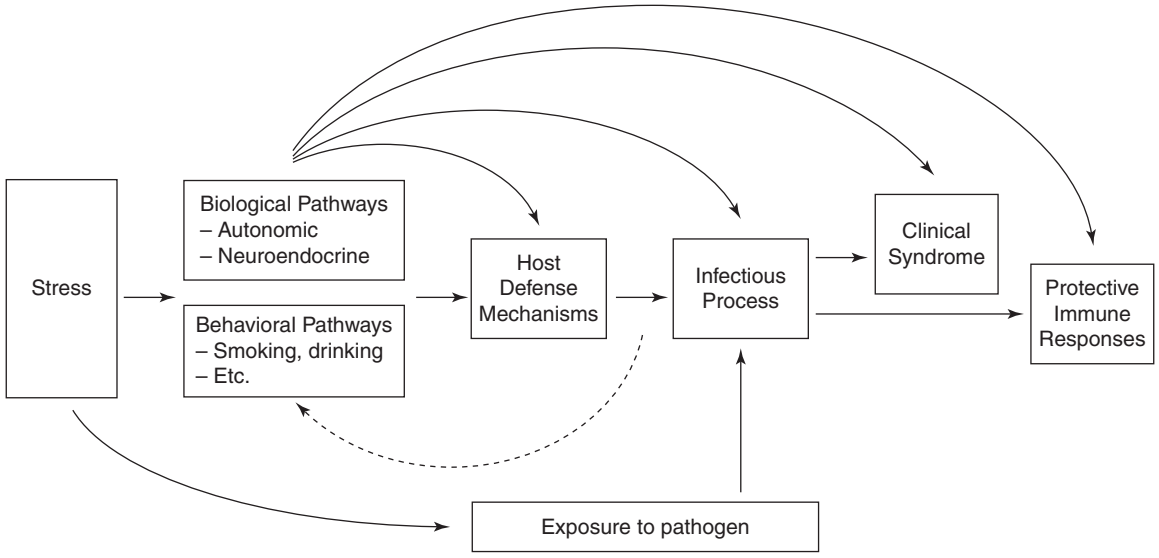

Figure 31.1 ■ Pathways linking stress to infectious disease.

released under stress, including cortisol and epinephrine, may increase mucous secretion and vasodilation, and the same hormones may influence reflex responses such as irritation and sneezing. Stress-induced behavioral changes, for example, increased smoking, may also irritate nasal and lung tissues, thereby increasing the severity of symptoms. Fifth, stress may affect recovery from infectious disease. For instance, studies have suggested that stress can cause delays in the third line of defense, the proliferative response of antigen-specific cells, which may extend the duration of symptoms. Furthermore, stress may also affect individuals' use of medication and in that way indirectly influence the course of the disease.

METHODS

Articles reviewed in this chapter were identified through computerized literature searches and through additional searches of reference lists. MEDLINE and PsycINFO were searched for the period between 1960 and 2007. We followed the examples of previous reviews of stress and disease and used the terms *stress*, *hassles*, and *life event*. These terms were combined with upper respiratory tract infection, common cold, influenza, infectious illness, herpes, and Epstein-Barr virus (EBV). The reference lists of four review articles on stress and the immune system were also inspected to identify additional relevant articles.

Articles were excluded if they did not meet a number of criteria. First, a study was excluded if the participants in the study were exposed to a physical challenge with a possible effect on the susceptibility to infectious disease that would be indistinguishable from effects of psychological stress. Furthermore, animal studies and studies with psychiatric patients were excluded. Studies were also excluded if the participants had infections that target the immune system, such as HIV/AIDS. The search yielded publications that fell within three broad categories: upper respiratory infections (URIs), herpes virus latency, and herpes outbreaks. For each of these categories, Tables 31.1 to 31.3 show information about the type of stressor, sample characteristics, length of follow-up, outcome variables, and main results. The articles in the tables are listed in an order that reflects (a) the design of the study (cross-sectional, longitudinal, and viral-challenge), and (b) the results (positive and negative). In this review, we have followed the literature and distinguished between four different stress categories: acute naturalistic stress (confrontation with a real-life short-term challenge such as academic examinations), chronic stress (a real-life challenge that lasts for a protracted period of time such as caregiving for a sick spouse), stressful life events (discrete events assessed with checklists), and perceived stress (self-report assessments).

UPPER RESPIRATORY INFECTIONS

The most familiar types of URIs are common colds and influenza. Colds can be caused by more than 100 different viruses, whereas influenza is primarily caused by two types of virus (A and B). Most colds and influenzas recede by themselves but can sometimes be complicated by secondary bacterial infections of the respiratory airways. A total of 12 cross-sectional studies and 25 longitudinal studies have focused on the effect of stress on susceptibility to URI. In addition, six viral-challenge studies have examined the effect of psychological stress on susceptibility to an inoculated rhinovirus. These 43 studies are summarized in Table 31.1.

CROSS-SECTIONAL FIELD STUDIES

Several cross-sectional studies have been conducted to investigate the association between naturally occurring stress and episodes of URIs. Although a few of these studies have used objective indices of URIs, the vast majority have relied on self-reported symptoms. As levels of stress and URIs have been assessed at the same time point in cross-sectional studies, the results from these studies can be interpreted bidirectionally, that is, individuals with a high number of URIs may be stressed for that reason or the stress may have caused increased illnesses.

All of the cross-sectional studies have supported an association between URI and various types of stress, including chronic stress, job-related stress, stressful life events, and perceived stress. Some representative examples of these cross-sectional studies are described in the following sections. Jacobs et al. (1970) reported results from a study of 106 male college students who had sought medical care for respiratory symptomatology. Of these, 50 students were diagnosed with serious URI and were asked to complete a questionnaire measuring life changes in the past year. The same questionnaire was completed by 73 students who had not sought medical attention and were free of serious illnesses. Students diagnosed with URI reported significantly more life changes. Dyck, Short, and Vitaliano (1999) investigated 70 caregivers of schizophrenic patients. The results revealed that the frequency of self-reported URIs in the past 6 months among those in highest quartile of self-reported caregiver burden was four times more compared to those in the lowest quartile. Koh, Yong, Ng, and Chia (2002) reported a study of 132 emergency-room nurses (ERNs) and general-ward nurses completing questionnaires assessing work-related stress, episodes of URIs, as well as sick days due to URIs in the past 6 months. The results revealed that ERNs reported significantly higher levels of stress, more episodes of URIs, and more sick days compared to general-ward nurses. Mohren et al. (2001) reported results from a survey of 5,896 employees with a wide range of jobs and educational levels. At baseline, the participants completed a

Table 31.1 ■ Results of Studies Investigating the Association Between Stress and Upper Respiratory Infections

Study	Design	Stressor	Stress Measure	N	Subjects	Length of Follow-Up	Assessment of URI	Results
Jacobs et al., 1969	Cross-sectional	Life events	SRRS	58	Male students		Clinically verified	+
Jacobs et al., 1970	Cross-sectional	Life events	SRRS	179	Male students		Clinically verified	+
McClelland et al., 1980	Cross-sectional	Life events	SRRS	27	Male students		Self-reported	+
McClelland et al., 1982	Cross-sectional	Life events	Current worries	133	Male prisoners		Self-reported	+
Sarason et al., 1985	Cross-sectional	Life events	LES	165	Navy students		Self-reported	+
Divale 1995	Cross-sectional	Perceived stress	3-item scale designed to the study	142	Students		Self-reported	+
Dyck et al., 1999	Cross-sectional	Chronic		70	Caregivers		Self-reported	+
Folkedal et al., 2000	Cross-sectional	Chronic		120	Employees		Self-reported	+
Schaubroeck et al., 2001	Cross-sectional	Chronic		217	Employees		Self-reported	+
Mohren et al., 2001	Cross-sectional	Chronic		5,896	Employees		Self-reported	+
Koh et al., 2002	Cross-sectional	Chronic		132	Female nurses		Self-reported	+
Wilson et al., 2005	Cross-sectional	Life events		769	Students		Self-reported	+
Meyer et al., 1962	Longitudinal	Life events	Diary	100	Family members	1 year	Biologically verified	+
Graham et al., 1986	Longitudinal	Life events	LEI	235	Family members	6 months	Biologically verified	+
		Perceived stress	Kanner's daily hassles scale					
Linville, 1987	Longitudinal	Life events	College student life events scale	106	Students	2 weeks	Self-reported	+
		Perceived stress	PSS					+
Stone et al., 1987	Longitudinal	Life events	ADE	79	Husbands and wives	12 weeks	Self-reported	+
Kiecolt-Glaser et al., 1991	Longitudinal	Chronic		138	Caregivers and controls	13 months (on average)	Self-reported	+
Gröer et al., 1993	Longitudinal	Perceived stress	PSS	65	Women	1 month	Self-reported	+
Lyons & Chamberlain, 1994	Longitudinal	Life events	Hassles and uplifts scale	169	Students	2 weeks	Self-reported	±
Lee et al., 1995	Longitudinal	Acute		89	Male cadets	13 weeks	Clinically verified	+
Cobb et al., 1996	Longitudinal	Life events	76-item version of the LEI	107	Adults	15 weeks	Clinically verified	+
		Perceived stress	PSS					
Sheffield et al., 1996	Longitudinal	Life events	ADE	48	Students	5 days	Self-reported	+
Cobb et al., 1998	Longitudinal	Life events	Coddington's	116	Children	15 weeks	Clinically verified	+
		Perceived stress	Children's hassles scale					
Lutgendorf et al., 2001	Longitudinal	Acute		58	Elderly subjects	6 weeks	Self-reported	+
Takkouche et al., 2001	Longitudinal	Life events	Schedule of recent events scale (16 items)	1,149	Employees	1 year	Self-reported	+
		Perceived stress	PSS					+
Cohen et al., 2002*	Longitudinal	Stressful life events	Cohen's major stressful life events ecale	115	Students	12 weeks	Clinically verified	+
		Perceived stress	PSS					
Hamrick et al., 2002*	Longitudinal	Stressful life events	Cohen's major stressful life events scale	115	Students	12 weeks	Clinically verified	+
Mohren et al., 2005	Longitudinal	Perceived stress	Karasek's job content questionnaire, job satisfaction assessed by one item (good, fair, moderate, not good)	7,482	Employees	9 months	Self-reported	+

Smolderen et al., 2007	Longitudinal	Perceived stress	PSS	5,404	Respondents from the general population	4 weeks	Self-reported	+
Boyce et al., 1977	Longitudinal	Life events	SRRS	58	Children	1 year	Biologically verified	−
Chapar et al., 1988	Longitudinal	Life events	SRRS	49	Children	5 months	Self-reported (by mothers)	−
Evans et al., 1988	Longitudinal	Life events	ADE	65	Students	9 weeks	Self-reported	−
Clover et al., 1989	Longitudinal	Life events	SRRS	246	Family members	Influenza epidemic	Biologically verified	−
Evans & Edgerton, 1991	Longitudinal	Life events	ADE	100	Clerical staff	10 weeks	Self-reported	−
Evans et al., 1996	Longitudinal	Life events	LES	35	Students	6½ weeks	Self-reported	−
Stone et al., 1993	Longitudinal	Life events	ADE	79	Husbands and wives	12 weeks	Self-reported	−
Deinzer & Schüller, 1998	Longitudinal	Acute		66	Students	13 days	Self-reported	−
Totman et al., 1977	Viral-challenge	Laboratory		48	Healthy volunteers	6 days	Cold symptoms	+
							Virus shedding	−
Totman et al., 1980	Viral-challenge	Life events	SRRS SEI DEI TLI	52	Healthy volunteers	6 days	Cold symptoms	−
Cohen et al., 1991	Viral-challenge	Stress index	LRS PSS NAS	394	Healthy volunteers	7 days	Virus isolation, fourfold increase in neutralizing antibodies, cold symptoms	+
Stone et al., 1992	Viral-challenge	Life events	LES	17	Healthy volunteers	5 days	Virus isolation, fourfold increase in neutralizing antibodies, cold symptoms	+
		Perceived stress	PSS				Virus isolation, fourfold increase in neutralizing antibodies, cold symptoms	−
Cohen et al., 1998	Viral challenge	Life events, short-term	LEDS	276	Healthy volunteers	5 days	Virus isolation, fourfold increase in neutralizing antibodies, cold symptoms, mucus production, mucociliary clearance functions	−
		Life events, long-term	LEDS				Virus isolation, fourfold increase in neutralizing antibodies, cold symptoms, mucus production, mucociliary clearance functions	+
Cohen et al., 1999	Viral challenge	Perceived stress	PSS	55	Healthy volunteers	7 days	Virus isolation, fourfold increase in neutralizing antibodies, cold symptoms, mucus production cytokines	+

*Apparently, the studies are based on data from the same sample; + one or more significant differences in the expected direction, − no significant differences or differences in the opposite direction of the expected.
ADE, assessment of daily experiences form; DEI, Surtees' difficulties index; LEDS, life events and difficulties schedule; LEI, Tennant's life events inventory; LES, life experiences survey; LRS, list of recent experiences; NAS, negative affectivity scale; PSS, perceived stress scale; SEI, Surtees' events index; SRRS, social readjustment rating scale; TLI, Totman's loss index.

questionnaire assessing psychological job demands and reported episodes of common cold in the past 4 months. Significantly more employees experiencing high levels compared to employees experiencing low levels of psychological job demands reported having had a common cold. In a study of 769 first-semester college students, Wilson, Rosenthal, and Austin (2005) found that reporting of symptoms of URI during the first 2 months of the first semester in college was associated with both exposure to community violence during high school (e.g., being a victim of violence) and with the level of psychological distress experienced during the first 2 months of the first semester. Further analyses revealed that the relationship between exposure to community violence and URI symptoms was statistically mediated by distress.

LONGITUDINAL FIELD STUDIES

Longitudinal studies assessing subjects on more than one occasion allow for predictions of URIs from levels of stress reported before the occurrence of URIs and, therefore, allow stronger statements about possible causal relationships between psychological stress and URIs. However, such studies are still correlational and do not exclude the possibility that a third unknown variable may explain the observed relationships between stress and URIs. Though many of the longitudinal field studies are based on self-reported symptoms of URI, some include biological or clinical verification. As seen in Table 31.1, several of the longitudinal field studies have found evidence linking URI and prior stress.

An example of a longitudinal study with a positive finding comes from Takkouche, Regueira, and Gestal-Otero (2001). This study included 1,149 administrative and staff members of a Spanish university. Participants completed a questionnaire assessing stressful life events, perceived stress, and negative and positive affect at "baseline," and then every 10th week, during the next 12 months, they received a short questionnaire to identify new cases of a common cold. In the 28,199 person-weeks of follow-up, 365 cases were detected. Stressful life events, perceived stress, and levels of positive and negative affect reported at baseline were related to the risk of getting a cold, with negative affect showing the strongest associations. Participants in the highest quartile of negative affect were nearly four times more likely to develop a common cold than did those in the first quartile. Using a pre–post longitudinal study design with an explicit stressor, Lutgendorf et al. (2001) recruited 30 older adults planning to move to congregate living facilities and conducted assessments in their homes 1 month and 2 weeks pre- and post-move, respectively. Nonmoving comparison participants (n = 28) were assessed at similar time points. Movers reported more illness episodes between the two assessments than controls. A third example of a longitudinal design comes from Mohren et al. (2005) who focused on job-related stress as a predictor of increased risk of staying at home for infectious disease. At baseline, nearly 8,000 employees (in 687 different professions represented in the Maastricht Cohort study) completed a questionnaire assessing job stress, and 8 months later, episodes of self-reported common infectious diseases during the previous 4 months were assessed. Low levels of job commitment and satisfaction increased the chance of being absent from work with a common cold.

In a longitudinal study by Groer, Carr, and Younger (1993) the relationships between symptoms of common infectious illnesses, menstrual cycle phase, and cycle-related distress were examined. The study included 65 women who had regular menstrual cycles and were not taking birth-control pills. The participants completed questionnaires assessing menstrual distress, perceived stress, and infectious symptoms three times during the menstrual cycle. The results indicated a highly significant clustering of infectious illness symptoms during the perimenstrual period compared to midcycle. Menstrual distress and perceived stress were both related to the frequency and intensity of infection symptoms at the menstrual and premenstrual phase, but not at midcycle. It should be noted, however, that hormonal fluctuations may cause more physical symptoms (and/or increased focus on them) as well as increased perception of stress, and the association found between stress and symptoms may, therefore, not reflect causality.

An example of a longitudinal study with clinical verification of the URI was the one reported by Hamrick, Cohen, and Rodriguez (2002) that involved healthy college students (n = 115) completing questionnaires that assessed stressful life events and social network diversity; these students were interviewed weekly for 12 weeks for the presence of URIs, which was verified by a student health center nurse practitioner. An interaction was found between stressful life events and social network diversity, with greater network diversity being associated with increased risk of illness among those with high levels of life stress and fewer illnesses found among those with fewer stressful life events. In accord with these results, a more recent study by Smolderen, Vingerhoets, Croon, and Denollet (2007) found that high levels of perceived stress were related to increased risk of self-reported, influenza-like illness but that socially inhibited individuals reported less illness than their more outgoing counterparts. One reasonable explanation is that pathogen exposure is more likely for individuals with a larger social network than for socially inhibited people.

Several longitudinal studies have examined the possible influence of desirable and undesirable daily life events on URI symptom report, generally with mixed results. In one study it was found that undesirable daily life events increased 3–4 days prior to onset of an URI episode, whereas desirable events decreased 4–5 days prior to onset. In a second study, URI symptoms were associated with increases in both negative and positive life daily events over a 2-week interval. The results of a third study suggested a lagged relationship between daily events

and somatic symptoms, but only for undesirable experiences. In a subsequent study by this group, it was found that desirable events decreased 4 days prior to symptom onset, but undesirable events were not significantly related. Using a similar study design, 100 nonmanagerial staff members were followed for a maximum period of 10 weeks. Again, the results showed that, whereas the frequency of desirable events decreased significantly during the 4 days prior to cold onset, the tendency for the number of undesirable events to rise during the same period did not reach statistical significance. In another study, it is only positive but not negative experiences that predicted vulnerability to URI, but positive event scores were more than four times *higher* in participants experiencing a cold episode in the follow-up period. Finally, in a study of 79 middle-aged men, the researchers were unable to detect a relationship between mood and daily experiences—positive or negative—and the onset of illness episodes.

A number of longitudinal studies have not detected any association between URI and psychological stress. For example, a well-conducted cohort study during an influenza B epidemic in 1984 reported by Clover, Abell, Becker, Crawford, and Ramsey (1989) found no association between influenza B infection and family functioning or stress in 246 children. Baseline (pre-influenza) data included a serum determination of the presence of influenza A and B antibodies, family functioning, and self-reported parental stress. During the study, all family members of patients with fever or URI symptoms were examined, and throat swabs were obtained for viral culture. Approximately 2 weeks after the influenza epidemic ended, sera for antibodies were again collected for all family members. The results showed that infection, defined as a fourfold titer increase or a positive viral throat culture, was significantly associated with both cohesion and adaptability. Family stress, however, was not associated with influenza B infection. Unexpectedly, it was found that disengaged families had significantly lower incidence of influenza B infection. This finding may be caused by less physical proximity in these families compared to enmeshed families.

The potential complexity of relationships between stressful life events and childhood URIs is suggested by Boyce et al. (1977) in another well-conducted family study. In this study, 58 children in day care were observed on a daily basis for an entire year, during which all illnesses were clinically verified by a nurse practitioner. Moreover, nasopharyngeal cultures were taken biweekly, as well as at the beginning of each illness. At the end of the year, parents completed several questionnaires assessing major life events and family routines. Stressful life events in themselves were not associated with number of URIs. However, events interacted with family routine such that those children with strong family routines and parents who reported more life changes had more severe illnesses (e.g., longer disease duration) than other children, but not more illnesses. It was hypothesized that children accustomed to a highly routine life are more stressed than protected by their routines when a major life change is occurring. Despite the longitudinal design of this study, the number of major life events was measured only at the end of the study period, making causal interpretations more tenuous. It is impossible to rule out an explanation in which families with high levels of illness severity were stressed for that reason.

VIRAL-CHALLENGE STUDIES

In a number of experimental studies, healthy volunteers have been exposed to specific viruses and relationships between stress assessed prior to the viral challenge and susceptibility to URI were investigated. Viral-challenge studies have the major advantage over other studies of naturally occurring URI in that it is possible to control for exposure and prechallenge antibody titers against a particular virus. Furthermore, it is possible to verify the infection biologically, as the virus is known to the investigators. It should be noted, however, that from the perspective of relationships between infection and stress, most of the viral-challenge studies have been correlational because there was no manipulation of the independent variable, psychological stress.

In an early exception to that rule, Totman et al. (1977) sought to determine whether induced stress was related to susceptibility to common colds among 48 volunteers inoculated with rhinovirus. Stress, in the form of cognitive dissonance, was induced in 50% of the study participants who had to choose whether or not to receive an "antiviral drug" (a placebo). If they received the drug, they were told they had to get their stomachs examined, at the end of the study, by gastric intubation. In this procedure, a tube is inserted through the nose down into the stomach. Most of the participants in the choice group reported high levels of stress associated with the choice they had to make. Signs and symptoms of cold were rated daily by a clinician and virus shedding was assessed by nasal washings on the 3rd and 4th day after virus inoculation. Symptom scores were higher in the choice group than in the control group, but there was no difference with respect to virus shedding. In a later study with 52 participants, the same group of researchers found an association between stressful life events and subsequent susceptibility to virus-induced common colds. In contrast to the first study, stress was associated with increased virus shedding but not with clinical symptom scores. It was also found that introverts developed worse symptoms and more virus shedding than extroverts. In a later study by Stone and colleagues, 17 students were exposed to a rhinovirus infection and then isolated for 5 consecutive days. The average number of reported stressful life events for the previous year was significantly higher for those who developed colds than for those who did not. Preinoculation measures of affect and perceived stress were not related to susceptibility to the experimentally induced rhinovirus infection.

In a series of studies, Cohen and colleagues have examined the relationships between stress, psychosocial

factors, and susceptibility to experimental rhinovirus infection. Healthy volunteers completed questionnaires measuring stress, behaviors, and personality traits and were then inoculated with rhinovirus and quarantined for 5 to 7 days. Daily, the participants were examined by a clinician and nasal-wash samples were collected for viral isolation. All studies controlled for prechallenge antibodies to the specific rhinoviruses used. In an early study, evidence was found for a dose-dependent relationship between scores on a composite stress index and susceptibility to the viral challenge. In a later study, the effect of severe chronic and acute stressful events during the previous year was investigated in 276 adults inoculated with rhinovirus. Participants with chronic stressors (lasting 1 month or longer), especially interpersonal conflicts and work-related problems, were at higher risk for developing a cold than those without chronic stressors, whereas participants with acute stressful events (lasting less than 1 month) were not. In a study of the relationship between perceived stress and influenza by the same investigators, 55 participants completed a measure of perceived stress and were experimentally infected with an influenza A virus, quarantined, and monitored daily for URI symptoms. Higher stress measured prior to the viral challenge was associated with higher symptom scores. Stress was also associated with objective illness indices, including greater mucus weights and higher concentrations of IL-6, a proinflammatory cytokine.

In several additional studies, partly investigating data from the same groups of participants as in the viral-challenge studies described earlier, the same group of researchers has investigated the role of other factors that might be indirectly associated with susceptibility to common colds. One study found that participants with greater diversity of social relationships were less susceptible to common colds and that susceptibility decreased in a dose–response manner with increased diversity of the social network. In line with these results, they also found that a high level of sociability, defined as a combination of three personality factors—extraversion, agreeableness, and positive relationship style—was associated with a lower probability of developing a cold. In the most recent study, the influence of emotional style was examined. It was found that a tendency to experience positive emotions such as happiness and pleasure (positive emotional style) was associated with lower risk of developing a cold. On the other hand, the researchers were unable to confirm an association between a tendency to experience negative emotions such as anxiety, hostility, and depression (negative emotional style) and increased risk of developing a cold.

SUMMARY

With respect to the available cross-sectional studies, the evidence of a relationship between psychological stress and URI seems convincing, as the results of all the studies reviewed supported an association. However, findings from cross-sectional studies may be biased, as participants′ memories may be influenced by stress. Therefore, we may question whether the positive results reflect stress-induced pathology or rather stress-induced processes that drive symptom reporting, that is, increased sensitivity to physical sensations and/or an increased tendency to label bodily sensations as *symptoms*. Evidence from longitudinal studies allows stronger statements about causal relationships between psychological stress and URI. Of the longitudinal studies reviewed, 17 out of 25 found support for an association between stress and increased risk of URI. Many of these studies measured symptoms of infectious illnesses repeatedly with close time intervals thereby reducing the risk of distorted memories. The majority of longitudinal studies that were unable to support an association between stress and infectious disease used biological verification of the URI. Biological verification of URIs may decrease risk of Type 1 error, but may, at the same time, increase risk of Type 2 error, as attempts to verify illnesses caused by an unknown pathogen are only successful in about 15–28% of the cases. This methodological weakness is overcome in the viral-challenge studies in which the pathogen is known to the researchers. It also should be noted that in some of the studies with negative results the length of follow-up was rather short, and, as a consequence, few participants reported major life events as they may require a longer time span to occur.

The evidence of a relationship between psychological stress and increased susceptibility to infectious disease coming from the group of viral-challenge studies is rather persuasive. Four of the six viral-challenge studies provided rather distinct support of an association between stress and increased susceptibility to an inoculated virus. Two of the studies focused on stressful life events, and one study focused on perceived stress. The fourth study defined stress as a cumulative score based on stressful life events, perceived stress, and negative affect. The results of the remaining two studies were more ambiguous yet suggestive. In one study, stress was related to increased symptoms of URI but not to virus shedding. Another study found that stressful life events of long duration had an effect on susceptibility to the inoculated virus, whereas stressful life events of shorter duration did not.

Two longitudinal studies have found an increase in the number of negative daily life events and a decrease in number of positive daily life events (uplifts) close in time to the incubation period of many common cold viruses (2–4 days), suggesting a critical period with respect to vulnerability to URI. Such data may indicate that the observed association between stress and self-reported illness is attributable to pathology. However, during the incubation period, the antigen-induced release of cytokines may affect mood and sickness behavior that may bias stress reporting even before clear URI symptoms are

noticed by the individual. Furthermore, as shown earlier, later studies attempting to replicate these results have had inconsistent results. As noted by Evans and Pitts, there may be several reasons for the mixed findings, including different definitions of a cold episode and the use of the target-observer method in some of the studies. The purpose of the target-observer method is to increase reliability, as the partner of the participant is requested to help the participant to recall the events of the day. However, findings from other studies have indicated that because the partner gets insight into the diary of the participant, some participants omit information, especially when it comes to events that involve disagreements between the two. The use of financial incentives in one of the studies may also have contributed to the negative results. The requirement that all questionnaires had to be completed and returned before receiving incentives may have encouraged less careful responding to achieve a complete record, thereby reducing the reliability of the data.

Considered as a whole, the existing studies investigating the effect of stress on susceptibility to URIs provide rather strong evidence that stress does influence the risk of infection and the severity of symptoms. The results from the well-controlled viral-challenge studies and longitudinal studies using clinical verification are particularly compelling. Negative findings from studies in the literature may be indicating the limits of these effects (e.g., daily negative events may have little effect on the common cold), but proof of principle has been established.

HERPES VIRUS INFECTIONS: HERPES VIRUS LATENCY

The most frequently studied herpes virus infections in the stress literature are herpes simplex virus (HSV) and EBV. As with all herpes viruses, they induce lifelong latent infections with continuing viral presence in cells long after resolution of the initial infection. Later, during periods of impaired cellular immunity, the virus may reactivate. There are two types, 1 and 2, of HSV, both causing lasting infection with recurrent lesions during periods of immune compromise. As one factor that can contribute to immune-suppression, stress would be expected to increase the risk of reactivation of the virus and recurrence of HSV lesions.

Quantification of antibodies to herpes viruses is commonly used as an indirect measure of herpes virus reactivation. During periods of compromised cellular immune function, the replication of herpes viruses increases thereby increasing the production of antibodies in response to the herpes viral replication. Observations of symptoms have also been used as a measure of virus reactivation. However, reactivation of herpes viruses does not always result in a full-blown clinical presentation, and less apparent manifestations of the reactivation may also have health implications. For instance, the immunological changes during herpes virus infections have been implicated in the pathogenesis of vascular disease through increased production of cytokines and various growth factors associated with inflammation.

A total of 19 correlational studies have examined the effect of different types of naturally occurring stressors on herpes virus latency. Seven of the 19 studies are cross-sectional, with 5 comparing individuals exposed to a long-term stressor to a nonstressed control group. The majority of the studies have used longitudinal designs (12 studies) and involved an examination stress model. Details are shown in Table 31.2.

CROSS-SECTIONAL FIELD STUDIES

When investigating herpes virus latency, the cross-sectional approach may not have the same methodological limitations as mentioned with respect to studies of stress and URI, as it seems less likely that increased levels of herpes virus antibody titers can be perceived and cause increased levels of self-reported stress, although prodromal influences on mood need to be considered. When compared with nonstressed control groups, higher levels of EBV antibodies have been found among subjects exposed to different types of chronic/long-lasting stressors, for example, marital disruption and being a family caregiver to an Alzheimer's disease victim. Similarly, higher levels of HSV antibodies were found in a group of chronically stressed individuals living near the damaged Three Mile Island nuclear power plant, when compared to demographically comparable controls. However, other cross-sectional studies have not supported the hypothesis of a relationship between stress and herpes virus latency. For instance, one study examined the association between chronic stress and cytomegalovirus and HSV Type 1 and 2 antibody titers in individuals exposed to caregiving stress, but did not find support for the association. Also, in two studies (reported in one article), there was no association found between students' levels of perceived stress and immunoregulation of EBV. The first study included 121 students who completed questionnaires on daily hassles, coping style, and loneliness. The results showed no significant associations between the psychological measures and levels of antibodies to EBV. However, as psychological stress levels were generally low, a second study was conducted. In this study, 95 participants were selected on the basis of either very low or very high stress scores, but again, no significant relationship between stress and levels of antibodies to EBV was found.

LONGITUDINAL FIELD STUDIES

Several longitudinal studies have compared herpes virus antibody levels in students during examination periods with levels measured before or after the examinations.

Table 31.2 ■ Results of Studies Investigating the Association Between Stress and Reactivation of Latent Herpes Viruses

Study	Design	Stressor	Stress Measure	N	Subjects	Length of Follow-Up	Dependent Variable	Results
Kiecolt-Glaser et al., 1987a	Cross-sectional	Chronic		76	Married and separated women		Antibody titers to EBV	+
Kiecolt-Glaser et al., 1987b	Cross-sectional	Chronic		68	Caregivers and controls		Percentages of: T lymphocytes, helper T lymphocytes, suppressor T lymphocytes, NK cells, antibody titers to EBV	+ – (NK cells)
McKinnon et al., 1989	Cross-sectional	Chronic		20	Damaged nuclear power plant neighbors		Antibody titers to HSV and CMV, total number of leucocytes and lymphocyte subpopulations	+
Glaser et al., 1997	Cross-sectional	Chronic		129	Caregivers and controls		HSV antibody titers, proliferative memory T-cell response	+
Pariante et al., 1997	Cross-sectional	Chronic		36	Caregivers and controls		T cell number, Antibody titers against HSV-1, HSV-2, and CMV, markers of inflammation, serum immunoglobulins and titers for nonlatent virus	–
Benschop et al., 1998	Cross-sectional	Perceived stress	EPCL	121	Students		EBV antibody titers	–
	Cross-sectional	Perceived stress	EPCL	95	Student with extreme scores		EBV antibody titers, specific cytotoxic activity against autologous EBV-transformed B-cells	–
Kiecolt-Glaser et al., 1984	Longitudinal	Acute		42	Students	4 months	EBV transformation levels	+
Glaser et al., 1985	Longitudinal	Acute		49	Students	4 months	HSV antibody titers	+
Glaser et al., 1987	Longitudinal	Acute		40	Students	1 year	EBV antibody titers, proliferative memory T-cell response, Interferon production by lymphocytes stimulated with concanavalin	+
Glaser et al., 1991	Longitudinal	Acute		15	Students	3 × 1 month	EBV VCA antibody titers in plasma and throat washings	+
Glaser et al., 1993	Longitudinal	Acute		25	Students	1 month	Memory T-cell proliferative response to EBV	+
Glaser et al., 1994	Longitudinal	Acute		45	Male students	1 month	EBV VCA antibody titers	+
Glaser et al., 1999	Longitudinal	Acute		95	Male and female cadets	6 weeks	Antibodies to EBV, HSV-1, and HHV-6	+ (EBV) – (HSV-1 and HSV-6)
Sarid et al., 2001*	Longitudinal	Acute		54	Female students	4 months	Level of salivary EBV antibodies	+
Sarid et al., 2003*	Longitudinal	Acute		54	Female students	4 months	Level of salivary EBV and HCMV antibodies	+
Lee et al., 1992	Longitudinal	Acute		37	Cadets	4 weeks	EBV antibody titers	–
Ockenfels et al., 1994	Longitudinal	Acute		20	Students	92 days	Antibody titers to HSV-1 and Adenovirus	–
Lutgendorf et al., 2001	Longitudinal	Acute		58	Elderly movers and controls	4 months	NKCC, IL-6, EBV antibody titers	– (IL-6, EBV) + (NKCC)

*Apparently, the studies are based on data from the same sample; + one or more significant differences in the expected direction, – no significant differences or differences in the opposite direction of the expected.
EPCL, everyday problem checklist.

Evidence of an association between examinations and compromised immunosurveillance of latent EBV has been reported. However, the findings in this area are not clear cut. Glaser et al. (1985, 1991, 1993, 1994) found an association between academic stress and reactivation of latent EBV. Sarid et al. (2001, 2003) found higher levels of antibodies during examination period compared to baseline levels, but the fluctuations in EBV antibody titers were unrelated to reported distress. In a third study, 30 older adults exposed to housing relocation were compared to 28 older nonmovers. EBV antibody titers, measured 1 month premove and 2 weeks and 3 months postmove, were unaffected by the stress associated with moving. However, 1 month premove and 2 weeks postmove, movers had lower NK-cell cytotoxicity (NKCC) than controls, suggesting a compromised immune system. Other longitudinal studies have also failed to find a relationship between stress and reactivation of both HSV-1 and EBV.

SUMMARY

Concerning the effect of stress on herpes virus latency, a greater proportion of prospective studies (9 out of 12) than of cross-sectional studies (4 of 7) have found support for such a relationship. The longitudinal studies have used similar designs as the majority (9 out of 12) have monitored antibody to herpes virus in students before, during, and/or after exam periods. One study with negative findings monitored elderly individuals during a housing relocation. This could be taken to suggest that younger individuals are more vulnerable than the elderly to stress-induced changes in the immune system. However, one study using young male cadets as study participants was also unable to find evidence of a relationship between stress and herpes virus latency. It should be noted that this group of participants were likely to be in excellent physical condition and perhaps, therefore, less vulnerable to stress-induced immunological changes. In contrast, another study with positive results also used cadets as study participants. This study included both male and female cadets, and it could be that women are more vulnerable to stress-induced vulnerability.

In contrast to the prospective studies, none of the cross-sectional studies has focused on acute life stress, but all of them have investigated chronic or perceived stress. Three of the four studies examining chronic stressors, such as caregiving stress and marital disruption, found an effect on herpes virus latency. Neither of the two studies that examined the relationship between perceived stress and herpes virus latency found evidence of an association. However, in one of the studies, the reported stress levels were generally low, and in both studies there was a time lag up to 3 weeks between assessment of perceived stress and blood collection. If it is assumed that perceived stress is a transient state rather than a more chronic condition, this time lag could be one explanation for the negative results.

ORAL AND GENITAL HERPES OUTBREAKS

A number of studies have explored the extent to which the stress-induced changes in antiviral antibody increase the risk of oral or genital outbreaks of herpes virus. Although HSV-1 generally is associated with oro-labial lesions, and HSV-2 with genital disease, this is not always the case. A considerable proportion of genital herpes outbreaks are caused by HSV-1. HSV-2, on the other hand, seems less frequently associated with oral herpes. A genital herpes outbreak typically lasts from 2 to 3 weeks, is often painful, and may require hospitalization. Genital herpes outbreaks, therefore, often have a negative effect on patients' quality of life. Less frequently, HSV infects the mucous membrane of the eye, which can lead to impaired vision due to scars on the cornea.

A total of 14 correlational studies have investigated the relationships between stress and herpes outbreaks. The 14 studies can be divided into two groups. The first group consists of studies with some methodological weaknesses as they are based on a cross-sectional design and on patient self-reports. The second group includes studies that are generally methodologically sound, as they have used longitudinal designs and have verified the outbreaks, either by clinical examination or by obtaining swabs of the lesions for isolation of HSV. One study used a longitudinal design but was based on patients' self-reported symptoms of herpes virus outbreaks. Details of these studies are presented in Table 31.3.

CROSS-SECTIONAL FIELD STUDIES

The results of four cross-sectional studies support an association between oral and genital herpes outbreaks and stressful life events and perceived stress. For instance, Stock et al. (2001) investigated risk factors for HSV-1 infection in a population of 770 German and Spanish university students. Data on clinical manifestations and risk factors were obtained with standardized questionnaires. A high level of perceived stress was independently associated with symptoms of oral herpes, and drinking alcohol more than one time per week was found to be a protective factor. As the number of herpes recurrences tends to decrease after the first year, the moderating effects of disease duration was investigated in a separate study. It was found that when disease duration was less than 4 years, stress and frequency of HSV recurrences were positively related, but for longer disease duration, this relationship was not maintained. Three additional cross-sectional studies have not documented a relationship between chronic stress or stressful life events and oral and/or genital herpes outbreaks. For instance, in a study of 116 patients with a known history of genital herpes, recurrence frequency was related to patient coping style, with both problem- and emotion-focused coping being less prevalent among patients reporting a high number

Table 31.3 ■ Results of Studies Investigating the Association Between Stress and Herpes Outbreaks

Study	Design	Stressor	Stress Measure	N	Subjects	Length of Follow-Up	Assessment of Outbreaks	Results
Levenson et al., 1987	Cross-sectional	Life events	SRRS	31	Patients with genital herpes		Self-reported genital herpes outbreaks	+
VanderPlate et al., 1988	Cross-sectional	Life events	SRRS	59	Patients with genital herpes		Self-reported genital herpes outbreaks	+
Longo & Clum, 1989	Cross-sectional	Perceived stress	Kanner's hassles scale	46	Patients with genital herpes		Self-reported genital herpes outbreaks	+
Stock et al., 2001	Cross-sectional	Perceived stress	PSS	770	Students		Self-reported cold sores	+
Silver et al., 1986	Cross-sectional	Life events	LES	67	Patients with genital herpes		Self-reported genital herpes	−
Cassidy et al., 1997	Cross-sectional	Life events	LES	116	Patients with genital herpes		Self-reported genital herpes outbreaks	−
Schmidt et al., 1985	Longitudinal	Life events	12-item scale modified after Dohrenwends' list of events	18	Patients with oral herpes	Varying	Self-reported cold sores	+
		Perceived stress	Kanner's hassles scale					+
Hoon et al., 1991	Longitudinal	Life events	LES	148	Students	6 months	Verified recurrences of genital herpes simplex	−/+
Katcher et al., 1973	Longitudinal	Life events	SRRS	38	Students	6 months	Verified cold sores	−
Goldmeier et al., 1986	Longitudinal	Life events	LEQ	57	Patients with genital herpes	Varying	Verified genital herpes simplex	−
Kemeny et al., 1989*	Longitudinal	Life events	LES	36	Patients with genital herpes	6 months	Verified recurrences of genital herpes simplex	−
		Perceived stress	Daily hassles scale					
Rand et al., 1990	Longitudinal	Perceived stress	Vuchinch & Tucker's daily stress questionnaire	56	Patients with genital herpes	3 months	Verified recurrences of genital herpes	−
Cohen et al., 1999	Longitudinal	Life events	LES	58	Women with genital herpes	6 months	Verified recurrences of genital herpes simplex	−
		Perceived stress (short-term and persistent)	A stress log developed to the study					−
Herpetic Eye Disease Study Group, 2000	Longitudinal	Perceived stress	Life arenas stress measure/a weekly stress log developed to the study	308	Patients with a history of HSV eye disease	15 months	Verified recurrence of HSV eye disease	−

*Apparently, the studies are based on data from the same sample; + one or more significant differences in the expected direction, − no significant differences or differences in the opposite direction of the expected.
LEQ, life events questionnaire; LES, life experiences survey; PSS, perceived stress scale; SRRS, social readjustment rating scale.

of HSV-2 recurrences, whereas stressful life events were unrelated to recurrence frequency of genital herpes outbreaks.

LONGITUDINAL FIELD STUDIES

A few studies using a longitudinal design have yielded results that are suggestive of a relationship between psychological stress and increased frequency of herpes recurrences. In one study, reported by Schmidt, Zyzanski, Ellner, Kumar, and Arno (1985), 18 volunteers between 20 and 43 years of age with recurrent oral herpes completed a questionnaire assessing stressful life events and hassles during a dormant and again during an active stage of infection. In the week prior to the appearance of a lesion, the participants experienced an increase in daily hassles and stressful life events. Another study found persistent stress (lasting more than 7 days) was associated with increased risk of a genital herpes outbreak in the following week. In a study of university students, psychological stress was found unrelated to genital herpes recurrence but seemed to predispose subjects to more generalized illnesses, which in turn statistically mediated recurrence.

Seven longitudinal field studies found no effect of stressful life events or perceived stress on oral and genital herpes outbreaks. Providing clear evidence of inconsistencies in this literature, one of the studies failed to replicate the results of an earlier study by the same group of researchers showing that levels of anxiety and depression were inversely related to time of recurrence. The results of another study suggest an overreporting of stress due to recurrence of ocular HSV disease. In this study, adults with a documented history of ocular HSV disease completed a weekly stress log. When cases for which the weekly log assessing psychological stress was completed after the onset of symptoms were excluded, the results did not support an association between stress and risk of ocular HSV recurrence. In contrast, when these cases were included in the analyses, stress was found associated with risk of ocular HSV recurrence.

SUMMARY

The evidence of an association between stress and clinical outbreaks of herpes virus is sparse. Results from 4 out of 6 cross-sectional studies support an influence of stress on herpes virus outbreaks. However, the cross-sectional designs of the studies make the results susceptible to systematic biases in recall, a notion confirmed by a study showing that the severity of reported symptoms could be related to the psychological consequences of the attacks. Only 1 out of 8 longitudinal studies supported an association between stress and clinical herpes outbreaks, and the longitudinal study that did report an association between stress and clinical herpes outbreaks utilized self-reported HSV recurrences, whereas the remaining 7 negative studies were based on biologically verified herpes outbreaks. However, until recently, it was believed that outbreaks of oral and genital herpes could only be caused by HSV-1 and HSV-2, respectively, and some investigators have only been searching for one type of HSV when attempting to verify the outbreaks by isolation of virus in swabs from lesions. This implies that some lesions may have been removed from the analyses because they erroneously had been classified as not being caused by HSV, which may have confounded the results.

Hoon showed that though psychological stress did not affect genital herpes recurrence directly, it predisposed participants to more generalized illnesses, which in turn affected herpes recurrence. This possibility is in accord with our previous conclusion that stress is likely to be related to increased susceptibility to URI, as this could be an indirect pathway linking stress and herpes outbreaks. As has been suggested, it may also be important to differentiate between patients with longer disease duration and patients who have had their first outbreak recently, as the number of recurrences tends to decrease after the first year. This possibility has received little consideration in the literature and may at least in part account for the negative findings regarding effects of stress.

DISCUSSION

The published studies reviewed in this chapter provide proof of the principle that psychological stress can increase susceptibility to infectious diseases and may cause reactivation of latent viruses. The evidence can be organized in four areas.

First, cross-sectional studies have consistently shown associations between self-reported stress and higher levels of self-reported URI symptoms. Even though results of cross-sectional studies have to be interpreted with caution due to possible recall bias, the results of the great number of cross-sectional studies are suggestive of an association between symptoms of URI and *various* types of stressors, for example, stressful life events and perceived and chronic stress.

Second, longitudinal studies have consistently found associations between psychological stress and increased susceptibility to infectious diseases. The longitudinal approach largely overcomes the problem of possible recall bias associated with cross-sectional studies. The methodology concerning assessment of infectious disease has been heterogeneous in the series of longitudinal studies. Thus, some studies have used participants' self-reports of URI symptoms as a measure of infectious disease, whereas other studies have verified the infectious diseases, either clinically by health personnel or biologically by establishing evidence of a particular infectious agent in tissue or fluids. The results of longitudinal studies, including those making use of participant self-report or clinical verification of the diseases, have rather

consistently supported an association between psychological stress and increased susceptibility to infectious disease. In contrast to these, the results of four longitudinal studies in which the infectious diseases were only assessed biologically have been mixed, with two studies supporting a relationship between stress and infectious disease, and two not. One reason for the mixed findings could be variations in number of participants; one of the studies did not support an association between stress and infectious disease that had fewer participants compared to the two studies that were supportive of an association. A second explanation could be that the two unsupportive studies used children as study participants, which may have reduced reliability of the self-reported stress levels or may suggest reduced effects of stress among children. Finally, naturalistic studies relying on biological assessment of a particular infectious agent have a high risk of Type II error, as search for an unknown pathogen is only successful in 15–28% of the cases.

Third, viral-challenge studies have consistently found relationships between stress and susceptibility to an inoculated virus and, in some cases, in a dose–response manner. The viral-challenge studies have methodological advantages, including an exceptional opportunity to investigate an association between stress and verified infectious disease to a known agent. In addition, these studies can control for prechallenge levels of antibodies against that particular antigen, removing this major source of variability in successful defense against infection.

The fourth type of evidence stems from the studies of associations between psychological stress and reactivation of latent viruses. When investigating the relationship between stress and reactivation of latent viruses, the investigators have often focused on temporary, naturalistic stressors such as academic examinations, and the results of these studies have consistently suggested an association between stress and reactivation of latent viruses. The effect of other types of stressors on virus latency have also been examined, but to a much lesser extent and with slightly more mixed results. A skeptic could argue that the increase in antibodies to latent herpes virus observed during examination periods does not necessarily reflect a stress-induced herpes activation but could merely reflect a nonspecific increase in serum antibody levels in response to stress. However, a few studies have also assessed stress-related changes in nonlatent viruses and have found no association between stress and antibody levels of the nonlatent viruses. The increase in antibodies, therefore, seems to be specific to latent viruses. The mechanisms of how latent viruses are reactivated during stress are not well understood. Recent research has suggested the stress-induced shift in the cytokine profile from a Th1 profile to a Th2 profile as a possible mechanism linking stress to reactivation of latent herpes virus. This shift in cytokine profile favors virus-induced pathogenesis and survival as it downregulates the production of cytokines necessary for the T-cell response to the virus.

METHODOLOGICAL ISSUES

Although the relevant studies taken together seem to support an association between psychological stress and infectious diseases, the evidence is not without weaknesses.

First, even though studies have revealed an association between stress and reduced immunosurveillance of latent viruses, there is only scattered evidence of an association between stress and increased rate of oral and genital herpes outbreaks. In addition, the majority of studies that have revealed an association between stress and herpes outbreaks have been cross-sectional and are based on patients' self-reported symptoms, which may be susceptible to recall bias.

Second, studies have shown that some people may show biological evidence of infection but not manifest symptoms of the disease. In general, investigators do not find asymptomatic infections very relevant, as they do not cause reduced quality of life or absence from work or school. This may be true for the immediate effect of URIs, but not necessarily so when it comes to reactivation of latent viruses or the longer-term consequences of infection. For instance, we know that about 25% of all genital herpes recurrences are asymptomatic or invisible, but even invisible recurrences increase risk of transmission to a sexual partner. The effect of stress on such risk is not well investigated, but recent results have shown high levels of anxiety to be associated with asymptomatic shedding of HSV-1 in seropositive patients attending dental treatment. It has also been suggested that asymptomatic low-grade systemic inflammation may increase the risk of coronary heart disease, possibly due to chronically elevated levels of C-reactive protein. This possible side effect of low-grade inflammations typically associated with infection highlights the need for more research examining the consequences of stress on infection.

Third, in several viral challenge studies, the researchers have assessed for prechallenge antibody level against the specific virus to be inoculated, and only individuals with low or absent titers (≤2) of serum neutralizing antibody were enrolled. Though this increases homogeneity, it is also a potential weakness. First, it limits generalizability to the more common situation in which individuals do have some level of preexisting antibody response. Second, because virtually all antibody-free persons become infected after an intranasal rhinovirus challenge, the failure to find infection in all cases may reflect technical problems, with either the exposure or the assessment of viral shedding.

Fourth, some of the studies investigating the relationship between stress and infectious illnesses used families as targets of the investigation. Although the statistics used are often based on the assumption of independency between observations, family members cannot be considered independent. The occurrence of disease in one family member cannot be treated as independent of

the others, as the occurrence of contagious disease in a family member increases the risk of disease among the other members. Therefore, one is at risk of drawing the conclusion that it is the effect of stress related to family functioning that is responsible for the increased susceptibility to infectious diseases; however, in reality, it may be the exposure due to family membership that is responsible for the increased incidence of infection.

POSSIBLE MEDIATORS OF THE LINK BETWEEN STRESS AND INFECTIOUS DISEASE

Although attempts have been made to identify physiological pathways between stress and URIs, these attempts have yet to yield clear conclusions. For instance, Cohen et al. (1998) and Cohen, Doyle, Skoner, Rabin, and Gwaltney (1997) demonstrated relationships between colds and baseline measures of norepinephrine and epinephrine, as well as associations between life events and two types of immune cells: helper T lymphocytes, and neutrophils. However, statistical analyses provided no support for the possibility that these effects were responsible for the observed stress–disease association. As long-term increases in cortisol concentrations may decrease immune functions and apparently stimulate growth of some pathogens, for example, various types of bacteria, this hormone has often been suggested as a potential physiological mediator of the association between stress and infectious diseases. However, the results of studies investigating this hypothesis have been mixed. In some studies, the results revealed either no association between reported stress and cortisol or no association between cortisol and immunocompetence. Even in the studies that did support the hypothesis of cortisol as the mediating factor in the stress–disease association, one cannot be certain that the association is causal, as the observed changes in cortisol concentrations may be due to factors other than stress that were not controlled, for example, stress-related sleep deprivation. Cortisol has likewise been suggested as the hormone linking stress to reactivation of latent herpes viruses. However, even though *in vitro* studies have shown glucocorticoids to enhance EBV reactivation and replication, circulating cortisol *in vivo* has not been found to correlate with EBV reactivation, operationalized as antibody titers to the virus.

The mixed results concerning investigations of cortisol as a physiological link between stress and infectious disease may in part be caused by problems with the reliability of cortisol assessments. Thus, the standard errors of cortisol assessments are very often quite large and there are large intraindividual variations due to diurnal cycles that can confound results. Only two studies have revealed an association between circulating cortisol levels and self-reported URI symptoms. Individuals with relatively flat cortisol cycles did report fewer symptoms of URI, but in contrast to what was expected, a flat cortisol cycle was not related to increased stress levels. Results of more recent studies suggest that individual differences in the *reactivity* of the sympathetic nervous system and HPA axis may be more important than absolute levels of stress hormones when searching for potential mechanisms of interaction between stress and immunity.

In one of the viral challenge studies, higher levels of psychological stress were associated with higher symptom scores and higher IL-6 lavage concentrations in response to infection. It has been proposed that IL-6 may act as a pathway through which stress is associated with increased symptoms of illness. The results of another study have suggested that stress may interfere with the body's ability to regulate cytokine production, possibly through it's effect on cortisol production. In this study, dexamethasone (Dex), which is a synthetic cortisol-like substance, was added to blood samples from a group of chronically stressed individuals and a nonstressed control group. One of the functions of cortisol is to regulate (terminate) cytokine production, and when Dex was added to the blood samples, it was found that it was significantly less effective in terminating cytokine production in blood samples from the chronically stressed group compared to the control group. Thus, the effect of stress on susceptibility to infectious disease may not be due to a stress-induced suppression of immune function as often suggested, and stress may, instead, influence the ability of the immune system to respond to hormonal signals that turn off cytokine production. Thus, individuals under stress may in fact produce too much cytokine resulting in a massive symptomatic response. The associations between stress, cortisol, and cytokine production are clearly complicated, however, and need further investigation.

The possible role of sleep quality as a mediator of the relationship between psychosocial factors and susceptibility to infectious diseases has received increased attention in recent research. For instance, the results of a recent study revealed an association between low subjective perceived socioeconomic status and increased susceptibility to colds and, further, that the effect of low subjective social status on susceptibility to common colds might partly be mediated by reduced sleep duration. The authors suggest that subjects with low subjective socioeconomic status worry more, or feel a need to be more vigilant, which may influence their ability to sleep and, subsequently, there susceptibility to disease. It is interesting that objective markers of socioeconomic status were not associated with susceptibility to common colds.

POSSIBLE MODIFIERS OF THE ASSOCIATION BETWEEN STRESS AND INFECTIOUS DISEASE

In this review, the focus has been on stress. However, in some studies, not only the effects of stress on susceptibility to infectious illness but also the effects of other psychosocial variables have been investigated. Some studies

have revealed that factors such as optimism, positive mood, depression, and anxiety are related to infectious disease. Moreover, some studies indicate that psychosocial factors such as social support and personality variables are potential moderators of the association between stress and infectious disease, as these factors may act as a buffer against negative health consequences of stress.

The associations between stress, social support, and infectious illness are presumably complex, and social support may in some instances act as a confounder of the stress–illness association. In one study, it was shown that social support may increase the risk of infection in individuals with reduced immunocompetence due, for example, to stress or various treatments, as social contacts increase the risk of being exposed to antigens. Contrary to these findings, the results of viral-challenge studies have revealed that diverse social networks decrease susceptibility to URI. In these particular studies, however, the participants were isolated from each other, and all participants had received the same amount of virus, thereby eliminating the possible negative consequences of social support in the form of increased risk of exposure.

Two studies have shown an avoidant coping style to be a moderator of the relationship between stress and infectious disease. In one study of children, an interaction between hassles and avoidant psychological coping was found. The results indicated that an avoidant coping style was protective against URI, but only when the child's daily life was relatively free of stressors. When hassles were frequent, more infectious illnesses were suffered by children who responded to stress with an avoidant coping style. This interaction was independent of age, gender, family composition, social class, negative affect, parental perceived stress, parental smoking, and alcohol consumption. The aim of another study that involved a sample of 107 adults was to assess the influence of stressful life events and hassles on susceptibility to URI, as well as the moderating effects of psychological coping style, social support, and family environment. During the 15-week study period, 29 individuals experienced at least one clinically verified episode of URI. The results revealed that risk of infectious illness was greater in those who experienced high life-event stress both before and during the study period, and the effect of stressful life events on infectious illness was moderated by coping style, with avoidant coping being protective under conditions of high number of stressful life events. Another study has shown self-efficacy to have a moderating effect on the stress–illness relationship. In this study, the interactive effects of job demands, control, and individual characteristics on upper respiratory illnesses and immune function were examined. Having high job control appeared to lessen the association between job demands and poor health among individuals with high self-efficacy, and, on the other hand, experiencing high job control exacerbated the association between job demands and poor health among inefficacious individuals.

Other factors related to the infectious disease itself have also been suggested as moderators of the association between stress and infectious illnesses. For instance, results from one study examining the effects of stress on clinical herpes outbreaks suggested that the duration of the herpes infection may be a moderator of the relationship between stress and herpes outbreaks. The results showed that when disease duration was short (less than 4 years), psychological stress and number of recurrences were positively associated, but when disease duration was longer, there was no relationship. The suggested moderating effect of disease duration could be explained by the fact mentioned earlier, that most individuals who suffer from recurrences of HSV infections show a decrease in clinical outbreaks over time.

Finally, stressor characteristics may also play a role. The results of a well-controlled viral-challenge study showed that whereas severe *acute* stressful life events (less than 1 month long) were not associated with developing colds, severe *chronic* stressors (1 month or longer) were associated with a substantial increase in risk of disease. Thus, a short duration of the stressor seems to lessen the linkage between psychological stress and the risk of developing a cold among infected individuals. Although the generalizability of this finding remains to be determined, these results are in accord with recent theorizing by McEwen. The primary stress mediators of glucocorticoids and catecholamines may serve the body well as an initial response, but can turn on the body and cause problems, depending on the time course. For instance, glucocorticoids enhance conversion of protein and lipids to usable carbohydrates and act on the brain to promote appetite and food-seeking behavior. These effects are useful after a period of high-energy consumption like flight from a predator or delivery of a child. However, if the high levels of glucocorticoids are maintained, for example, due to prolonged psychological stress, the increased food intake will continue and symptoms of allostatic overload will appear (e.g., in the form of obesity). This possibility has been termed the "allostatic overload," which refers to the cumulative effects of an allostatic state and reflects a "wear and tear" situation as adaptive bodily changes begin to occur, thus causing problems when prolonged. It seems paradoxical that organisms would have evolved a response to stressors that involves release of immunosuppressive hormones at a time when an active immune response may be crucial for survival, for instance, if the organism has been injured, and results from animal studies have shown both positive and negative effects of physiological stress mediators on immune function. It has been shown that low doses and acute administration of corticosterone and epinephrine (to mimic acute stress) result in immunoenhancement, whereas high doses or an increase of the duration of the corticosterone exposure (to mimic chronic stress) result in immunosuppression. The two opposite effects of physiological stress mediators depending on dose and time span are also known

from pharmacology in that low doses and acute administration of corticosterone and epinephrine generally have immunoenhancing properties, whereas long-term administration of the same drugs are used for suppression of immune function in treatment of inflammatory diseases and to prevent rejection of transplanted tissue.

INFLUENCES OF IMMUNE ACTIVATION ON BEHAVIOR

Substantial research has shown that stress may alter susceptibility to URI as well as trigger reactivation of latent viruses. However, as highlighted in the review by Cohen and Williamson (1991), there is some controversy about the role of the timing of the stressor in the development of infectious diseases. Some evidence suggests that stress occurring *after* viral exposure may increase susceptibility, whereas stress *prior* to viral exposure may both increase and decrease susceptibility, and it is possible that stress affects various aspects of infectious diseases differently depending on when the stress occur. For instance, stress that occurs around the time of exposure may be crucial to whether one gets infected or not, whereas stress occurring after viral exposure may primarily have an effect on the severity of the clinical syndrome or the time needed for recovery. The research that shows a lagged relationship (3–4 days) between stress and subsequent symptomatology raises the possibility of an alternative pathway between stress and infectious diseases. Originally, these results were interpreted as evidence of stress-induced susceptibility to URI, rather than higher levels of symptom reporting due to the stress associated with being sick. However, as this lagged relationship corresponds very well to the incubation period of many common cold viruses (24–72 hours), it may be that subtle changes in the immune response to the infectious agent cause infected individuals to report more stress. The nervous, endocrine, and immune systems are interrelated in a dynamic multidirectional system. Research suggests that the central nervous system does influence the immune system, and, in turn, more important, the immune system is also capable of influencing the CNS through, for example, release of cytokines and inflammatory mediators that can act as neurotransmitters and neuropeptides. Activated lymphocytes produce a number of regulatory substances, including interleukin-1 (IL-1), interferons, and adrenocorticotropic hormone, which stimulate the secretion of other substances, which ultimately influence activity in the brain. For instance, proinflammatory cytokines have been shown to increase activity of the HPA axis and to influence the uptake of the amino-acid tryptophan that influences synthesis of serotonin in the brain. These mechanisms could be responsible for the occurrence of cytokine-induced depression, which is observed in cancer patients treated with IFN-α and patients with systemic infections. Further studies exploring the causal direction of relationships between stress and symptom reports are needed.

CONCLUSION

In the last major review of this area from the beginning of the 1990s, it was concluded that the existing literature was suggestive of an association between stress and increases in illness behaviors and that stress was associated with increased onset and reactivation of verified infectious disease. In the same review, it was concluded that the weaknesses in the existing literature were that the studies (a) used designs that limited causal inference, (b) were characterized by unrepresentative samples, and (c) lacked adequate examination of potential pathways. Since that time, about 70 additional studies examining the association between stress and infectious disease have been published. The literature examined in this review continues to support an association between stress and infectious disease. The vast majority of studies that have examined the effect of stress on upper respiratory illnesses have found evidence of an association between stress and URI, both concerning symptom report and verified illness, with the exception that brief, naturally occurring stress does not seem to be a risk factor of susceptibility to URI. Among the studies published since the last major review, the base for an assumption of an association between stress and onset and reactivation of verified infectious disease has expanded in scope, particularly as a result of additional viral-challenge studies.

Additional studies have also shown a lagged relationship between stress and symptoms of URI, indicating that stress at the time of exposure may be crucial to susceptibility. However, the lagged relationship could also reflect behavioral changes due to antigen-induced release of cytokines during the incubation period. The majority of studies that have investigated the effect of stress on herpes virus latency have supported this interpretation. The results have also suggested that the relationship between stress and herpes virus latency is weakened in subjects who are in good physical shape. In contrast to the case for URI, acute naturalistic stress seems to be the type of stress that most consistently has been found to be associated with herpes virus latency. In spite of this finding, this stress category has not been investigated in the group of studies examining the effect of stress on herpes outbreaks. This could be one of the reasons why the results of studies investigating the effect of stress on herpes outbreaks have been inconsistent. Furthermore, many of the studies in this area may be characterized by insufficient statistical power due to small samples, and it is not yet clarified whether

duration of the herpes infection may be a moderator of the relationship between stress and herpes outbreaks. Even in the more recently published studies there is still a lack of adequate examination of potential pathways between stress and infectious disease, and the attempts to identify possible physiological pathways have often been unsuccessful. Another question that remains unanswered is whether stress has an effect on long-term asymptomatic low-grade inflammations, which have recently been related to the development of coronary heart disease.

DIRECTIONS FOR FUTURE RESEARCH

This evidence clearly establishes proof of the principle that psychological factors can influence infectious disease processes. Future research should move beyond demonstration studies to begin the challenging process of elucidating mechanisms for these influences within the context of specific diseases of clinical importance. The research done so far has mainly focused on the effect of stress on the body's second line of defense, that is, the body's capability to combat antigens that have entered the body. The effect of stress on the first line of defense, exposure to pathogens, and the clinical syndrome of the disease have not yet received much research attention. Recently the focus of interest has widened and the role of stress on the development of immune defenses has been investigated. In the past 5 to 10 years, the effects of stress on the immune response after vaccination with influenza vaccines have been investigated, revealing associations between psychological stress and lowered protective responses. However, future studies need to determine whether these stress-related disparities in vaccine response are sufficient to increase the susceptibility to clinical infection with influenza. Future studies also need to explore how different types of stress can differ in their effect on various aspects of infectious disease as suggested in this review. We know from previous research that bereavement and trauma, which are both examples of long-term stressors, are associated with different neuroendocrine changes. For instance, bereavement is often associated with increased cortisol production and decreased NKCC, whereas trauma and posttraumatic stress disorders are often associated with decreased cortisol production and increased NKCC and proliferation. To what extent these different neuroendocrine changes may explain how some types of stress are associated with increased susceptibility to URIs, and other types of stress with increased risk of HSV recurrences, needs further investigation. Furthermore, it would be relevant to examine whether the possible relationship between stress and infectious diseases suggested in this review is also seen in individuals in whom an infectious disease could have fatal consequences, for example, cancer patients receiving immunosuppressive treatments.

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32 Effects of Stress on Health in HIV/AIDS

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INTRODUCTION

The utilization of highly active antiretroviral therapy (HAART) has revolutionized the treatment of HIV/AIDS and thus has allowed many people living with HIV/AIDS (PLWHA) to live longer and healthier lives. Although the mortality rate for HIV/AIDS has decreased over the past decade, an increasing number of deaths have been documented for women, certain minority populations, and individuals aged 45 and older (Center for Disease Control [CDC], 2007). In fact, HIV/AIDS is now the leading cause of death for young African American or Hispanic individuals in the United States (CDC, 2007). Thus, despite the notable medical advances in the pharmacological treatment of HIV/AIDS, there remain individual variations with response to HAART, which may result from numerous biological factors such as differences in metabolism or drug–drug interactions as well as sociocultural and psychosocial factors that may affect adherence to HAART regimens and health behaviors.

There is increasing evidence supporting an association between stress and disease states in HIV disease (Cohen, Janicki-Deverts & Miller, 2007; Leserman, 2003). Cumulative life stress, current distress states, specific maladaptive coping responses to stressors, and lack of adequate social support to deal with stress have all been implicated in altering the course of HIV disease, although the specific mechanisms involved remain unclear (Kopniski, Stoff & Rausch, 2004; Leserman, 2003). By eliciting affective, behavioral, cognitive, and physiological changes, stress may impair the immune system and impact subsequent health outcomes.

This chapter will review some of the more recent studies that examine major psychosocial stressors that impact PLWHA, and it will also explore potential mechanisms that may link psychosocial stress and HIV disease progression. We will note the effects of stress on physiological systems as well as the impact of life stressors on affective states, coping strategies, social support, and adherence behavior within the context of HIV/AIDS. Additionally, we will highlight some of the demographic and individual difference factors (e.g., age, gender, race/ethnicity, and personality traits) that have been shown to modulate the relationship between stress and HIV disease. Although there is increasing evidence that stress impacts the health of PLWHA, less is known about the experience of stress and its deleterious effects on the health of minority populations. Thus, we will conclude this chapter with suggestions for future work in this area.

BIOLOGICAL MECHANISMS UNDERLYING EFFECTS OF STRESS ON HEALTH AMONG PLWHA

HIV significantly corrupts the immune system by infecting cells crucial to the person's defense against viral and bacterial pathogens, thus leaving an infected person vulnerable to a myriad of opportunistic infections. Weakened immune functioning resulting from HIV infection also increases susceptibility to developing specific cancers. In addition, HIV has deleterious effects on physiological stress systems within the body. The following section will provide a brief overview of some of the cellular mechanisms compromised during HIV infection; the rest of the chapter will then accentuate some of the research that describes a number of the ways stressors initiate changes in these immune parameters, accelerate HIV pathogenesis, and perhaps eventually lead to HIV-related mortality.

HIV/AIDS AND IMMUNE PARAMETERS

T LYMPHOCYTES

HIV infection produces widespread changes in the immune system, infecting and altering the distribution and functionality of cells, particularly CD4 and CD8 T lymphocytes, macrophages, and Natural Killer (NK) cells that are essential for protecting humans from disease (Antoni, 2003b; Antoni & Cruess, 2007; Nott, Vedhara, & Spickett, 1995). HIV is transmissible through blood, semen, vaginal fluids, and breast milk (Goodkin, 2006; Morin, 2007; Morin et al., 2007) and, once inside the body, it self-replicates primarily by infecting CD4 T lymphocytes (Lambotte et al., 2002; Nott et al., 1995). CD4 cells are a subtype of a group

of T helper cells that play an important role in the body's immune defense by activating B cells and cytotoxic cells. By attaching itself to the CD4 receptor, HIV not only replicates but it also impairs the functioning and decreases the number of CD4 cells in the body. In fact, studies have demonstrated an inverse association between HIV viral burden or load and CD4 cell counts (Goodkin, 2006; Mellors et al., 1997). Although these findings would then suggest that increases in a marker of HIV progression, such as viral load, would predict faster CD4 cell decrements, studies have shown that this is not necessarily the case (Rodríguez et al., 2006). Thus, there may be additional factors that lead to reductions in CD4 cell levels in HIV disease, such as HIV proteins harbored in the lymph nodes that can drive CD4/T-cell activation and cell death.

In addition to affecting CD4 T lymphocytes, HIV also infects CD8 T lymphocytes, which are important in controlling the virus by directly killing HIV-infected cells (i.e., cytotoxic CD8 cells) or by releasing factors that reduce the rate of HIV replication (Fauci, Pantaleo, Stanley, & Weissman, 1996; Grivel, Malkevitch, & Margolis, 2000). Initial infection with HIV yields elevated levels of CD8 cells, which might be expected to prevent further viral replication; however, as HIV disease progresses, there are reductions in CD8 cell levels (Fauci et al., 1996; Grivel et al., 2000; Ho et al., 1993; Saksena, Jing, Potter, Wilkinson, & Bin, 2008). It has been determined that activation of CD8 cells and the subsequent manifestation of a CD4-like binding site leave the cell vulnerable to viral infection (Flamand et al., 1998). Overall, HIV impacts the ability of CD8 cells to lyse infected cells and further compromises the immune system.

NK CELLS

NK cells, and their functional capacity commonly referred to as Natural Killer Cell Cytotoxicity (NKCC), are another important component of the natural immune defense that is involved in attacking and killing tumors and viruses by lysing the implicated cells (Douglas et al., 2003; Whiteside & Herberman, 1994). Studies examining factors that contribute to altered NKCC levels during HIV disease mostly focus on related increases in stress and depression. For example, many studies have pointed to decreased NK cell activity in individuals suffering from stressful life events (Byrnes et al., 1998) and depressive symptoms (Alciati, Gallo, Monforte, Brambilla, & Mellado, 2007; Evans et al., 2002; Pike & Irwin, 2006). In particular, a recent study by Pike and Irwin (2006) within the context of HIV disease found impaired functioning of NK cells and enhanced levels of a proinflammatory cytokine (interleukin-6, IL-6) in a depressed group in comparison to a nondepressed group. Similarly, a study by Alciati and colleagues (2007) determined that HIV-positive depressed individuals had fewer NK cells when compared to HIV-positive nondepressed controls. Moreover, they found that antiretroviral (ART) adherence did not help restore NK cell levels among the depressed patients. These findings are substantiated by prior investigations showing that NKCC is restored among individuals on HAART upon remission of depressive symptoms (Cruess et al., 2005). Thus, NK cells and NKCC are impacted during HIV disease and also related to distress states.

HIV/AIDS AND PHYSIOLOGICAL STRESS SYSTEMS

HIV infection leads to systemwide dysfunctions that move beyond the typical immunocellular impairments. In fact, many studies exploring the underlying mechanisms that explicate the stress-immune association have found support for HIV-elicited alterations of two major stress axes: the Hypothalamic-Pituitary-Adrenal Axis (HPA) and the Sympathetic Nervous System (SNS). The HPA axis is a part of the neuroendocrine system in which the hypothalamus signals the pituitary to secrete adrenocorticotropic hormone, which in turn causes the adrenal cortex to release stress hormones, including cortisol, as part of its homeostatic response to stress and distress states (Herman, Ostrander, Mueller, & Figueiredo, 2005; Tsigos & Chrousos, 2002); likewise, the principal agents of the SNS and adrenal medulla, norepinephrine and epinephrine, are also released in response to stress and function to prepare an organism for action (Goldstein & Kopin, 2007).

HIV has been implicated in the physiological stress response; for example, it has been shown to incite changes in the HPA axis (Kumar, Kumar, Waldrop, Antoni, & Eisdorfer, 2003; Kumar et al., 2002). More specifically, HIV progression has been linked to elevated basal cortisol activity, blunted cortisol response to behavioral stressors, and abnormal circadian rhythms (Antoni, 2003a, 2003b). Similarly, an intricate relationship between the HIV disease and the SNS has also been established. For instance, there is evidence for dysregulated autonomic activity in PLWHA, more specifically in the sympathetic component of stress responses (Kopnisky et al., 2004). The direct influence of HIV on the SNS in unclear, with some research suggesting that norepinephrine activity is largely diminished in HIV seropositive individuals (Hurwitz et al., 2005; Kumar et al., 2002); yet, heightened sympathetic activity has been related to disease progression (Cole et al., 2001). Taken together, these findings suggest that HIV does modulate the functional status of the HPA axis and SNS, and these neuroendocrine alterations may form the basis for the stress–immune relationship.

HIV/AIDS AND PSYCHONEUROIMMUNOLOGY (PNI)

Thus far we have reviewed some of the immunological and neuroendocrine changes that are impacted by HIV

disease. In addition to HIV infection, other stressors unambiguously stimulate activation of the HPA axis and SNS and are also related to decrements in immune functioning (Goldstein & Kopin, 2007; Irwin, 2008). These findings therefore suggest a mechanism in which acute and chronic stressors can provoke immune alterations that accelerate HIV progression via activation of these major physiological stress systems. Products of the HPA axis (i.e., adrenocorticotropic hormone/corticotropin and cortisol), for example, have been evidenced to engender changes in localization and functionality of immunocellular components vital for viral control, including T lymphocytes, cytokines, tumor necrosis factor-alpha, and NKCC (Antoni, 2003a; Himmerich et al., 2006; Kopnisky et al., 2004; Leserman, 2003). One study proposed that these stress-related immune alterations are only evident in individuals who have heightened basal cortisol levels (Petitto et al., 2000). Further support for the link between the HPA axis and immune impairment has been found in intervention research among HIV-positive individuals. For example, a randomized control trial investigating the effects of a Cognitive Behavioral Stress Management intervention on the immune system found that intervention-related reductions in norepinephrine and cortisol levels were related to maintenance of CD8 cells and the reconstitution of naive T Lymphocytes, respectively (Antoni et al., 2000, 2005), cells that are essential in eliciting defense against novel pathogens. However, despite this evidence, findings relating cortisol levels to HIV status remain inconsistent and further work is necessary (Antoni, 2003a, 2003b).

Researchers have speculated that the SNS may influence immunity through sympathetic postganglionic neurons that synapse directly onto beta adrenergic receptors located in lymphoid tissue (Bellinger et al., 2006; Cole, Kemeny, Fahey, Zack, & Naliboff, 2003; Cole, Korin, Fahey, & Zack, 1998). The dispersal of neuronal processes onto lymphoid tissues, in turn, has been suggested by researchers to vary as a function of stress level (Sloan, Capitanio, & Cole, 2008), with greater stress levels associated with greater sympathetic neural proliferation. For instance, elevated SNS activity has been shown to impact the reconstitution of CD4 T cells in individuals undergoing HAART treatment (Cole et al., 2003). These data are in line with previous findings from an in vitro study also providing evidence for attenuated response to HAART (Cole et al., 2001). However, the data relating SNS dysregulation to immune dysfunction continues to produce conflicting results. While some researchers report negative immunological consequences related to elevated SNS activity, such as SNS-mediated reduction of Type 1 interferon activity (Collado-Hidalgo, Sung, & Cole, 2006), and elevated basal viral load levels (Cole et al., 2003), other studies have found more positive outcomes relating moderate amounts of norepinephrine (between 10nM and 1μM) to decreased HIV replication (Moriuchi, Yoshimine, Oishi, & Moriuchi, 2006). One recent meta-analysis that may help explain the discordance in the data proffers that the impact of stress on immune functioning may be context specific (Segerstrom & Miller, 2004). In fact, Segerstrom and Miller determined that the immune system effectively responds to acute stress by increasing the number of natural immune factors, such as neutrophils, Interferon-gamma, IL-6, and NK cells, and allocating them to areas that help optimize the defense system; conversely, chronic stress levels elicited negative changes in immunocellular activity. Based on these reports, it is clear that stress-induced overstimulation of the SNS results in immune alterations; however, the data remain inconclusive as to whether the effects are positive or negative in nature.

MAJOR PSYCHOSOCIAL STRESSORS REPORTED BY PLWHA

PLWHA are faced with an array of acute and chronic stressors related to their diagnosis and treatment. For example, altered appearance (Reynolds, Neidig, Wu, Gifford, & Holmes, 2006), muscle wasting (Dudgeon, Philips, Bopp, & Hand, 2006), unemployment, lack of partner or other social support, risk of physical and health complications (Dray-Spira et al., 2005), and fatigue (Henderson, Safa, Easterbrook, & Hotopf, 2005) are just some of the many physical, psychosocial, and socioeconomic stressors commonly reported by PLWHA. Because a review of all the possible psychosocial stressors is beyond the scope of this chapter, we will focus our attention on four of the major psychosocial stressors commonly reported by PLWHA: caregiving, social stigma, unemployment, and trauma.

CAREGIVING AMONG PLWHA

The emotional, psychological, and physical sequelae associated with caregiving may leave HIV-positive individuals feeling encumbered and lacking adequate resources to cope with various life stressors, including the demands of their own disease. PLWHA in the role of caregiver are not only forced to deal with the medical demands and impending death of their loved ones, but they are also confronted with managing their own HIV infection and physical deterioration. Studies looking at the effects of caregiving on the physical and mental health in healthy samples have identified a relationship between caregiver stress, increased psychological vulnerability (Zivin & Christakis, 2007), and elevated risk of cardiovascular disease (Mausbach, Patterson, Rabinowitz, Grant, & Schulz, 2007). Similarly, research on HIV-positive caregivers of HIV-positive loved ones has also found that caregiving coupled with perceived HIV burden predicts increased depressive symptoms and poorer health in PLWHA compared to their HIV-negative counterparts (Land, Hudson,

& Stiefel, 2003; Pirraglia et al., 2005). Although little is known about how the caregiving experience directly impacts on HIV disease processes, it is plausible that it may affect treatment adherence and other aspects of health care (i.e., delay in seeking treatment) in HIV seropositive caregivers (Stein et al., 2000).

STIGMA AND DISCLOSURE AMONG PLWHA

HIV-related stigma continues to prevail even in the era of potent HAART treatment (Siegel & Schrimshaw, 2005) and may have devastating consequences for individuals diagnosed with this chronic illness. For example, one study reports that individuals who perceive HIV-related stigma as a chronic and severe stressor are more likely to endorse suicidal thoughts (Heckman et al., 2002). As a result, PLWHA may attempt to cope with their illness by withholding their HIV status from family, friends, significant others, and sexual partners (Nachega et al., 2005). Nondisclosure of HIV status, in turn, has been widely associated with immune deficits. In fact, studies of PLWHA who are open about their homosexuality found that they had higher CD4 cell levels 2 years later when compared to those concealing their sexual orientation (Ullrich, Lutgendorf, Stapleton, & Horowitz, 2004). In accordance with these data, a more recent study of HIV-positive psychiatric outpatients reported increases in CD4 cell levels in individuals who did not hide their HIV status and homosexuality (Strachan, Bennett, Russo, & Roy-Byrne, 2007).

Some researchers speculate that the immune decrements apparent in individuals who conceal their HIV status are precipitated by changes in health behaviors, such as medication adherence (Kumarasamy et al., 2005; Nachega et al., 2006). For example, individuals may be more inclined to miss a dose of their medications when in the presence of a socially significant other due to fear of revealing their HIV status (Catz, Kelly, Bogart, Benotsch, & McAuliffe, 2000). In addition, nondisclosure also leads PLWHA to become socially isolated, thereby removing a potential buffer for the stress–disease relationship (Kalichman, DiMarco, Austin, Luke, & DiFonzo, 2003). One particular study conducted in a cohort of 221 HIV-positive men and women found that approximately 70% of people feel socially isolated as a result of their HIV serostatus (Vanable, Carey, Blair, & Littlewood, 2006). In fact, individuals reporting greater physical ailments also reported feeling greater instances of stigma. The investigators did not find evidence to support a relationship between stigma and viral load, although stigma was significantly correlated with greater depression.

Gender-related stigmatization or discrimination has also been suggested to influence the pathogenesis of HIV disease. Some researchers suggest that women are more vulnerable to the effects of HIV-related discrimination, particularly in the context of low social status (Wingood et al., 2007); indeed, studies have shown that HIV positive women report lower quality of life in comparison to men (Mrus, Williams, Tsevat, Cohn, & Wu, 2005). Some studies suggest that gender-related disease differences may be explained by hormonal differences between men and women, leaving one gender more susceptible to the influences of stress on the immune system (Segerstrom & Miller, 2004). One recent study exploring gender differences in immunological status discovered CD4-dependent virologic differences between men and women. Donnelly and colleagues (2005) found that for men and women with low CD4 concentrations, women had higher viral loads than men. In addition, for men and women who had higher CD4 concentrations, women had lower viral loads than men (Donnelly et al., 2005). Importantly, other studies suggest that any apparent gender differences in HIV status are related to medication adherence (Kuyper et al., 2004).

There are also reported gender differences in HIV progression related to the prevalence of depressive states. Rates of depressive disorders are higher among both healthy and HIV-positive women (Barry, Allore, Guo, Bruce, & Gill, 2008; Grigoriadis & Robinson, 2007; Israelski et al., 2007), leaving them at elevated risk for accelerated disease progression. One study of Tanzanian women found that after controlling for social support, HIV stage at study entry, and other psychosocial factors, women who endorsed a greater number of depressive symptoms had higher HIV-related mortality rates than their nondepressed counterparts (Antelman et al., 2007). In addition, other studies have found that women with depressive symptoms frequently engage in risky sexual practices, thus increasing their likelihood of developing recombinant variants of HIV (e.g., superinfection) or other viruses implicated in accelerating HIV progression (Antoni & Cruess, 2007; Herbst et al., 2005; Valverde et al., 2007). These studies suggest that the experience of stress and its physiological effects in HIV disease may differ among men and women and perhaps alter the stress–immune relationship.

UNEMPLOYMENT AMONG PLWHA

There are also a number of studies that report an association between the stress of unemployment and HIV disease progression. Dray-Spira and colleagues (2005) prospectively followed 319 early-stage, HIV-positive patients for a period of 2.5 years, assessing them on a variety of demographic, physiologic, socioeconomic, and risk behaviors to determine factors associated with increased risk of hospitalization and mortality. The authors found that lack of stable employment and lack of a stable romantic relationship were independently and significantly associated with increased risk of hospitalization and death. In another study, Cohen, Kemeny, Zegans, Johnson, Kearney, and Stites (2007) reported an association between unemployment and decreased number and altered functioning of NK cells in a healthy sample followed over a period

of 4 months; however, the researchers found that these immune decrements were reversed as soon as individuals regained employment. In fact, once employed, these individuals attained NK cell levels similar to those observed among individuals who maintained stable employment. This outcome is consistent with other findings that suggest alterations in NK cell functioning are reversible upon termination of the immediate stressor (Cohen et al., 2007). Thus, loss of employment is a major stressor among PLWHA that has been evidenced to impact health status through alterations in immunity.

TRAUMA AMONG PLWHA

Incidents of reported trauma are high in PLWHA, and numerous studies have observed associations between traumatic life events and accelerated onset of AIDS and AIDS-related mortality. Rates of sexual assault in PLWHA may be as high as 68% in women and 35% in men (Kalichman, Sikkema, DiFonzo, Luke, & Austin, 2002). Furthermore, individuals exposed to more instances of sexual assault were significantly more likely to engage in sexual risk behaviors, experience more emotional distress, and also to have a personality disorder diagnosis (Kalichman, Sikkema, et al., 2002). Another study, by Leserman et al. (2005), determined that individuals with a history of trauma (i.e., sexual or physical abuse) who endorsed current posttraumatic stress disorder symptoms were significantly more likely to be physically impaired, to frequent health care centers, and to have extended hospital stays. A more recent prospective study found that mortality rates increased on average by 71% in HIV seropositive individuals for each three-unit increase in lifetime trauma (Leserman et al., 2007). Specific predictors of increased rates of AIDS-related deaths in this study included CD4 levels less than 200, high viral load, lifetime trauma, and symptoms of depression. Thus, these results are consistent with findings that suggest that the accumulation of significant life stressors and traumatic events may impact the long-term health status of PLWHA (Evans et al., 1997; Leserman, 2000; Leserman et al., 1999, 2002, 2007).

DEPRESSION AMONG PLWHA

Depression is a common affective response to life stress that may function to suppress the immune system, thus providing another link between stress and health among PLWHA. There is a large body of literature dedicated to exploring the role of affective states in HIV seropositive individuals in attempts to understand how these psychological states may impact disease progression (Cruess et al., 2001; Leserman, 2003; Kopnisky et al., 2004). Data from these reports indicate that chronically depressed, HIV seropositive individuals experience mortality rates that are twice as high as PLWHA not diagnosed with a mood condition (Ickovics et al., 2001). Other studies suggest that the presence of depressive symptoms alone is enough to hasten disease progression (Golub et al., 2003; Leserman et al., 2007). Accordingly, a recent longitudinal study by Ironson, O'Cleirigh, et al. (2005) determined that cumulative depressive symptoms, hopelessness, and avoidant coping were related to both CD4 and viral load changes. In fact, individuals scoring at the top 75th percentile in terms of severity of depressive symptoms experienced increasingly greater rapid decrements in CD4 cell counts and increases in viral load than individuals scoring in the 25th percentile, even after adjusting for medication adherence. Similarly, Huang, Leu, and Liu (2006) reported that men diagnosed with major depression demonstrated reductions in CD8 levels when compared to their nondepressed counterparts. There are multiple other pathways by which depression may affect disease progression; given the particular focus of this chapter on stress, readers are referred to other sources that provide a more in-depth exploration of the association between depression and HIV immune indices (e.g., Alciati et al., 2007; Antelman et al., 2007; Carrico, Antoni, Weaver, Lechner, & Schneiderman, 2005; Carrico et al., 2006; Cruess et al., 2005; Cruess, 2006; Huang, Leu, & Liu, 2006; Leserman, Douglas, Gettes, Ten Have, & Evans, 2003; Leserman et al., 2007).

MECHANISMS OF STRESS EFFECTS ON HEALTH AMONG PLWHA

The influence of demographic and individual difference factors on the stress experience has been widely studied. For example, differences in age, gender, ethnicity, personality, coping strategies, and social support have been broadly examined as characteristic features that may exacerbate or protect against the immune declines associated with the stress experience (Barclay et al., 2007; Berg et al., 2004; Chesney, Chambers, Taylor, & Johnson, 2003; Heckman, 2006; Heckman et al., 2000; Ironson, Balbin, et al., 2005; O'Cleirigh, Ironson, Weiss, & Costa, 2007). Although many studies recognize the impact these personal, psychosocial, and behavioral variations may have on clarifying the path between stress and HIV pathogenesis, few studies fully control for these factors, perhaps thereby contributing to inconsistencies in findings. It may be especially important to consider the effects of these factors when studies are carried out among minority populations. We will now review several of the main demographic and individual difference characteristics that have been hypothesized to moderate the stress–immune relationship.

CHRONOLOGICAL AGE

Age has been identified as a moderator of the stress and HIV disease relationship (Segerstrom & Miller, 2004). For example, one study looking at potential risk factors

for accelerated HIV disease progression determined that older age predicted rapid progression to a clinical AIDS state, earlier onset of AIDS dementia, and quicker time to death (Farinpour et al., 2003). In fact, older men were 31% more likely to die than younger men, even after controlling for baseline CD4 values and adherence behaviors. Although older individuals tend to have more impaired immune systems and also may have altered HPA and SNS functioning, some speculate that older individuals are also more susceptible to experiencing more stressful life events (Heckman et al., 2001; Schrimshaw & Siegel, 2003), placing them at higher risk for cognitive impairment (Pukay-Martin, Cristiani, Saveanu, & Bornstein, 2003). These findings have significant implications for HIV disease progression, since impaired cognitive functioning may engender disadvantageous health behaviors (such as poor medication adherence) that may lead to immune suppression (Barclay et al., 2007). Despite these reports, there are data to suggest that older age is actually associated with better medication adherence (Barclay et al., 2007). Overall, age is an important characteristic in the stress–health association among PLWHA.

RACE/ETHNICITY

There is a paucity of research exploring the influence of race and ethnicity on the effects of stress on health among PLWHA. Much of the research discussed thus far has primarily looked at Caucasian populations; in contrast, few studies have included large multiethnic samples. Those investigations that have sampled from multiethnic/multiracial groups tend to oversample African American males, leaving African American women and Hispanics understudied. Currently, the research that has been done with diverse groups points to higher HIV-related mortality rates for both African American and Hispanic individuals (Anastos et al., 2005). Some researchers attribute these disparities to poor medication adherence (Golin et al., 2002); yet recent studies have demonstrated that even under conditions of perfect adherence minority populations (especially women) are still prone to having more difficulty achieving optimal viral suppression (Pence et al., 2008). Similarly, compared to Caucasians, African Americans experience greater immunological consequences when they are nonadherent to their HIV regimen (Schackman et al., 2007). These findings underscore the need for further research with these populations to delineate the underlying factors that contribute to the disparate immune responses.

COPING/PERSONALITY

Recent interest has grown in examining how personality characteristics interact with distress states to influence HIV disease status. For example, researchers following a multiethnic sample of 119 HIV positive individuals over 1 year determined that having a conscientious personality style predicted levels of specific immune parameters (O'Cleirigh, Ironson, Weiss, et al., 2007). In particular, individuals scoring above the top 75th percentile in conscientiousness experienced an average increase of 59 CD4 cells and an average decrease of 1,300 viral load copies per year. In contrast, individuals low in conscientiousness lost an average of 27 CD4 cells and experienced an increase of 1,727 viral copies per year. These findings suggest that individuals who are thoughtful and meticulous by nature possess qualities that render them better able to control their illness, though the mechanism underlying this connection remains unclear. Similarly, studies have shown that having an optimistic outlook protects against the emergence of depressive symptoms (O'Cleirigh, Ironson, & Smits, 2007), buffers against declines in CD4 T cell values and increases in viral load (Ironson, Balbin et al., 2005), and decreases risk of mortality (Ickovics et al., 2006). In fact, Ironson and colleagues (2005) concluded that less optimistic individuals lost on average 55% more CD4 cells per year when compared to individuals who were more optimistic. However, current research posits that the health benefits of optimism depend on a combination of factors, including where individuals lie on the optimism spectrum and other psychological characteristics. For example, one study showed that PLWHA who, despite low levels of global optimism, perceived positive life changes stemming from HIV diagnosis (posttraumatic growth), evidenced greater increases in CD4 cells (Milam, 2006).

Just as studies have supported the notion that positive personality characteristics, such as conscientiousness and dispositional optimism, often bring about positive health benefits, other studies illustrate an opposite trend between less desirable traits and health outcomes. For instance, a socially inhibited personality style has been associated with early, elevated viral load levels, incomplete viral suppression, and poor immune reconstitution in response to HAART (Cole et al., 2003). Similarly, Solano, Costa, Temoshok, Salvati, Coda, and Aaiuti (2002) determined that PLWHA who possess a Type C personality, which is characterized by repressed emotions, dysregulated physiology, denial of needs, and perceived uncontrollability of disease (Solano et al., 2002), experience hastened disease progression when they are already immunocompromised. Clearly, these findings highlight the complex relationship between personality style and other cognitive, behavioral, and physiological correlates that have an impact on disease progression. One implication of these associations is that interventions that attempt to modify cognitions and behaviors must attend to the individual's personality.

Additionally, a number of studies on stress and coping have generally found support for an effect of coping style on HIV pathogenesis. For example, studies have shown that HIV-positive individuals who use maladaptive coping strategies in response to stress, such as denial, tend to perceive higher stress levels (Penedo et al., 2003; Weaver et al., 2004). In contrast, optimism and religiosity

have been identified as coping strategies that buffer against the deleterious effects of life stress in both healthy and chronically ill persons (Ironson, Balbin et al., 2005; Ironson, Stuetzle, & Fletcher, 2006; Segerstrom, 2006). The role of stress appears to be a particularly important element in the perceived ability to cope with stressors, and it may also have an impact on immunity within the context of HIV/AIDS. Lazarus and Folkman's (1984) general psychological stress and coping model postulates that individuals who appraise stressful events as threatening and who believe they lack sufficient psychological resources to successfully manage stressors will be most negatively impacted. Several studies examining the effects of stress appraisal on health in PLWHA have shown that threat perception has negative immunological consequences. More specifically, one recent study determined that perceived stress at baseline predicted CD4 cell counts at 6 month follow-up, such that each one-point increase in perceived stress was associated with a nearly fivefold reduction in CD4 cell levels (Remor, Penedo, Shen, & Schneiderman, 2007). However, another study reported an association between perceived stress and HIV progression only in individuals who had lower viral load levels (Motivala et al., 2003). Correspondingly, a recent meta-analysis reviewing the literature on the effectiveness of Cognitive Behavioral Interventions (CBI) in improving both mental and physical health concluded that CBIs ultimately did not bring about significant improvements in immune functioning in PLWHA, even though many included stress management components (Crepaz et al., 2008). There is research to suggest that primary and secondary stress appraisals may differ in minority populations, thus suggesting a plausible explanation for the inconsistencies in findings that are readily apparent in the literature.

SOCIAL SUPPORT

As mentioned earlier, PLWHA who perceive stigmatization because of their HIV seropositive status are often left feeling distressed and socially isolated (Chesney, Chambers, Taylor, & Johnson, 2003). However, there are conflicting reports relating the experience of social support and HIV disease progression. For example, numerous studies have underscored the significance of social support as a valuable predictor of medication compliance in seropositive individuals (Godin, Côté, Naccache, Lambert, & Trottier, 2005; Gonzalez et al., 2004; Weaver et al., 2005). A study looking at the effects of psychosocial factors on HIV status in a sample of HIV positive, homosexual men revealed that perceived lack of social support was also associated with rapid progression to AIDS (Leserman et al., 2002). However, a longitudinal study of 205 gay and bisexual HIV-positive men determined that greater perceived quality of social relationships (i.e., lower levels of loneliness), not isolation, was related to steeper declines in CD4 levels over 3 years of follow-up, despite statistical control for variables likely impacted by loneliness (Miller, Kemeny, Taylor, Cole, & Visscher, 1997). In addition, a cross-sectional study of HIV-positive women reported by Eisenberger, Kemeny, and Wyatt (2003) found no evidence to support a relationship between social support and CD4 cell levels. In this case, the authors defined social support as the number of people the individuals identified as being comfortable with discussing and sharing their HIV status. Therefore, it appears that the discrepancies in the data related to the impact of social support on health outcomes may be due to varying definitions of social support employed in these studies, in addition, perhaps, to effects of gender, sexual orientation, and disease status that are widely reported in the literature (Eisenberger et al., 2003; Miller et al., 1997). Social support is a multiple component construct (Knowlton & Latkin, 2007; Schwarzer, Dunkel-Schetter, & Kemeny, 1994), with distinct facets such as disease-specific as opposed to more generic support. Disease-specific support in this context refers to the type of daily, informal care that PLWHA typically need (e.g., physical assistance, reminders about medical appointments), whereas more generic support refers to nondisease-specific forms of assistance, including emotional and financial help. In particular, researchers have found that PLWHA who perceive aspects of disease-specific and generic support, particularly emotional support, are often adherent to their HAART regimen (DiMatteo, 2004; Knowlton et al., 2007). The need for disease-specific support may increase as an individual's symptoms progress, while the desire for certain forms of generic support, such as emotional support, remains stable (Pakenham, Dadds, & Terry, 1996); accordingly, the provision of disease-specific support and other features of generic support, such as financial assistance, have been proffered to be most beneficial for individuals in the later stages of their HIV disease (Carrico, Antoni, Periera, et al., 2005). As a result, disease-specific support has been associated with perceived lower quality of life since it is most often present when individuals are most ill (Friedland, Renwick, & McColl, 1996). In light of this evidence, it is clear that social support is a multifaceted construct; as a result, research findings should be examined with caution when evaluating the impact of social support on HIV disease progression.

HEALTH BEHAVIORS

Symptoms of depression that occur in the context of stress can interfere with health behaviors that are central in maintaining the physical well-being of PLWHA. Changes in health behaviors often occur as a response to stress, thus providing another route by which stress impacts the immune system (Leserman, 2003). We will now provide a brief overview of some of the major health behaviors impacted by life stress among PLWHA, including substance use, sexual risk behaviors, and medication adherence.

ALCOHOL, DRUGS, AND SEXUAL RISK BEHAVIORS

Substance use is a common maladaptive coping mechanism used by seropositive individuals in response to daily and chronic life stressors. Both alcohol and injection drug use have been found to play direct and indirect roles in symptom progression in PLWHA. For example, one study by Samet, Cheng, Libman, Nunes, Alperen, and Saitz (2007) found that heavy drinkers not on HIV medications experienced greater suppression of CD4 cells (approximate decrease of 48.6 cells/μl). However, HIV treatments helped buffer against the negative effects of alcohol consumption on CD4 cells. Another study conducted with a sample of injection drug users found that current use of injection drugs placed PLWHA at greater risk of becoming unresponsive to HAART (Palepu, Tyndall, Yip, Shaughnessy, Hogg, & Montaner, 2003). Thus, injection drug use and alcohol abuse have been shown to impact HIV disease progression by directly affecting vital immune parameters or by blocking the effect of HIV treatment.

Substance use behaviors also increase an individual's likelihood of engaging in risky sexual practice (Kalichman, Weinhardt, DiFonzo, Austin, & Luke, 2002). Ibanez, Purcell, Stall, Parsons, and Gomez (2005) found that injection drug use in HIV-positive men who have sex with men was associated with greater likelihood of unprotected anal and sexual intercourse with seronegative partners and partners of unknown serostatus. Furthermore, injection drug users were more likely to endorse greater symptoms of depression, greater loneliness scores, and were more likely to have progressed to AIDS (Ibanez et al., 2005). Unprotected sexual behaviors further threaten the disease status for PLWHA by increasing risks for reinfection with HIV as well as exposure to other sexually transmitted pathogens implicated in accelerating the course of the disease (Antoni et al., 1995). Thus, stress may exacerbate the use of substances and subsequently increase risky behaviors that impact the health of PLWHA.

MEDICATION ADHERENCE

Medication adherence is a health behavior that is important for symptom management and for achieving optimal viral suppression, and adherence is often impacted during periods of high stress (Bottonari, Roberts, Ciesla, & Hewitt, 2005). HIV treatments demand high rates of adherence to the degree that optimal outcomes are achieved when near-perfect adherence to HIV medications are maintained (Patterson et al., 2000). In fact, less than 95% medication compliance has been associated with inadequate viral suppression and subsequent resistance to ART medication (Bangsberg et al., 2000; Sethi, Celentano, Gange, Moore, & Gallant, 2003). Studies investigating psychosocial factors that predict nonadherence have found that being non-White, female, endorsing depressive symptoms, carrying misinformed or dysfunctional beliefs regarding medication use, experiencing two or more medication side effects, poor adherence self-efficacy, lack of communication with physicians regarding drug use, avoidance-oriented coping, and negative mood all have been associated with ART nonadherence (Arnsten et al., 2007; Berg et al., 2004; Catz et al., 2000; Marc et al., 2007; Weaver et al., 2005). Psychoactive substance use, in particular, has been shown to be a major risk factor for nonadherence to HIV medication (Gebo, Keruly, & Moore, 2003; Carrico et al., 2007). In examining the relationship between affect regulation, stimulant use, and viral load in a cross-sectional substudy of 858 HIV positive individuals, Carrico and colleagues (2007) determined that regular stimulant users had viral loads that were five times higher than nonstimulant users, despite statistically controlling for medication adherence. Conversely, affect regulation was inversely associated with stimulant use; in the adjusted model, each unit increase in affect regulation corresponded to a 23% decreased likelihood of using stimulants and a 15% decreased likelihood of being nonadherent. Therefore, adherence to HAART is strongly influenced by stress and affective states, providing yet another mechanism through which stress impacts health among PLWHA.

CONCLUSION AND FUTURE DIRECTIONS

This chapter has covered a wide range of factors that function as potential moderators and mediators of the effects of stress on health in HIV disease. Based on this review, it is quite evident that stress significantly alters HIV disease progression, working by way of biological, physiological, and neuroendocrinological mechanisms and modifiable by intrapersonal, sociocultural and psychosocial factors; however, the exact paths that define these associations remain uncertain. Some of the factors underlying the overall discordance in the literature point to differences in the methodological framework used in these research studies, including differences in the variables assessed. For example, Kemeny (2003) argues that the concept of stress is too diffuse, thus leading to the conflicting findings in the literature surrounding the role of stress on the immune system. Stress can elicit many different emotions, attributions, and responses, each individually impacting the immune system through its unique physiological effects (Kemeny, 2003). Future studies should therefore include both subjective (i.e., perception of event as stressful) and more objective measures of stress (i.e., number of stressful life events, stress biomarkers). In addition, future studies should include cumulative measurements of key variables (e.g., depressive symptoms), rather than one-time estimates, to account for the variability in mood. Other methodological strategies that may be incorporated to strengthen research findings include utilizing more precise measures of medication

adherence. Self-reported medication adherence may not accurately depict actual levels of adherence (Arnsten et al., 2001); therefore, medication adherence should be assessed using improved instruments, such as electronic monitoring or home-based adherence assessments (Kalichman et al., 2007). Furthermore, given the obvious burden of mood disorders in this population, it is imperative that future research continue to investigate the collective effect of antidepressant medications and HAART on the immune system. Few studies have assessed and controlled for antidepressant medication use in their samples, thus introducing additional confounds that may influence their results.

Most importantly, additional research investigating the relationship between stress and HIV disease progression is warranted in minority samples, especially African American women and Hispanic populations. Although the relationship between stress and HIV status has been established, not much is known about how this relationship manifests in underrepresented and diverse groups. As we mentioned earlier in the chapter, most studies that have been reviewed have been carried out using predominantly Caucasian men, and fewer have been carried out with African American women and Hispanic samples. Amongst the limited studies that have included Hispanic or African Americans in their samples, few have incorporated the use of culturally sensitive psychosocial instruments. Moreover, studies that have included these minority groups have suggested that these populations may at times experience better health outcomes than their Caucasian counterparts (Leserman, 2000; Siegel, Schrimshaw, & Pretter, 2005); yet, despite this encouraging fining, African American and Hispanic populations continue to die from HIV disease at alarming rates (Anastos et al., 2005; CDC, 2007). Some may speculate that these populations are at risk of not receiving proper medical care. For instance, Kalichman, Graham, Luke, and Austin (2002) have reported disparities in HIV treatment and other, related diseases among minority populations. In addition, Pence et al. (2008) reported lower rates of women and minorities on a stable ART regimen, which they attributed to higher treatment dropout rates.

Furthermore, minority populations may be disproportionately impacted by many of the same stressors discussed thus far in addition to other stressors not commonly measured (e.g., acculturative stress). We have already pointed out how stigma may impact disease progression by causing changes in health behaviors necessary for managing HIV disease. HIV-related stigma, for example, may be more detrimental for Hispanic and African American populations, since it adds to already existing stressors related to racial prejudice (Ramirez-Valles, Fergus, Reisen, Poppen, & Zea, 2005; Wingood et al., 2007). For example, a study by Wingood and Colleagues (2007) found that the health of HIV-positive African American women was more affected by discriminatory events than their Caucasian counterparts. Equally important, study findings revealed that perceived discrimination reduced the likelihood of their seeking HIV care (Wingood et al., 2007). These findings are further corroborated by a more recent study of predominantly African American and Latino men, which found that stigma-related experiences associated with their physicians decreased their access to health care (Vanable, Carey, Blair, & Littlewood, 2006). In addition to concerns about their HIV status, African American and Hispanic homosexual PLWHA may experience increased stress associated with their sexuality since they are not carrying out the expected social roles defined by their culture (Körner, 2007). Findings from reports in the cardiovascular literature looking at the effect of perceived racism suggest that it functions as an additional stressor that augments the risk of cardiovascular disease (Brondolo, Rieppi, Kelly, & Gerin, 2003; Lepore et al., 2006); therefore, future research with HIV positive minority groups should explore the plausible role of perceived racism as an additive stressor that contributes to disease progression.

Minority populations may encounter additional, culturally laden stressors that may increase their chances for poorer disease prognosis. For example, acculturation, the process of change by which an individual learns and acquires the behaviors and values of a nonnative culture (Berry, 1980, and Padilla, 1980, as cited in Miranda, Bilot, Peluso, Berman, & Van Meek, 2006), is a stressor that has been shown to impact health and health behaviors in African American (Ard, Skinner, Chen, Aickin, & Svetkey, 2005; Guevarra et al., 2005) and both U.S.-born and recently immigrated Latinos living in the United States (Gorin & Heck, 2005; Lara, Gamboa, Kahramanian, Morales, & Bautista, 2005; O'Malley, Kerner, Johnson, & Mandelblatt, 1999). Acculturation may uniquely account for some of the variance in stress responses reported in the literature.

In addition to acculturative stress, future studies looking at factors impacting disease status in HIV might emphasize the significance of the family as both a source of support and of stress. Familism, a strong allegiance to the family and a tendency to place their needs ahead of your own (Halgunseth, Ispa, & Rudy, 2006), is a central cultural feature of the Hispanic population that has been suggested to contribute to the stress experience and to influence many of the health care behaviors in Hispanic women living in the United States (Larkey, Hecht, Miller, & Alatorre, 2001; Maly, Umezawa, Ratliff, & Leake, 2006). For example, a study by Finnegan et al. (2000) found that some Hispanic women delayed seeking medical attention when presented with symptoms of a heart attack to assume responsibility for their family.

The family has been demonstrated to be a source of stress in African American women as well. For example, a study by Jones, Beach, Forehand, and Foster (2003) looking at factors contributing to changes in health status in a sample of African American women determined that, after adjusting for CD4 levels, familial stressors rather

than nonfamily-related stressors predicted self-reported physical health declines 1 year later. This relationship was explained by the manifestations of depressive symptoms, such that family-related stress lead to depressive symptoms, ultimately impacting perceived physical health. Of the family stressors reported by women in the study, nearly two thirds reported worries around a family member in jail, 45% reported concerns about an abortion, and 40% reported witnessing family violence (Jones et al., 2003).

Nevertheless, studies have demonstrated that family is a source of support for many minority populations (Maly, Umezawa, Leake, & Silliman, 2005). Despite this knowledge, few studies have identified interventions that incorporate the family network as an additional component of treatment. Some of the work that can take place in a family setting includes providing education about how HIV causes disease, reviewing possible methods of viral transmission, discussing how medications function, and emphasizing the implications surrounding medication nonadherence. Introducing a family component into treatment will not only help reduce the stigma and misconceptions surrounding an HIV diagnosis but it will also strengthen many individual's main support system. Secondary benefits, such as engaging less in negative health behaviors and increasing medication adherence, may follow.

In conclusion, there is evidence that even during the era of highly effective antiretroviral treatment, PLWHA continue to confront a multitude of acute and chronic stressors that have been associated with systemwide perturbations. Almost in a hierarchical fashion, these stressors and distressed states are proposed to trigger excitability of large stress systems (i.e., HPA and SNS) that are identifiably intertwined with fundamental immunocellular components of the defense system. Yet despite delineation of this intricately designed pathway, multiple, coexisting factors (e.g., coping strategies, health behaviors, personality traits) have been shown to redefine the course of the disease. It is likely the complex interaction of these factors with the variability in conceptualization and measurement of stress and other cofactors that contributes to the conflicting evidence reported in the literature. In particular, what constitutes a stressor may vary across cultures; yet minority groups remain understudied. Future research in this area may therefore profit from further investigation of cross-cultural differences in the stress–immune relationship in PLWHA. Exploration of these differences will help address some of the disparities evident in the literature.

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33 Pain: The Biopsychosocial Perspective

Robert J. Gatchel, Krista Howard, and Rob Haggard

Pain affects people from all backgrounds and is present in every social tier of our society. Pain management represents a socioeconomic challenge to our culture, and the lack of adequate pain management methods adds to the emotional suffering of individuals who are distressed from the physical and emotional burden of chronic pain. Nearly 48 million people in the United States are subject to chronic pain and find little relief from current medications, which often produce harmful side effects while providing little symptom relief (LeMoult, 2006). According to the Centers for Disease Control and Prevention (CDC) National Center for Health Statistics (NCHS) (2006), one in four U.S. adults reported a pain experience that lasted at least a full day during the previous month, and one in ten adults reported a pain condition that persisted for a year or more. This report also revealed that one fifth of adults above the age of 65 years reported pain that lasted more than 24 hours, while three fifths of these older adults reported that they had endured a pain condition for more than 1 year.

According to the 2004 Americans Living with Pain Survey (LeMoult, 2006), 72% of people experiencing chronic pain have lived with this pain for at least 3 years, and approximately one third of these individuals have lived this way for more than a decade. Additional findings from the NCHS (2006) indicated that low-back pain, migraine (or severe headache), and joint pain (aching or stiffness) are among the most commonly reported pain complaints. More than a quarter of those surveyed by the NCHS (2006) had experienced low-back pain in the preceding 3 months, and 15% reported migraine in the preceding 3 months. Although adults in the 18–44 age range were three times as likely to have experienced a migraine in the previous 3 months compared to adults 65 years and older, it was found that incidences of severe joint pain increased with age in the NCHS sample. Additionally, women reported joint pain more often than men. Although pain has a profound effect on people's daily lives, nearly half of the people who experience pain wait months or longer before consulting a physician (LeMoult, 2006). When people experiencing pain do finally seek professional help for their condition, they are often faced with personal and financial challenges. For example, the NCHS (2006) reported that 7% of adults with chronic pain below the age of 65 years did not get the help they needed in the preceding year because of high costs. Moreover, findings from NCHS (2006) also indicated that the percentage of adults who took a narcotic drug to alleviate pain during the previous month had increased from 3.2% to 4.2% between the survey periods of 1988–1994 and 1999–2002. The professionals whose mission it is to treat these patients also face challenges in identifying pain relief methods that are both therapeutic and cost-effective (LeMoult, 2006).

While the entire financial impact of chronic pain has yet to be determined, the socioeconomic impact of unrelieved pain costs was estimated at approximately $100 billion per year at the turn of the century (Curtiss, 2001). Further estimates have reported lost productivity time ranging from $61 to $80 billion per year resulting from common pain conditions such as backache among active workers (Doheny, 2002). Most (76.6%) of this loss in productivity was not attributed to work absence but, rather, to reduced performance while at work, a concept often referred as *presenteeism*. Many chronic and recurrent pain patients reportedly suffer for several years, often while enduring major surgeries and paying large sums of medical bills without any guarantees of relief. The Social Security Administration predicted that in 2008, nearly $608 billion in Social Security benefits would be distributed amongst almost 50 million Americans, with around 18% ($109.4 billion) of these total benefits being allocated to disabled workers and their dependents (Social Security Administration, 2008). This large sum does not account for employees who continue to work while in pain, albeit at a reduced level of productivity.

In fact, a considerable proportion of the costs associated with chronic pain may be the result of reduced productivity. A telephone-based survey conducted in New South Wales, Australia, among 484 adults aged 18 or above who were currently living with chronic pain illustrated that it was more common to continue working with pain (on an average 83.8 days in 6 months) than to miss work because of pain (4.5 days in 6 months; Blyth, March, Nicholas, & Cousins, 2003). It was determined that when both lost work days and reduced-effectiveness work days were summed, an average of 16.4 total lost work-day equivalents occurred in a 6-month period,

which was approximately three times that of the average number of lost work days.

ACUTE VERSUS CHRONIC PAIN

Categorizing and describing pain has its own intrinsic complications. At what point does pain transition from acute to chronic status? The Federation of State Medical Boards (FSMB) defines acute pain as "the normal, predicted physiological response to a noxious chemical, thermal or mechanical stimulus and typically is associated with invasive procedures, trauma and disease . . . (which is) generally time-limited" (FSMB, 2004). It is common to see acute pain described as having a duration of less than 2–4 weeks (Atlas & Deyo, 2001). Further delineations for subacute (duration of up to 12 weeks) and chronic (duration of more than 12 weeks) are also common. Additional discrepancies in terminology occur in the psychiatric literature; Fourth Edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV-TR* [American Psychiatric Association (APA), 2000]) describes the difference between acute and chronic conditions to occur at a 6-month boundary (less than 6 months as acute; greater than 6 months as chronic). The FSMB is more general in defining chronic pain as "a state in which pain persists beyond the usual course of an acute disease or healing of an injury, or that may or may not be associated with an acute or chronic pathological process that causes continuous or intermittent pain over months or years" (FSMB, 2004). This latter consideration for intermittent or chronic recurrent pain (in which periods of pain are interspersed with pain-free periods extending over months or years) is important because it may best describe how a large proportion of the general population experiences pain (Gatchel, Peng, Peters, Fuchs, & Turk, 2007).

Gatchel (1991, 1996) developed a three-stage model that describes a progression from acute pain to chronic pain disability with associated psychosocial distress. In this model, anxiety is considered to be a common reaction to acute pain, whereas other severely disabling psychopathologies like major depressive disorder (MDD) or substance use disorders are more often linked to chronic pain. As pain becomes more chronic, patients undergo a significant "psychological metamorphosis" in which behavioral/psychological problems are layered over the original pain experience (Gatchel, 1991). Stage 1 of the model therefore comprises normal emotional reactions like fear, anxiety, and worry, resulting from the perception of pain during the acute phase. If the pain persists longer than 2–4 months (a time frame in which the majority of musculoskeletal conditions would normally improve), the patient enters into Stage 2. This phase consists of increased psychological and behavioral distress, often including instances of learned helplessness, anger, and somatization that are seen to result from this extended duration of pain. According to this hypothesis, preexisting psychological characteristics, socioeconomic factors, and other environmental conditions collude in determining the form these problems take. Thus, the stress of living with chronic pain intensifies the patient's premorbid characteristics in a *diathesis–stress process*. Further, if these problems persist, they will become the focus of the patient's attention as his/her life begins to be restructured around the pain. This culminates in Stage 3, in which the patient habituates into a sick role by avoiding normal responsibilities and obligations, thus further reinforcing the malfunctioning state (Gatchel, 1991). Because of the complex interactions of physical, psychological, and social processes, the patient may become accustomed to avoidance of responsibility and will often maintain a maladaptive approach to daily life tasks because of operant conditioning processes (Anagnostis, 2001; Gatchel, 1991, 1996).

A comorbid phenomenon referred to as "physical deconditioning syndrome" often occurs during Stage 3 as part of the transition from an acute injury to a chronic disabling condition. This has been described as a decrease in strength, flexibility, and endurance at the injury site subsequent to disuse and atrophy (Anagnostis, 2001; Mayer & Gatchel, 1988). The avoidant behavior that occurs as part of this phenomenon synergistically feeds into another process of "mental deconditioning," which can result from a compromised emotional well-being. This is asserted to be a synergistic process because, as patients with chronic pain become more emotionally compromised, they will begin to find their avoidant behaviors to be reinforced by those making up their social cohort (family, friends, or coworkers), thereby resulting in a further decrease in motivation to participate in occupational, social, or recreational activities. When these psychosocial factors are combined with financial compensation issues, they can represent a significant obstacle to spontaneous recovery of function (McMahon, Gatchel, Polatin, & Mayer, 1997).

HISTORICAL OVERVIEW OF THE CONCEPTUALIZATION OF PAIN

EARLY MODELS OF PAIN/ THE BIOMEDICAL APPROACH

Similar to the distinction between acute and chronic pain (with the latter involving a complex interaction of physiological and subjectively experienced psychological and social factors that result from an objective and purely physical acute injury), pain is often distinguished in the literature from nociception (Gatchel, 2005). Although these psychophysiological processes will be touched upon later in this chapter, it is important to have an understanding of the terms before proceeding. Nociception is a primarily objective response to the stimulation of nociceptors, which are the nerves responsible for conveying information to the brain as a warning of potential tissue damage. Pain entails a subjective experience resulting from awareness of

nociceptive sensory processes to which meaning is assigned after being filtered through an individual's psychological and sociocultural expectations (Gatchel et al., 2007).

Early biomedical models from the 19th through the 20th century were rooted in a Cartesian view of a reflective relationship between pain and tissue injury. The earliest theories of pain first proposed by Hippocrates, the ancient Greek physician and philosopher, were rooted in the proposal of four bodily humors: sanguine, choleric, melancholic, and phlegmatic. It was asserted that personality arose from these humors, which could in turn affect the body, and therefore influence an individual's perception of pain (Gatchel, 1991). An artificial distinction between mind and body, termed *dualism*, became the more popular view with Descartes' hypothesis that the perception of pain directly results from physical injury, or stimulation, being transmitted from skin to brain. According to this hypothesis of pain, there must be observable, objective evidence of physical damage or impairment.

One of the earliest examples of this dualistic view was "specificity theory," in which specific receptors transmit explicit information regarding pain from the peripheral nerves to the spinal cord and then to the brain. As the methods for analyzing and describing anatomy and physiology advanced, pain theories became more formalized, as was the case with one of the earliest and best known of the modern specificity theorists von Frey (Melzack & Wall, 1965). The work of von Frey in the late 19th century involved labeling and describing various mechanical and thermal receptive fields on the skin. Furthermore, von Frey was the first to propose that specialized nerve endings were responsible for transmitting painful information from the skin to the brain (Gatchel et al., 2007). In response to the limitations of specificity theory, early- to mid-20th century pain theorists proposed what has become known as the "pattern response." In this model, sensory or nociceptive information does not arise from the activation of specific nociceptors, but rather is initiated because of a pattern of responses in sensory systems. Perceptual response to the nociceptive input is determined by the intensity of the stimulus and the processing of a pattern of responses (Gatchel et al., 2007).

Although these two early models advanced the understanding of pain and nociception, they were limited in their ability to account for sensory experiences that were not objective or directly evidenced. The lack of adequate resolutions and explanations for pain and suffering spurred the next advance in our understanding of nociception and the individual experience of pain. In the 1960s, Melzack and Wall (1965) moved to a more integrative model in their postulation of the *gate control theory of pain*.

THE GATE CONTROL THEORY OF PAIN: A MAJOR THEORETICAL BREAKTHROUGH

The gate control theory of pain, introduced by Melzack and Wall (1965), emphasizes the significant role that psychosocial factors potentially play in the perception of pain. In a more integrated approach, pain is viewed as an intricate assortment of occurrences instead of as a single, straightforward, continuous phenomenon. Considered from this comprehensive perspective, pain arises from an interaction of (1) specific nerve function, (2) pattern recognition of noxious pain stimuli, and (3) an alteration of these incoming signals by higher cortical functions of emotional amplification and cognitive interpretation (Anagnostis, 2002; Gatchel et al, 2007). The term *gate-control* refers to the proposed mechanism of the substantia gelatinosa located in the dorsal horn of the spinal cord. Melzack and Wall (1965) asserted that a gate-like function of the substantia gelatinosa modulates the amount of sensory input from peripheral nerves to dorsal horn transmission cells and thereby regulates not only the transmission but also the intensity of signals to the central nervous system. They further theorized that transmissions from higher cortical functions affect this spinal-gating mechanism and thereby allow psychological phenomena to directly affect the experience of pain. This model allows for psychological factors such as depression, anxiety, and memory to be examined in addition to the data that are ascertained from observational methods and patients' pain reports as part of the pain experience.

THE BIOPSYCHOSOCIAL APPROACH TO PAIN

The biopsychosocial (BPS) perspective runs counter to the traditional biomedical reductionist viewpoint which states that the body and mind are dual mechanisms (Susman, 2001). The BPS model consists of multiple components (physiological, behavioral, and sociological) interacting in a dynamic manner that is unique to each individual. Engel (1977) initially introduced what became known as the BPS model in the 1970s and 1980s. Prior to this time, pain was divided into dual categories of organic pain and psychogenic pain. The term *psychogenic* insinuates that the experience of pain is not "real" because no organic etiology can be determined. Individuals with psychological pain etiology often received inadequate treatment because this dualistic perspective impeded the development of interdisciplinary strategies that combine psychology and medicine. Fortunately, contemporary diagnostic criteria from *DSM-IV-TR* (APA, 2000) do not include *psychogenic pain* as a descriptive term, nor does the assessment of organic pain preclude the critical function of psychosocial factors for particular individuals (Dersh, Polatin, & Gatchel, 2002). *Pain disorder* as a diagnostic category is defined according to the relative extent with which psychological and medical conditions correspond with extant pain. Pain, as viewed by the BPS model, is a unique, individualized experience (Gatchel, 2004). Symptoms are modulated by the complex interaction among psychological, sociological, and physical pathology factors in variant ways.

As Melzack and Wall (1965) expanded the understanding of pain to include not just physiological but also psychological mechanisms and Engel (1977) initiated the discussion of pain as an individual experience that included social factors, the studies in 1980s added to the BPS model with an even more comprehensive conceptualization. From this multidimensional approach, biological, cognitive, affective, behavioral, physiological, and social factors are all postulated to contribute to the individual experience of pain, with no singular factor exclusively responsible for the complexities encountered in pain assessment and treatment (Turk, 1999).

STRESS AND CHRONIC PAIN

The evolutionary function of stress serves as a mechanism of adaptation such that individuals will appropriately react and respond to lessen the consequences of threatening or challenging situations. The body's chemical response to perceived stressors has been studied extensively. Upon appraisal of a situation, if the circumstances are interpreted as threatening, there is increased activation of two neuroendocrine systems, namely, the sympathetic–adrenomedullary system and the hypothalamic–pituitary–adrenalcortical (HPA) system. These responses operate to prepare the body for immediate reaction (fight or flight). The HPA negative feedback loop is designed to provide inhibitory effects, or to shut down the response, and maintain homeostasis (Henderson & Baum, 2004). In a chronic stress condition, hyperactivity in the HPA system may indicate, or possibly cause, a malfunction in the negative feedback loop that can consequently promote biological damage.

Several recent studies have linked HPA dysfunction to chronic pain conditions, such as fibromyalgia, rheumatoid arthritis, temporomandibular pain disorder, and chronic fatigue syndrome. Lariviere (2002) argued that irregularities in the HPA system can be seen as factors in the development of chronic pain syndromes, operating through the pain mechanisms in the central nervous system. Garofalo, Robinson, and Gatchel (2006) evaluated both low-back pain and temporomandibular disorders in relation to cortisol levels. They concluded that patients at higher risk for developing chronic pain conditions exhibited greater variability in cortisol output than did the low-risk patients. Furthermore, in animal studies focusing on the association between pain and the HPA system, chronic pain has been termed an "inescapable stressor" (Blackburn-Munro & Blackburn-Munro, 2001). Finally, stress and chronic pain have been linked in many studies, and the bidirectionality of their relationship can be seen to enhance negative effects on the body. Many view this as a "chicken and the egg" phenomenon such that as stress exacerbates pain the increased level of pain, in turn, inevitably becomes a stressor.

NEUROSCIENCE OF PAIN

Pain involves sensory input from the periphery, passing through the dorsal horn of the spinal cord and ultimately ending up in specified regions of the brain, such as the hypothalamus. Pain can be divided into two separate categories: nociceptic pain and neuropathic pain. As noted earlier, nociception is the response to perceived or actual tissue damage and does not always lead to the experience of pain. Sensory receptors, including thermal, mechanical, polymodal, and silent receptors, are the primary means through which noxious insults are registered and conveyed to the brain from the periphery. Neuropathic pain, on the other hand, represents actual disease of the nerves located in the periphery or the central nervous system (Basbaum & Jessell, 2000).

Allodynia and *hyperalgesia* are two instances of atypical pain states. Pain resulting from a typically innocuous stimulus is termed allodynia. For example, clothing does not cause pain in normal instances; however, if a person has sunburn, the sensory input from the clothing is perceived as being painful. Hyperalgesia reflects an excessive response to a noxious stimulus such that the perceived pain is seen to elicit even more pain (Basbaum & Jessell, 2000). Both allodynia and hyperalgesia are often observed in chronic pain populations (Staud, 2006).

Genetic factors have also been shown to play a role both in the perception of chronic pain and in healing processes. Specific genes identified through the mapping of the human genome (Jasny & Kennedy, 2001) are associated with sensory transmissions. Genetic testing allows for identification of the genes responsible for the modification of protein synthesis related to pain, which involves neurotransmitters, receptors, and enzymes. Furthermore, research on inflammation, neuropathic pain, and pain associated with cancer have helped in the creation of various pain models that have led to a better understanding of the underlying mechanisms involved in chronic pain. Thus, by allowing for a greater knowledge of these mechanisms, researchers have been able to develop more appropriate treatment options based on the dynamics of each individual condition (Gatchel et al., 2007).

Recent tools used to evaluate pain include functional magnetic resonance imaging and positron emission tomography. These instruments identify blood flow changes in specified regions of the brain that are thought to be associated with the experience of pain. Although there are questions about the interpretation of results from imaging studies, these noninvasive tools have shed light on the anatomical and pathological structures within the central nervous system that are involved in pain (Gatchel et al., 2007).

THE BPS INTERDISCIPLINARY APPROACH TO PAIN ASSESSMENT

The BPS perspective has considerable heuristic value for developing therapies for the successful treatment of chronic pain (Turk & Rudy, 1987). The BPS treatment model employs a collaborative, multidisciplinary approach, in which patients are evaluated and treated by providers from multiple areas of expertise, including medicine, physical therapy, behavioral health, and other specialties (Wright & Gatchel, 2002). Clinical research has clearly demonstrated the treatment- and cost-effectiveness of such an approach for chronic pain conditions (Gatchel & Okifuji, 2006; Turk & Swanson, 2007). Of course, chronic pain and chronic recurrent pain patients often present challenges to a multidisciplinary pain management team that may prevent their entry into, and success within, comprehensive treatment programs (Miller et al., 2005). Therefore, psychological and behavioral prescreening instruments are routinely used in pain management and rehabilitation settings, particularly those that utilize a multidisciplinary approach to predict (based upon prior research findings) which individuals are more likely to successfully complete a particular regimen (Gatchel, 2001), as well as to uniquely tailor treatment goals based upon screening responses. Among the factors that are evaluated in these settings are psychosocial variables for clinical syndromes, personality disorders (PDs), and substance misuse. Chronic pain patients with comorbid psychiatric disorders are often at particular risk for denial of treatment, either by their insurance carrier or by their physician, because mental health issues are commonly "carved out" or excluded from medical treatment. The end result in these situations is that comorbid psychological and behavioral factors are left unattended, and subsequent treatment complications may arise (Dersh et al., 2002). Indeed, such "carve-out" policies significantly reduce the overall efficacy of interdisciplinary programs (Gatchel et al., 2001; Robbins et al., 2003; Hatten, Gatchel, Polatin, & Stowell, 2000).

PSYCHOPATHOLOGY AS A FACTOR IN PAIN MANAGEMENT

The individual experience of pain may be intensified by comorbid psychopathology, thereby perpetuating the dysfunction and disability associated with pain. Assessment is therefore a vital component in determining which psychiatric variables contribute to each patient's progress, and to what degree they do so, throughout an interdisciplinary regimen (Dersh et al., 2002). Psychiatric factors vary depending on individual patients and clinical setting, but several key issues have been identified in pain populations. The three major psychiatric concomitants of chronic pain are mood disorders, anxiety disorders, and substance use disorders, often manifested by depression, suicide, and sleep problems (Dersh et al., 2002). Emotional factors become more significant in the maintenance of dysfunction and suffering as pain becomes more chronic (Gatchel, 1996).

Several key relationships between psychopathologies and the individual experience of pain have been demonstrated. Among these, anxiety has been linked to a lowered pain threshold and tolerance; depression has been linked to less successful treatment outcomes; anxiety and depression have both been linked to the amplification of medical symptoms; and emotional distress has been associated with multiple physical symptoms (Dersh, Gatchel, Mayer, Polatin, & Temple, 2006). Chronic low-back pain (CLBP) researchers in the 1980s documented increased prevalence rates for depression, anxiety, substance abuse/dependence, somatization, and PDs in their patients (Fishbain, Goldberg, Labbe, Steele, & Rosomoff, 1988; Katon, Egan, & Miller, 1985; Magni, Caldieron, Rigatti-Luchini, & Merskey, 1990; Reich, Rosenblatt, & Tupin, 1983). These patients also reported rates of MDD ranging from 34% to 57%, in sharp contrast to the rates of MDD in the general population at this time, which were estimated at between 5% and 26% (APA, 1987).

IDENTIFYING PSYCHOPATHOLOGY IN PAIN MANAGEMENT

As a benchmark for addressing the physiological and psychosocial components of chronic pain with a systematized approach, the multiaxial classification system was first introduced with the *DSM-III* during the 1980s (Reich, Rosenblatt, & Tupin, 1983; APA, 1980). Direct comparisons of psychopathology prevalence rates across different contexts have been made possible by using semi-structured and structured clinical interviews based upon criteria from the various revisions of the *DSM* (Gatchel, Garofalo, Ellis, & Holt, 1996). One of the primary methods for assessing psychopathology in protocol-based studies involves use of the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I [First, Spitzer, Gibbon, & Williams, 1994]) and the Structured Clinical Interview for *DSM-IV* Axis II Personality Disorders (SCID-II [First, Spitzer, Gibbon, & Williams, 1994; First, Spitzer, Gibbon, Williams, & Lorna, 1994]). The SCID allows for the determination of current and lifetime diagnoses of psychopathology, which are useful in determining whether the current pain episode preceded the occurrence of psychopathology or vice versa (Gatchel, 1996). In addition to having demonstrated good reliability and validity, the SCID helps clinicians to distinguish the onset of pain from the onset of psychopathology, illuminating the synergistic relationship between the two domains (Gatchel, 1991).

A study examining the relationship between the onset of pain and the current and lifetime prevalence of psychiatric disorders in CLBP patients showed that 77% met lifetime diagnostic criteria for at least one psychiatric

diagnosis (Polatin, Kinney, Gatchel, Lillo, & Mayer, 1993). In a further analysis, 59% of these patients demonstrated current symptoms for at least one psychiatric diagnosis as measured with the SCID-I and SCID-II for the *DSM-III-R* (Kinney, Gatchel, Polatin, Fogarty, & Mayer, 1993; Polatin et al., 1993; Spitzer, Williams, Gibbon, & First, 1988). Again, this demonstrates a marked difference between patients with CLBP when compared to then current estimates in the general population for lifetime and current rates of Axis I and Axis II diagnoses ranging from 15% to 38% (APA, 1987; Regier et al., 1988; Robins et al., 1984). MDD, substance abuse, and anxiety disorders were reported more frequently in this sample than any other Axis I or Axis II diagnoses.

While prevalence rates for psychopathology were significantly higher among the chronic pain population than in the general population, it is also conspicuous that approximately half of these patients displayed features of at least one Axis II PD. Among chronic pain patients who had a lifetime history of anxiety disorders, 95% reportedly experienced symptoms of anxiety prior to the onset of pain. MDD appeared to develop before the onset of pain in some cases and developed subsequent to the onset of pain in others; 54% of chronic pain patients experienced symptoms of depression prior to the onset of pain (Polatin et al., 1993). Chronic pain patients with a lifetime history of substance demonstrated a similar prevalence rate as patients with anxiety disorders; 94% of this sample reported substance misuse prior to the onset of pain. Gender differences were also demonstrated among chronic pain patients. Males were more likely to have a substance use diagnosis, and females were more likely to have a diagnosis of MDD or an anxiety disorder (Polatin et al., 1993).

When psychiatric comorbid disorders were examined in a comparison of acute low-back pain (ALBP) versus CLBP, higher rates of psychopathology were found among the chronic pain population (Kinney et al., 1993). These chronic pain patients had higher rates of MDD, substance use disorders, and PDs than the ALBP group. Conversely, acute pain patients had higher prevalence rates for anxiety disorders. All the foregoing results seem to indicate that higher prevalence rates of mental health disorders are linked not only to the onset of acute pain but also to the development of chronic pain (Gatchel, 1991).

As is the case in all correlational research, no direct causal relationship between chronic pain and psychiatric disorders can be demonstrated, but there is much to be inferred from the high prevalence rates of psychiatric comorbidity among chronic pain patients. Much of the aforementioned material and research pertains primarily to chronic musculoskeletal pain, but it is important to note that high rates of comorbid psychiatric disorders have also been demonstrated in other conditions, including temporomandibular joint disorder , headaches, pelvic pain, and fibromyalgia (Epstein et al., 1999; Kight, Gatchel, & Wesley, 1999; Okasha et al., 1999; Savidge & Slade, 1997; Wright et al., 2004). Research continues to document a relationship between medical conditions, especially those chronic in nature, and higher prevalence rates of behavioral and psychiatric conditions (Maier & Falkai, 1999). Only 2–4% of the general population suffers from a mood or anxiety disorder at any given time; one study found that between 15% and 33% of medically ill inpatients suffered from such disorders (Katon & Sullivan, 1990).

PREVALENCE OF SPECIFIC AXIS I DIAGNOSES IN PAIN POPULATIONS

Depression

There is a general acknowledgement that depression is often linked to chronic pain, but identifying and diagnosing depression is complicated due to the lack of uniformity in the assessment of its symptoms. Depression has, in different contexts, been defined as a mood, symptom, or syndrome and has been assessed by multiple methods that make it difficult to standardize and compare results across studies (Dersh et al., 2002). Perhaps because of the high prevalence of depression in chronic pain populations, research investigating the association between chronic pain and depression is much more abundant than other psychiatric disorders associated with pain. Several previously discussed studies (Kinney et al., 1993; Polatin et al., 1993) have revealed substantially high rates of MDD in chronic pain patients, with current rates of about 45% and lifetime rates of approximately 65% for this disorder. In a review of 14 studies that diagnosed depression in chronic pain patients using *DSM-III*, *DSM-III-R,* or *DSM-IV* criteria, 9 studies reported current prevalence of MDD between 30% and 54% (Banks & Kerns, 1996). Again, these rates contrast with estimates around this time period for MDD in the U.S. population, which were reported as 5% for current major depression and as 17% for lifetime major depression (Blazer, Kessler, McGonagle, & Swartz, 1994).

Comparisons across study designs are somewhat complicated by the heterogeneity of chronic pain populations. Some researchers have examined patients with assorted pain sites and in multiple treatment contexts, and demonstrated relationships between pain and depression. Other researchers have demonstrated specific pain sites to be more frequently associated with depression, which may vary across treatment contexts. Further confounding any inferences made from this line of research is an overlap in the symptoms attributed to chronic pain and depression, such as sleep disturbance, motor retardation, fatigue, and changes in weight and appetite (Dersh et al., 2002). As a consequence, the diagnostic criteria for depression in a chronic pain population are not consistently clear-cut. Considering the resulting impact these confounds have on assessing depression in a chronic pain population, standardized diagnostic systems based on the *DSM* are the most reliable methods for valid diagnoses of MDD. The structured format of the SCID helps to alleviate assessment variability between and within

study designs, thus allowing for direct comparisons across studies and clinician ratings (Dersh et al., 2002).

Some efforts to understand the temporal relationship between chronic pain and depression seemed to demonstrate depression as subsequent to chronic pain (Magni, Moreschi, Rigatti-Luchini, & Mersky, 1994). However, Polatin et al. (1993) found depression to both precede and succeed chronic pain conditions. Chronic pain and depression were described as similar from a physiological standpoint by Roy, Thomas, and Matas (1984). Physiological similarities between chronic pain and depression include anatomically coinciding affective and nociceptive pathways (Hodgkiss, 1997; Magni & de Bertolini, 1983) and the fact that neurotransmitters (norepinephrine and serotonin) involved in the gate-control mechanism for pain are thought to be involved in mood disorders. Further evidence for this physiological similarity comes from the use of antidepressant medications that have also demonstrated efficacy in treating some chronic pain patients.

Substance Use Disorders

Evidence for a high degree of comorbidity of substance use disorders among chronic pain populations is abundant (Fishbain, Goldberg, Meagher, Steele, & Rosomoff, 1986; Katon et al., 1985; Polatin et al., 1993; Reich, Rosenblatt, & Tupin, 1983). In a meta-analytic review that included the SCID as part of a diagnostic assessment battery, Brown, Patterson, Rounds, and Papasouliotis (1996) found that the rates of current substance use disorders ranged from 15% to 28%, whereas those of lifetime substance use disorders ranged from 23% to 41%. These disorders were higher for males than for females in the chronic pain population, comparable to how they are distributed in the general population. However, the prevalence rates of lifetime and current substance use disorders for both males and females in a chronic pain cohort were significantly higher than those in the general population (Dersh et al., 2002).

As evidenced by a study that found 94% of chronic pain patients experienced lifetime substance use disorders prior to the onset of chronic pain, chronic pain may not trigger the onset of substance use disorders as frequently as once believed (Polatin et al., 1993). It is likely, though, that rates of current substance use disorders are higher in chronic pain populations than in the general population. The aforementioned review by Brown et al. (1996) found chronic pain patients no more likely than other patients in a medical setting to have current substance use disorders, suggesting that there is not a unique risk for substance abuse among chronic pain patients, though they do have an increased risk for new substance use disorders during the 5 years following the onset of chronic pain. Iatrogenic factors (i.e., conditions induced inadvertently by a physician or as a result of medical treatment) may be partially responsible for this increased risk, though those individuals predisposed to such disorders are at the greatest risk for new or recurrent disorders. Patients with substance use disorders more often had higher comorbidity rates of other *DSM-III-R* disorders, including MDD, anxiety disorders, and Axis II PDs, than those without substance use disorders. This may be indicative of patients with multiple comorbidities who are self-medicating their psychiatric symptoms with drugs or alcohol (Dersh et al., 2002).

Anxiety Disorders

Among chronic pain patients, high rates of anxiety disorders have been documented. Panic disorder and generalized anxiety disorder tend to be the most commonly diagnosed of the specific anxiety disorders, which also include agoraphobia, specific phobia, social phobia, posttraumatic stress disorder, and obsessive–compulsive disorder (Burton, Polatin, & Gatchel, 1997; Dersh et al., 2002; Fishbain et al., 1986; Polatin et al., 1993). In studies that used the SCID and other structural interviews based on *DSM* criteria, the overall prevalence for anxiety disorders was similar to that estimated in the general population (Dersh et al., 2002). Recent findings suggest, however, that anxiety disorders are more often linked to chronic pain than has been previously reported (Dersh et al., 2002). In distinguishing between lifetime and current prevalence rates of anxiety disorders, studies have found lifetime prevalence rates similar to the general population, whereas current prevalence rates in chronic pain patients tend to be significantly higher (Burton et al., 1997; Polatin et al., 1993).

Anxiety disorders have been diagnosed frequently in both acute and chronic pain populations, though higher prevalence rates of overall psychopathology have been found in chronic pain patients (Gatchel et al., 1996; Kinney et al., 1993). Anxiety appears to be a common reaction to acute pain, whereas other psychiatric disorders such as depression are more closely associated with chronic pain. These findings support Gatchel's model of progression from acute pain to chronic pain disability (Gatchel, 1991). Diatheses may include genetic predispositions to one of the anxiety disorders that are then activated by the stress of a chronic pain experience. Chronic pain conditions seem to be maintained by physiological mechanisms following the activation of an anxiety response. Fear of pain, movement, or reinjury contributes to the continuation of pain through avoidance of activities, such as exercise, that are known contributors to pain reduction. Moreover, unwanted responsibilities and social obligations are often avoided, leading to decreased self-esteem and increased cognitive beliefs that physical exertion will increase pain. This cognitive behavioral mediation cycle may be followed by anxiety-sensitive patients who catastrophically misinterpret sensations of arousal as indicative of pain (Reiss, 1991).

Somatoform Disorders

The *DSM-IV-TR* (APA, 2000) categories of somatoform disorders include pain disorder, somatization disorder, conversion disorder, and hypochondriasis. According to

DSM-IV-TR criteria, diagnosing a patient with pain disorder is appropriate when pain (1) is the focus of clinical presentation, (2) causes significant distress or functional impairment, and (3) includes psychological factors that have an important role in the onset, severity, or maintenance of the pain (APA, 2000). *DSM-IV-TR* criteria for somatoform pain disorder no longer consider an absence of organic etiology as relevant to the diagnosis because failure to find organic causes does not mean they are truly absent. Pain disorders can be diagnosed in both acute and chronic pain conditions. Clinicians may also specify whether the condition is associated with psychological factors or a combination of psychological factors along with a general medical condition (American Psychiatric Association, 2000). By this standard, pain disorder likely applies to most chronic pain patients.

PREVALENCE OF AXIS II DIAGNOSES IN PAIN POPULATIONS

The presence of Axis II PDs can affect both the assessment and treatment phases of pain management programs. PDs precede the development of chronic and acute pain disorders because, by definition, they are long-term patterns of behavior or traits that likely developed early in life (no later than early adulthood). Although they develop early in life, PDs may never be identified in many individuals because of lack of presentation or assessment for such a diagnosis. Comorbidity of Axis II and Axis I disorders typically indicates a poor psychiatric prognosis and higher relapse rate than comparable psychiatric patients with only Axis I diagnoses (Joffe & Regan, 1988). High rates of PDs have been documented among chronic pain patients, with prevalences ranging from 31% to 81% (Burton et al., 1997; Fishbain et al., 1986; Polatin et al., 1993; Reich, Tupin, & Abramowitz, 1983; Weisberg, Gallagher, & Gorin, 1996). Studies for which the PDs have been evaluated within their 10 distinct categories indicate that these Axis II disorders are more prevalent in the chronic pain population than in the general population (Weisberg & Keefe, 1997, 1999). The PDs identified as most common in chronic pain patients in different studies are histrionic (Reich, Rosenblatt, & Tupin, 1983), dependent (Fishbain et al., 1986; Wright et al., 2004), paranoid (Polatin et al., 1993), borderline (Weisberg et al., 1996), avoidant (Wright et al., 2004), and obsessive–compulsive (Wright et al., 2004) PDs. Overlap in diagnostic criteria and discrepancies in assessment methods and patient samples may explain some of the inconsistencies across different studies (Dersh et al., 2002). As with Axis I disorders, numerous techniques exist for assessing Axis II disorders, including nonstructured interviews, the SCID-II (First, Spitzer, Gibbon, & Williams, 1997), Minnesota multiphasic personality inventory (MMPI)-2 (Butcher, Dahlstrom, Graham, Tellegen, & Kaemmer, 1989), and Millon Clinical Multiaxial Inventory-III (Millon, 1997). Although these instruments can provide information necessary for making an individual diagnosis, they are intended to be used in aggregate.

Impact of PDs on Pain Treatment Outcomes

Further support for Gatchel's model of the progression from acute to chronic pain (Gatchel, 1991) was documented in a sample of patients with CLBP, in which the prevalence of PDs was much higher (60%) than in a comparable sample of patients with ALBP (Kinney et al., 1993). Using the SCID diagnostic criteria, Gatchel, Polatin, & Kinney (1995) found that the presence of any PD was predictive of which ALBP patients had not returned to work 6 months later, although no specific PD predicted chronicity. Gatchel and colleagues thus proposed that any Axis II diagnosis may indicate a broad deficit in coping skills associated with chronic disability. In a follow-up to this study, PDs were not found to be predictive of patients who had returned to work 1 year later (Gatchel, Polatin, & Mayer, 1995). Further inconsistencies were documented with patients who exhibited a preexisting chronic pain condition. One study of CLBP patients found no association between PDs and 1-year return to work status (Gatchel, Polatin, Mayer, & Garcy, 1994). In a sample of patients with chronic upper extremity disorders, an association was found between a diagnosis of borderline PD and lower 1-year return to work status (Burton et al., 1997).

Gatchel additionally has researched whether psychiatric disorders are a limiting factor in the successful rehabilitation of chronic pain patients. Using the SCID to assess prevalences of current and lifetime diagnoses in CLBP patients ($N = 52$) beginning an intensive 3-week rehabilitation program, Gatchel et al. (1994) found that despite high rates of Axis I and Axis II psychiatric disorders, neither type nor degree of psychopathology were predictive of a patient's ability to successfully return to work 1 year after program completion. A later study compared completion status on chronic pain patients who were admitted to a tertiary rehabilitation program and found that Axis I and Axis II diagnoses were more prevalent within the noncompletion cohort than for those who successfully completed the treatment program (Proctor, 2001).

More recently, researchers have investigated whether psychopathological changes occur after intensive rehabilitation of chronic pain patients. Two studies in particular have demonstrated that effective rehabilitation can significantly diminish the prevalences of Axis I and Axis II disorders in CLBP patients (Owen-Salters, Gatchel, Polatin, & Mayer, 1996; Vittengl, Clark, Owen-Salters, & Gatchel, 1999). One such study used the SCID to evaluate CLBP patients ($N = 56$) for current psychiatric disorders as part of a pretreatment screening for a comprehensive 3-week rehabilitation program (Owen-Salters et al., 1996). These patients were again assessed with the SCID at 6 months following completion of the program. There

was a significant decline in the prevalence of psychiatric disorders following treatment; in particular, somatoform pain disorder and MDD decreased significantly.

In a similar study design, rates of SCID-diagnosed Axis I and Axis II psychiatric disorders in a sample of CLBP patients preceding and following treatment in a comprehensive pain rehabilitation program were documented (Vittengl et al., 1999). The prevalence rates of several Axis I disorders, such as somatoform pain disorder and MDD, declined following treatment (approximately 6 months). Notably, the authors also documented a decrease in the overall rates of PDs. Decreases in the rates of specific PDs (paranoid, obsessive–compulsive, passive–aggressive, and self-defeating PDs) were also found. These findings for Axis II disorders were unexpected considering the chronic nature of PDs and the lack of focus on treating these disorders in a rehabilitation setting (Dersh et al., 2002). Self-report measures of maladaptive personality traits like the Schedule for Nonadaptive and Adaptive Personality (SNAP [Clark, 1993]) and the original MMPI (Hathaway & McKinley, 1943) demonstrated much less change preceding and following treatment than the SCID's categorical measure results (Vittengl et al., 1999). The SNAP and both versions of the MMPI assess personality pathology using a trait-dimensional approach in which individuals are assessed with an array of distinct, continuous traits. In this study, only measures of anger/aggression and workaholism, as measured with the SNAP, decreased significantly from pretreatment to posttreatment. Although significant elevations in other dimensions (such as feelings of guilt, anxiety, and cynicism) were documented prior to treatment, these did not significantly diminish. The original MMPI demonstrated similar results, with only a minor decrease in social introversion (Scale 0) from pretreatment to posttreatment (Vittengl et al., 1999). In this sample, the SNAP and MMPI demonstrated stable mean scores and profiles from pretreatment to posttreatment in a physical rehabilitation program, indicative of trait measures. PD diagnoses did not show such stability when assessed with the SCID-II for *DSM-III-R*. Thus, it is questionable whether this structured interview is assessing a trait or state variable in chronic pain populations (Vittengl et al., 1999). These findings suggest that PD diagnoses derived from interview techniques may not be based upon stable or trait characteristics (Dersh et al., 2002). Alternatively, these findings may indicate that the presence of chronic pain may promote regressive defenses and intensify personality traits (Monti, Herring, Schwartzman, & Marchese, 1998).

CLINICAL EFFECTIVENESS OF INTERDISCIPLINARY PAIN MANAGEMENT

Although pain medication is useful to assist with alleviation of pain symptoms, it alone does not provide adequate means for reestablishing functional capacity in chronic pain patients. Furthermore, opioid dependence has been found to hinder both progression and subsequent positive outcomes (Dersh, Mayer, & Gatchel, 2007). As previously discussed, pain is not just a manifestation resulting from injury, but a culmination of physiological, psychological, and societal elements that often work together to exacerbate the condition. Unidimensional treatment focused solely on the injury itself has been shown to be ineffective with most chronic pain patients. Therefore, through recognition of the interaction of various physiological and psychological and social factors, interdisciplinary treatment options have been developed, implemented, and determined to be highly successful with chronic pain populations. It should also be noted that rehabilitation treatment for injured patients, through a BPS approach, can be categorized into three specific levels: primary care, secondary care, and tertiary care (Gatchel & Turk, 1996). These levels differ in both intensity and the extensiveness of therapeutic modalities. It has been determined that sequential progression through each level is not necessary for adequate treatment.

Primary care, relating to the acute pain stage, focuses on relieving symptoms associated with the injury such that the patient is able to regain function of the affected area. Furthermore, mobility and pathophysiological recovery are emphasized in this phase (Mayer, Gatchel, Porter, & Theodore, 2006). The psychosocial factors commonly addressed in primary care settings relate to alleviating anxiety and fear associated with the occurrence of pain. Educating the patient about the healing process and medication compliance is essential for an expedited recovery.

Although most patients regain function following primary care treatment, some do not progress well and will transition past the acute phase. At this point, secondary care is initiated. Patients exhibiting signs of chronicity are more likely to have pain-induced functional limitations and psychosocial barriers to recovery. Therefore, the main goals of secondary care focus more heavily on prevention of physical deconditioning along with the reduction of psychosocial barriers, such as fear and anxiety. An interdisciplinary team, often including primary care physicians, clinical psychologists, physical therapists, and other medical professionals, work together to assist with helping the patient to achieve his/her goals of recovery and to lessen the occurrence of developing into a chronic pain situation. For most patients, secondary care has been shown to have profound effects on recovery, along with positive outcomes (Hagen, Ericksen, & Ursin, 2000; Karjalainen et al., 2004).

The third level, called tertiary care and used after both primary and secondary levels of care, has not proven to be effective to help the patient lessen pain intensity, regain function of the injured area, or reduce the fear and anxiety associated with the injury.

Functional restoration is a form of tertiary care that uses a BPS interdisciplinary approach for chronic pain patients. The interdisciplinary team in this type of care consists not only of primary care physicians but also of clinical psychologists and psychiatrists, physical therapists, occupational therapists, disability case managers, nurses, biofeedback specialists, and other specialized medical practitioners. The foremost goal of functional restoration is to avert permanent disability. Along with the physiological and psychological factors associated with the injury, many socioeconomic factors are also seen to impede the recovery process. Therefore, an individualized comprehensive regimen is put forth not only to increase mobility and function of the injured area by reduction of pain but also to teach stress management and coping skills to help the patients handle the lifestyle changes associated with the impairment. Furthermore, disability case managers assist patients by intervening with employers to design work programs that compliment the physical challenges (e.g., Mayer et al., 1985).

An important part of the treatment regimen often includes some form of cognitive behavioral therapy (CBT). This type of therapy runs parallel with physical rehabilitation and aims at modifying the patient's perception of the injury and pain. Albert Ellis (1962) developed the first form of CBT in the 1960s, which was termed rational emotive therapy (RET) because it was thought that emotions were caused by cognitions. Another form of CBT, developed around the same time by Beck (1967), referred to as cognitive therapy, emphasized the correction of irrational views aligned with depression. Lazarus (1971) adopted the first behavioral therapy regimes and later introduced broad-spectrum behavioral therapy, which recognizes that different therapists can employ various techniques based on the psychopathology of the patient and the specifics of the situation.

Within the construct of CBT, different therapeutic techniques are often employed to assist with the treatment of patients experiencing chronic pain. Although success rates vary from study to study, some techniques such as biofeedback, hypnosis, acupuncture, relaxation, imagery, distraction (Baum, Gatchel, & Krantz, 1997), and even more controversial procedures such as transcranial magnetic stimulation (Borckardt, 2007), have been implemented in an attempt to reduce the cognitive acuity of pain. These types of strategies are employed in an attempt to lessen the perception of the pain.

Lack of mobility and atrophy are often due to the patient's fear of recurrence of injury. Fear avoidance and catastrophizing have been identified as indicators of chronicity in patients with musculoskeletal disorders (Leeuw et al., 2007; McWilliams & Asmundson, 2007). Treatment programs that include alleviating pain-induced fear and increasing pain tolerance through CBT have been identified to be successful in treating patients with chronic pain (Lohnbert, 2007).

SUMMARY AND CONCLUSION

Traditional methods of treating patients with pain, using the biomedical approach, have repeatedly been shown to be ineffective. Fortunately, the BPS model has emerged to provide a therapeutic- and cost-effective approach to the treatment of chronic pain disorders (Gatchel, 2004). With this perspective in mind, this chapter emphasized that the physiological condition or nociception alone is not sufficient to understand and treat the injured patient, especially those with chronic pain. Indeed, numerous studies have outlined the comorbidity of psychopathology in chronic pain populations that need to be managed in interdisciplinary pain treatment programs. For example, it has been found that Axis I clinical disorders, such as MDD, anxiety disorders, and substance use disorders, along with Axis II PDs, impede treatment and healing processes in patients experiencing chronic pain. By recognizing and accepting the existence of these psychological barriers, better treatment options can be employed.

Rehabilitation was discussed with regard to primary, secondary, and tertiary care. Functional restoration, a form of tertiary care, has been extensively studied and shown to be an effective form of interdisciplinary rehabilitation using the BPS approach. Patients who complete this form of treatment have been repeatedly shown to exhibit better outcomes, including reduction of pain and functional mobility, along with assuming regular activities including returning to and retaining work. A component of functional restoration programs that differs from other programs is the CBT element. Regardless of the physiological state, if the individual continues to perceive pain, the likelihood of healing is improbable. By using various techniques, the therapist focuses on modifying the individual's cognitions and beliefs about the current pain state, which, in turn, allows for more successful treatment outcomes. Furthermore, by helping the individual to cope better with the pain condition, decreased levels of stress hormones help to reduce the perception of pain. Finally, through the utilization of a BPS approach to understanding and treating pain-related conditions, specifically in chronic pain populations, studies have shown that patients are more capable of regaining function to the injured area and are better able to develop skills for coping and adaptation. Ultimately, they can return to normal activities of daily living.

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34 Stress Reduction in Chronically Ill Patients

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Stress plays multiple roles in the etiopathogenesis of a chronic illness such as cancer, heart disease, or diabetes. From a biopsychosocial perspective, stress can serve as a distal or proximal etiological factor for the illness itself, a means by which symptoms of the illness are made worse, a condition serving to maintain the illness, both biologically (e.g., negative effects on one's immune system) and behaviorally (e.g., poor lifestyle habits), and a force that engenders psychological distress, such as depression, anxiety, and anger (Schneiderman, Ironson, & Siegel, 2005). In other words, causal models of the pathogenesis of chronic illness have often identified stress as a process that has significant implications across multiple pathways (e.g., Andersen, 2001). Therefore, reducing the stress of patients with chronic illness can serve multiple roles, namely, to impact positively on a variety of adverse psychological, social, and biological consequences of the disease process.

Clinically, stress reduction strategies have generally addressed a variety of treatment targets, including enhancing one's ability to reverse or minimize the negative impact of the stress process on one's physical or emotional responses (e.g., progressive muscle relaxation [PMR] training), improving one's ability to cope more effectively with those situations that lead to a negative stress response (e.g., coping skills training), and fostering a person's ability to minimize the occurrence of stressors (e.g., problem-solving therapy [PST]). In this chapter, we provide a brief overview of these types of stress reduction strategies across major chronic illnesses—cancer, diabetes, and heart disease. Because it is beyond our scope, we are not able to address the research that focuses on reducing stress levels as a means of reducing one's risk or vulnerability to experiencing a chronic illness, such as by targeting tobacco or substance abuse.

STRESS REDUCTION AND CANCER

Patients diagnosed with various types of cancer experience high levels of continuing psychological distress, including depression, anxiety, sleep difficulties, and existential crises (Carlson & Speca, 2007; Nezu & Nezu, 2007a). For example, one large-scale study of approximately 4,500 cancer patients identified a prevalence rate of significant distress in excess of 35% (Zabora, BrintzenhofeSzoc, Curbow, Hooker, & Piantadosi, 2001). Additional data collected both in North America and around the world corroborate these findings, such that distress has been recently identified as the "sixth vital sign in cancer care" after temperature, respiration, heart rate, blood pressure, and pain (Bultz & Carlson, 2006). Given the significant stress that is present throughout the course of initial diagnosis, treatment, and even potential successful remission (Andersen, 2002), researchers have evaluated various interventions designed to reduce stress in cancer patients (Nezu, Nezu, Felgoise, & Zwick, 2003), including cognitive-behavioral stress management (CBSM) and PST.

COGNITIVE-BEHAVIORAL STRESS MANAGEMENT

Antoni et al. (2001) evaluated the effects of evidence-based CBSM by implementing a 10-week structured group intervention among a cohort of 100 women newly treated for Stage 0–II breast carcinoma. The CBSM protocol comprised both didactic and treatment components, including experiential exercises (e.g., PMR training, guided imagery) and between-session homework assignments. Treatment goals involved enhancing the woman's ability to cope more effectively with the daily stressors of both cancer- and treatment-related problems and optimizing the use of her social resources. In addition to traditional stress management techniques, participants were taught to better monitor stress responses, engage in appropriate emotional expression, and apply cognitive restructuring skills when thinking negatively.

Results of this initial randomized controlled trial (RCT) indicated that although the CBSM intervention did not affect overall general mood disturbance, it did reduce the prevalence of moderate depression. Moreover, it significantly enhanced "benefit finding" (i.e., the belief that cancer had made a positive contribution to one's life) and a generalized sense of optimism. Further, these positive effects were evident 3 months postintervention.

A more recent study evaluating the effects of CBSM among 199 breast cancer patients provides further support of the overall efficacy of this approach (Antoni, Wimberly,

et al., 2006). In this RCT (the control group was presented a 5- to 6-hour condensed version of the didactic component of CBSM), treatment was designed to reduce anxiety and distress during the period of medical intervention for nonmetastatic breast cancer. Results indicated that the structured group treatment engendered reduced patient reports of thought intrusion as well as interviewer ratings of patients' anxiety and emotional distress. Such benefits of the stress reduction protocol were found to be maintained after completion of adjuvant medical therapy.

A subsequent analysis of these data 1-year postbaseline indicated that CBSM led to reduced reports of social disruption, greater emotional well-being, positive states of mind, increased benefit finding, and positive lifestyle change, suggesting that the impact of treatment was broad (Antoni, Lechner, et al., 2006). Moreover, positive outcomes appeared to be mediated by increases in confidence regarding one's ability to relax.

Not only does CBSM appear to positively impact psychosocial variables but, in addition, biological parameters have been affected as well. For example, Cruess et al. (2001) found that CBSM appeared to lead to decreases in testosterone among female breast cancer patients and that such changes in androgen functioning were related to enhanced benefit finding. Moreover, another study found that CBSM reduced serum cortisol levels among breast cancer patients and that the effect of this intervention on cortisol was mediated by increases in benefit finding (Cruess et al., 2000). Further, McGregor et al. (2004) found that group CBSM led to improved lymphocyte proliferation, suggesting that a psychosocial intervention had a positive impact on cellular immune functioning.

Penedo et al. (2007) adapted the CBSM protocol, both linguistically and culturally, for use with a sample of monolingual Hispanic men being treated for localized prostate cancer. Results of this RCT indicated that the adapted CBSM protocol led to greater physical well-being, emotional well-being, sexual functioning, and overall well-being at posttreatment. This suggests that a stress reduction program previously found to be efficacious for female breast cancer patients is also useful for men suffering from a different form of cancer and who represent a differing ethnic background, thus enhancing the generalizability of this approach to stress reduction.

Traditional stress reduction programs have also incorporated elements of mindfulness training to enhance their effectiveness. Mindfulness-based stress reduction (MBSR) was originally developed by Kabat-Zinn (1990) and is rooted in spiritual traditions in which conscious awareness is specifically fostered. Beginning with an improved awareness of one's breathing, MBSR is designed to enhance relaxation and stress reduction by cultivating adoption of nonjudgmental attitudes, patience, acceptance, and a major focus on increased awareness of one's own experiences. Carlson, Speca, Faris, and Patel (2007) recently reported a 1-year follow-up of a pre–post trial that tested the effects of an 8-week MBSR program for 49 adults with breast cancer and 10 patients with prostate cancer. Their particular program included relaxation, meditation, gentle yoga, and daily home practice. Results indicated significant improvement in overall posttreatment stress symptoms that was maintained over the follow-up period. Specifically, there were decreases in cortisol levels, continued reductions in levels of proinflammatory cytokines, and lowered blood pressure. Although this investigation was an open trial and MBSR was not compared with a control condition, it does provide support for the promise of this approach for reducing both psychological and biological parameters of stress.

PROBLEM-SOLVING THERAPY

PST is an evidenced-based, cognitive-behavioral intervention that promotes the adoption and effective application of adaptive problem-solving attitudes and skills to solve stressful problems in living (D'Zurilla & Nezu, 2007; Nezu, 2004). In PST, patients are helped to cope more effectively with stressful problems by learning skills designed to successfully resolve the problem and/or by learning to better manage their negative emotional reactions to such stressors. The overarching goals of PST are to improve an individual's problem orientation and rational problem-solving skills, while inhibiting tendencies to be impulsive or avoidant. Training in *problem orientation* is geared toward providing patients with a rational, positive, and constructive cognitive set or appraisal style for problems in living and to equip them with specific problem-solving strategies as a means of coping with difficulties. One major therapeutic objective is to change those attitudes or beliefs that inhibit or interfere with attempts to cope adaptively with stressful problems. In addition, participants are taught to better manage negative emotions and to engage in effective rational problem-solving activities (e.g., setting realistic goals, identifying barriers that exist in reaching such goals, creatively thinking of various alternative solutions, deciding which alternatives have a higher likelihood of success, and monitoring and evaluating the implemented solution action plan).

Fawzy et al. (1990) developed a multicomponent treatment package that included both stress management and PST, along with group support and psychoeducation, in an attempt to help adults newly diagnosed with malignant melanoma. These individuals were randomly assigned to one of two conditions: a 6-week structured group intervention, and a no-treatment control. At the end of 6 weeks, treated patients began showing reductions in psychological distress as compared with control participants. However, 6 months posttreatment, the group differences were very pronounced. Moreover, 5 years following the intervention, treated patients continued to show significantly lower levels of anxiety, depression, and total mood disturbance (Fawzy, Fawzy, & Canada, 2001).

In addition, at the end of the original 6-week program, patients receiving the treatment evidenced significant increases in the percentage of large granular lymphocytes, suggesting a positive treatment effect on immune functioning. Further, 6 months posttreatment, this increase in granular lymphocytes continued, and increases in natural killer cells were also evident. Last, although this study was not originally set up to determine the effects of treatment on actual health outcomes, additional data indicated that at 6 years posttreatment, treated patients experienced longer overall survival as compared with control participants, as well as a trend suggesting delayed recurrence in the treated patients (Fawzy et al., 1993). Subsequently, this same intervention was culturally adapted for use in Japanese women with breast cancer and was found to be effective (Hosaka, 1996).

Mishel et al. (2002) paired training in problem solving with a cognitive reframing strategy as a means of helping 134 Caucasian and 105 African American men with localized prostate carcinoma. Participants were randomly assigned to one of three experimental conditions: (a) the combined psychosocial treatment provided only to the patient himself, (b) treatment provided both to the patient and to a family member, and (c) a "usual treatment" control condition. Both forms of treatment were provided by trained nurses through weekly phone calls made over an 8-week period. In general, regardless of ethnicity, participants who received either form of the intervention improved significantly as measured at the 4-month postbaseline assessment. It is during this period of time that cancer treatment side effects are most prevalent. As such, it is particularly noteworthy that the combined PST and cognitive reframing treatment led to significant improvement in control of incontinence at 4 months postbaseline.

Allen et al. (2002) assessed the efficacy of PST as a sole intervention, as compared with a no-treatment control, in a population of 164 women diagnosed with breast cancer and for whom a first course of chemotherapy had been recently initiated. The PST consisted of two in-person and four telephone sessions with an oncology nurse who provided problem-solving skills training to the women over a 12-week period. This treatment program was designed to empower women with breast carcinoma to cope more effectively with a range of difficulties when diagnosed in midlife. Participants in both conditions were assessed for physical and psychosocial adjustment.

At a 4-month evaluation, participants in general tended to have significantly fewer unmet needs and better mental health as compared with baseline. At the 8-month assessment, differences between the treated and control conditions emerged, pointing to the efficacy of the training. In general, PST led to improved mood and more effective coping with problems associated with daily living tasks. Further, the intervention was effective for the majority of women in resolving a range of problems related to cancer and its treatment, including physical side effects, marital and sexual difficulties, and psychological problems.

Nezu, Nezu, Felgoise, McClure, and Houts (2003) conducted an RCT entitled Project Genesis to assess the efficacy of PST among 132 distressed adult cancer patients. In this study, participants were randomly assigned to one of three conditions: (a) ten 1.5-hour sessions of individual PST; (b) ten 1.5-hour sessions of PST provided simultaneously to both the cancer patient and his or her designated significant other (e.g., spouse, family member); or (c) a "treatment as usual" control. The condition that involved a significant other was included to assess the enhanced effects of formalizing a social support system where the role of the significant other was conceptualized as a "problem-solving coach."

Results at posttreatment across several self-report, clinician ratings, and ratings by significant others provide strong evidence in support of the overall efficacy of PST for decreasing emotional distress and improving the overall quality of life of patients with cancer. Specifically, patients in both treatment conditions were found to evidence significant improvement as compared with individuals in the control condition. At posttreatment, no differences were found between these two conditions. However, at a 6-month follow-up assessment, on approximately half of the variables assessed, patients who received PST along with a significant other continued to improve significantly beyond those individuals receiving PST individually, highlighting the advantage of formally including a collaborative person in treatment. These positive effects of PST were not only statistically significant but also found to be highly clinically significant as well. Moreover, analyses indicated that improvements in problem solving correlated significantly with decreases in psychological distress and improvements in overall quality of life.

A study by Given et al. (2004) focused on 237 adult cancer patients recently diagnosed with a solid tumor who were undergoing a first course of chemotherapy. Participants were randomly assigned to either a "symptom management intervention" or conventional care. The intervention incorporated several PST-based strategies, following the suggestions of D'Zurilla and Nezu (1999), to generate a list of possible strategies for patients and caregivers to more effectively cope with a variety of cancer-related problems (e.g., alopecia, depression, fatigue, pain, insomnia). Based on guided discussions between a nurse and patient–caregiver dyad, various interventions were agreed upon for implementation. Treatment occurred through 10 contacts (in person and telephone) made over the course of 20 weeks.

Results indicated that treated patients who had higher baseline symptom severity levels reported lower depression at 10, but not 20 weeks. Unexpectedly, patients in the experimental condition who were characterized by higher baseline depression were found to be more depressed at 10 weeks than control patients. Further, the intervention was found to be more effective in lowering

depression at 10 weeks as a function of its impact on other symptoms rather than on depression directly. However, at 20 weeks, a significant main effect for treatment on depression was identified. The authors therefore concluded that the intervention influenced depression differentially over time. Specifically, it appeared initially to lower depression through enhanced ability to manage symptoms unrelated to depression and only later did it impact depression directly.

In a subsequent assessment of the impact of this intervention on the limitations imposed on patients by symptoms of cancer and its medical treatment, Doorenbos et al. (2005) found that on average, after 10 weeks, patients receiving the problem-solving-based intervention reduced such symptom limitations significantly more than the control group. Moreover, this positive treatment effect was maintained over the course of the remainder of the treatment. Parenthetically, these authors concluded that this intervention was particularly helpful for younger individuals in managing cancer-related symptom limitations.

SUMMARY

Stress reduction strategies for cancer patients have included CBSM (e.g., muscle relaxation, guided imagery), mindfulness-based interventions, and PST. Overall, this brief review suggests that such approaches do impact positively on both biological (e.g., serum cortisol, immune functioning, blood pressure) and psychological variables (e.g., depression, anxiety, coping ability). Although not initially designed to evaluate the effects of stress reduction strategies on actual health outcome, such as enhanced survival, one study did find that treated patients did live longer than control participants 6 years posttreatment (Fawzy et al., 1993).

STRESS REDUCTION AND NON-INSULIN-DEPENDENT DIABETES MELLITUS

Diabetes mellitus is a group of disorders characterized by abnormalities in the control of carbohydrate metabolism. Non-insulin-dependent diabetes mellitus, better known as type 2 diabetes, typically develops in adulthood, most commonly after age 40, and often in response to increased weight gain. The clinical management of this chronic illness is a lifelong commitment that places a great deal of responsibility on the patient on a daily basis. When diagnosed, a person must not only make changes in a few habits but must also make major changes in lifestyle activities. Changes can be difficult to make and to maintain, and these efforts can be stressful both in the short and long term. Both acute and chronic stress can impact an individual with type 2 diabetes in many ways. Appropriate self-care requires optimizing metabolic control and preventing acute and chronic complications while maintaining a positive quality of life. Stress not only directly affects glucose metabolism, but it can indirectly affect diabetic control by influencing self-care management behaviors, including diet, exercise, glucose monitoring, taking oral medication, performing insulin injections, and foot care. Overeating, skipping meals, missing insulin injections, forgetting to monitor glucose, and/or putting off physically activity because of distraction, feelings of time pressure, or feeling overwhelmed, are examples of difficulties in adhering to medical treatment that can lead to poor glycemic control, ultimately affecting the course of disease progression (McGrady & Bailey, 2005). Psychosocial interventions designed to help individuals with diabetes cope more effectively with such illness-related stress include self-management training, behavioral stress management, biofeedback, psychotherapy, and PST.

SELF-MANAGEMENT TRAINING

The National Standards for Diabetes Self-Management Education (1995) recommends that diabetes education incorporate the use of various cognitive-behavioral techniques, such as goal setting, contracting, problem solving, activity scheduling, and stress management. The purpose of self-management training is to enhance knowledge and provide skills in individuals with type 2 diabetes as a means of promoting the achievement of self-care goals. According to a systematic review of RCTs of self-management training for type 2 diabetic patients, training techniques have shifted from being mostly didactic to involving patient empowerment strategies that focus on increasing skills to improve adherence to the complicated medical and lifestyle regimes that are required (Norris, Engelgau, & Narayan, 2001).

Given the lack of a consistent positive relationship between diabetes knowledge and actual control, it has become increasingly clear that knowledge alone is insufficient to achieve long-term behavior change resulting in effective glycemic control. Therefore, it has been suggested that there exists a minimum threshold of necessary diabetes knowledge. Beyond that threshold, what is thought to be required to achieve long-term metabolic control are improved personal attitudes and motivations, and specific lifestyle changes, including healthy eating, physical activity, weight loss, stress management, cognitive behavior therapy (CBT), and social support (Norris et al., 2001). Overall, evidence supports the short-term effectiveness of both individual and group-based self-management training in type 2 diabetes, but programs geared toward long-term, sustainable changes in glycemic control, cardiovascular complications, and quality of life need to be further developed.

STRESS MANAGEMENT

Stress management and other cognitive-behavioral strategies not only appear to improve the diabetic patient's

ability to successfully engage in self-care and lifestyle changes, but increasing evidence suggests that they have independent effects on metabolic control via reduction of stress and psychological distress (Fisher, Thorpe, DeVellis, DeVellis, 2007; Innes & Vincent, 2006). Surwit et al. (2002), for example, evaluated a 5-week group-based stress management program that included PMR, training in the use of various cognitive and behavioral skills to recognize and reduce physiological stress levels (e.g., recognition of major life stressors, guided imagery, thought stopping, deep breathing), and psychoeducation regarding the health consequences of stress. At 1-year posttreatment, participants receiving stress management training showed a significant, albeit modest, improvement in blood glucose control measured by glycosylated hemoglobin (HbA_{1C}, a major indicator of blood glucose levels) independent of diet and physical activity effects, by comparison with patients receiving only 5 weeks of diabetes education.

BIOFEEDBACK AND RELAXATION TRAINING

Biofeedback is a psychophysiology-based technique that involves connecting patients to a feedback device that provides information about physiological activity (e.g., skin temperature, breathing rate, blood flow, muscle tension, heart rate, or skin conductance) in order that they can better understand, and potentially control, their body's response to stress (McGinnis, McGrady, Cox, & Grower-Dowling, 2005). Biofeedback is often used in conjunction with relaxation strategies, such as deep breathing, PMR, or guided imagery, to help change a maladaptive stress response to a more adaptive one. As a treatment for diabetic patients, the efficacy of biofeedback and relaxation training in improving glycemic control in patients with type 2 diabetes is mixed, but encouraging. For example, on the negative side, in a study by Jablon, Nabiloff, Gilmore, and Rosenthal (1997), patients trained in PMR with biofeedback demonstrated significant reductions in stress levels but no improvement in fasting blood glucose. An investigation by Lane, McCaskil, Ross, Feinglos, and Surwit (1993) that compared biofeedback-assisted relaxation to treatment as usual found that treated patients did not experience significant improvements in metabolic control as compared with participants receiving only conventional diabetes treatment. Moreover, in a study of 22 patients randomized to either relaxation training (six sessions of PMR plus six sessions of guided imagery) or routine medical care, there were no postintervention group differences in glycemic variables (Aikens, Kiolbasa, & Sobel, 1997).

On the positive side, Surwit and Feinglos (1983) compared six patients who received five daily sessions of PMR and biofeedback with a control group of six patients without these treatments and found that treated patients significantly improved their glucose tolerance. McGinnis et al. (2005) randomized 39 patients either to 10 weekly sessions of forehead muscle tension or finger skin temperature biofeedback plus PMR or to 3 individual sessions of diabetes education separated by 3–4 weeks. In comparison with patients in the control condition, treated patients experienced a significant decrease in HbA_{1C} and in average blood glucose immediately posttreatment and at a 3-month follow-up assessment point

PSYCHOLOGICAL INTERVENTIONS

Ismail, Winkley, and Rabe-Hesketh (2004) conducted a meta-analysis of RCTs involving various psychological interventions (i.e., counseling, cognitive-behavior therapy, and psychodynamic psychotherapy) aimed at improving glycemic control in patients with type 2 diabetes. Overall, psychological therapies resulted in significant reductions in psychological distress and better long-term glycemic control. More recently, Berger et al. (2007) examined an integrative approach to the treatment of type 2 diabetes that included nutritional instruction and stress reduction techniques such as CBT, PMR, and physical exercise. Significant reductions in lipids, HbA_{1C}, low-density lipoprotein cholesterol, and anxiety and depression were found in all participants compared with their baseline measures.

Often, stress is associated with an increase in symptoms of depression. Depression is more prevalent in patients with diabetes compared with the general population and is associated with poor glycemic control, decreased compliance with therapy, and increased risk of complications of diabetes (Fisher et al., 2007). Depression can significantly impact individuals with type 2 diabetes by interfering with self-care. CBT is an effective treatment for depression that represents a potentially efficacious approach for depressed patients with diabetes. For example, Lustman, Griffith, Freedland, Kissel, & Clouse, et al. (1999) randomly assigned a group of 51 patients diagnosed with major depression and type 2 diabetes to either a group that received 10 weeks of individual CBT plus education or an educational-only control. At posttreatment, 85% of patients in the treatment group, as compared with only 27.3% in the control group, achieved remission of depressive symptoms. At the 6-month follow-up, 70% of patients in the CBT group, as compared with 33.3% of the control group, achieved remission. Posttreatment HbA_{1C} was not found to be different between groups, but at 6 months past that point, mean HbA_{1C} levels were significantly better in the CBT group as compared with the control group.

PROBLEM-SOLVING THERAPY

Evidence from cross-sectional studies of adults consistently suggests that ineffective problem-solving ability is associated with poorer glycemic control in adults (Hills-Briggs & Gemmell, 2007). Moreover, problem solving has been found to be significantly related to self-management

behaviors (e.g., eating and exercise habits), biological variables (e.g., HbA_{1C} and lipids), and psychosocial measures (e.g., psychological distress) across ethnic groups (Hills-Briggs & Gemmell, 2007). Further, four studies have found improvements in dietary behaviors in response to problem-solving interventions (Glasgow et al., 1992; Glasgow, La Chance, Toobert, Hampson, & Noell, 1997; Glasgow, Toobert, Hampson, & Noell, 1995; Glasgow, Toobert, & Hampson, 1996). Improvements at 6 and 12 months have also been found in self-monitoring of blood glucose, exercise, and medication adherence (Hills-Briggs & Gemmell, 2007).

Several studies have also observed decreases in HbA_{1C} following problem-solving interventions (Glasgow et al., 1992; Trento et al., 2001, 2004). In fact, one investigation found maintenance of improved HbA_{1C} in the intervention as compared with control patients at 2- and 5-years posttreatment (Trento et al., 2001, 2004). Undergoing PST has also been found to improve symptoms of depression and psychological distress in patients with diabetes (Katon et al., 2004; Williams, Katon, & Lin, 2004). On the other hand, several of the studies assessing the efficacy of PST for adults with type 2 diabetes found a lack of significant improvement in HbA_{1C} as compared with controls (Hills-Briggs & Gemmell, 2007). As such, although there is some evidence that PST improves quality of life and metabolic control, as well as reductions in psychological distress, other findings identify no enhanced effects of PST directly on metabolic control among these patients. It is possible that not directly explicitly addressing stress reduction within the intervention approach may account for some of these latter null findings.

SUMMARY

In the previous section, we suggested that the main objective of attempts to reduce stress in cancer patients involved improvement in overall quality of life and decreases in psychological distress. For individuals with type 2 diabetes, the goal of treatment research has been based on the hypothesis that stress serves as a mediator of glucose metabolism and glycemic control. Intervention strategies to reduce such stress have included psychoeducation, CBSM, biofeedback, psychotherapy, and PST. Although not all treatment attempts have been successful in achieving significant improvements in blood glucose levels, the vast majority of studies demonstrate that stress reduction efforts are effective in improving quality of life and decreasing psychological distress, including depression.

STRESS REDUCTION AND CARDIOVASCULAR DISEASES

Research continues to demonstrate that stress and negative affectivity affect the etiopathogenesis of various cardiovascular diseases through their influence on underlying pathophysiological processes, as well as through promotion of unhealthy lifestyle activities (Claar & Blumenthal, 2003; see chapters elsewhere in this volume). For example, stress can lead to excessive stimulation of the nervous system that can engender myocardial ischemia and cardiac arrhythmias. It can also lead to poor coping behaviors, such as poor diet, lack of exercise, and increased substance abuse. The large-scale INTERHEART study conducted in 52 countries evaluated the effects of both physical and psychosocial risk factors in 15,152 individuals with a first myocardial infarction (MI) and in 14,820 age- and gender-matched controls. Psychosocial stress was found to be significantly related to the etiology, pathogenesis, and course of coronary heart disease (Rosengren et al., 2004). Specifically, an index comprising various psychosocial stressors (e.g., stress at home and work, financial stress, recent major life events, presence of depression) was found to account for a population risk of 33% independently of all physical risk factors.

Given the direct and indirect influence of stress on the development and course of various cardiovascular problems, it is no surprise that researchers have examined stress reduction as a means of improving the quality of life of heart patients and as a way to reduce the high rates of morbidity and mortality associated with heart disease. The majority of these attempts involve treatment packages comprising a variety of psychosocial intervention components. Over the past few decades, four separate meta-analyses have been conducted to evaluate the impact of such interventions on a variety of outcomes among cardiac patients, the results of which we briefly present next.

LINDEN, STOSSEL, AND MAURICE (1996)

This meta-analysis included 23 RCTs involving more than 3,100 heart patients and essentially evaluated the impact of adding various psychological interventions to standard cardiac rehabilitation (CR) programs. Although these outcome trials incorporated diverse clinical strategies and provided differing lengths of treatment, Linden et al. note that the psychosocial treatments generally shared a cognitive-behavioral orientation to stress reduction. The "standard" CR protocol typically consisted of a cardiac drug regimen, in addition to exercise and nutrition recommendations.

Results of this meta-analysis revealed that heart patients receiving psychosocial treatment (n = 2,024), as compared with control participants (n = 1,156), showed significantly greater reductions in psychological distress, systolic blood pressure, heart rate, and cholesterol levels. Specially, effect size differences were found to be 0.34, 0.24, 0.38, and 1.54 (absolute values), respectively. Moreover, untreated patients showed higher rates of mortality and recurrent cardiac disease during the first

2 years of follow-up: the adjusted odds ratios (ORs) for these two important outcomes were 1.70 and 1.84.

On the basis of these findings, Linden et al. (1996) concluded that the addition of psychosocial interventions to standard CR programs significantly reduced mortality and morbidity, psychological distress, and biological factors including heart rate and systolic blood pressure. Such benefits were most evident during the initial 2-year posttreatment and became weaker afterwards. Because of the combined nature of most of the intervention protocols, it was not possible to address the issue of which specific treatment components were responsible for these positive results.

DUSSELDORP, VAN ELDEREN, MAES, MEULMAN, AND KRAAIJ (1999)

This review of 37 studies asked a slightly different question than that of the Linden et al. (1996) analysis. Specifically, Dusseldorp et al. examined the effects of psychoeducational programs, including both health education and stress management protocols, in patients with coronary heart disease. In addition, these authors were interested in where achievement of proximal goals (e.g., decrease in systolic blood pressure, reduction in emotional distress) was associated with success for more distal outcomes (e.g., cardiac mortality and recurrent disease).

Overall, the findings indicated positive effects for the psychological interventions. Specifically, these programs were associated with a 34% reduction in cardiac mortality, a 29% reduction in recurrent MI, and a significant positive impact on blood pressure, cholesterol, body weight, smoking behavior, physical exercise, and eating habits. Moreover, success with proximal targets was found to moderate success regarding distal goals. For example, programs that successfully reduced emotional distress and increased exercise, compared with those that did not, were more effective in fostering reductions in cardiac mortality and recurrent MI. Such a finding supports the mediating role of psychosocial variables, including stress, in reducing "hard outcomes" (i.e., cardiac morbidity and mortality). However, somewhat surprisingly, this meta-analysis found no significant impact of the interventions on depression and anxiety. This was in large part due to the null findings of two sizable studies. One, by Frasure-Smith et al. (1997), included 1,376 post-MI patients and used a telephone monitoring system to identify and consequently provide counseling to those heart patients experiencing high levels of distress. The second, by Jones and West (1996), evaluated the effects of a group stress management program in more than 2,000 post-MI patients. Both interventions failed to reduce anxiety and depression and reported nonsignificant differences between treated and control participants with regard to mortality and recurrent disease. Interestingly, the Frasure-Smith et al. (1997) investigation had been encouraged by the report of positive results obtained in an earlier study by the same investigators (Frasure-Smith & Prince, 1985), in which at 1-year posttreatment, treated patients reported reduced distress levels and significantly lower cardiac mortality and morbidity.

REES, BENNETT, WEST, DAVEY, AND EBRAHIM (2004)

This Cochrane review was also conducted to evaluate the effectiveness of psychosocial interventions, primarily stress management programs, for mortality and morbidity in patients with coronary heart disease. This review was somewhat broader in scope than the two previously described meta-analyses and included 36 trials involving 12,841 heart patients. Of these studies, 18 were specific stress management interventions and included 5,242 participants.

In contrast to the findings of the Linden et al. (1996) and Dusseldorp et al. (1999) meta-analyses, these authors concluded that the combined results of all trials showed no strong evidence for an effect on cardiac mortality; results specific to the stress management protocols were also found to be weak. Rees et al. further suggested that there was little support for an effect regarding cardiac risk factors, such as smoking, cholesterol levels, and hypertension, among those studies that reported such outcomes. In addition, only a small reduction in anxiety and depression was found where those outcomes were the focus. Because of the small number of trials that evaluated the independent impact of stress management, Rees et al. (2004) were unable to determine the effectiveness of this approach separately from other CR strategies.

Why there are such differences in conclusions among these three reviews? Goldston and Baillie (2008) suggest that the Rees et al. (2004) review is characterized by several limitations: (a) it included trials that were extremely heterogeneous across samples, outcomes, and methods; (b) psychological outcomes were reported in only a few small studies; (c) most included trials that did not report baseline levels of psychological distress, thereby ignoring a possible floor effect (i.e., large numbers of patients may have had subclinical levels of initial distress and were therefore not in need of treatment); and (d) many studies apparently used untrained staff to administer the stress management protocols. Linden, Phillips, and Leclerc (2007) further noted that Rees et al. included multiple interventions that combined psychological and "other" (i.e., health education) components, making it difficult to properly isolate benefits that would be attributable to the psychological components.

LINDEN, PHILLIPS, AND LECLERC (2007)

In this most recent meta-analysis, Linden et al. (2007) attempted to isolate the effects due to psychological treatment (PT) by not including any trials in their review

that included exercise, dietary modification, or smoking cessation. To be included in their analysis, a study had to evaluate at least one treatment condition that involved a predominantly psychological or behavioral intervention that was contrasted with at least one "usual care" control condition. Using these criteria, 43 RCTs were identified, of which 23 reported mortality data, generating a combined sample size of 9,856 cardiac patients. The OR was found to be 0.72 for all-cause mortality at a follow-up assessment point of 2 years or less when comparing PTs plus usual care versus a usual care control. With longer follow-up evaluations, this effect weakened somewhat (OR = 0.89). Further analysis indicated mortality benefits only for men (OR = 0.73 versus 1.01 for women). In addition, protocols that were initiated at least 2 months after a cardiac event were associated with greater mortality benefits than those programs beginning PT sooner after the event. Interestingly, mortality benefits due to PTs were achieved despite small concomitant changes in negative affect.

On the basis of these results, Linden et al. (2007) concluded that PTs do, in fact, reduce mortality rates at least during the first 2 years. More importantly, they found gender differences, as well as a timing effect, highlighting the importance of focusing on potential moderators of treatment outcome. This is especially important given the lack of an effect of PT for depression on mortality in the large-scale (*N* = 2,481 post-MI patients), National Institutes of Health-sponsored, multicenter clinical trial referred to as ENRICHD (i.e., Enhancing Recovery in Coronary Heart Disease; ENRICHD Investigators, 2001). Specifically, CBT, a psychosocial approach widely recognized as particularly efficacious for depression and that also targeted social isolation, failed to demonstrate a significant effect above and beyond a usual care control with regard to morbidity and mortality at a 2-year follow-up. However, in concert with Linden et al.'s general findings across studies, the ENRICHD trial initiated treatment soon after a patient's heart attack. This suggests that patients recruited at a later time after a cardiac event may differ in significant ways from those recruited early. For example, even though one may experience depression soon after a heart attack, the depression may remit spontaneously without any formal PT (i.e., usual care might include antidepressant medications and CR). In the ENRICHD study, members of the usual care condition were found to improve in depression and social isolation at a rate nearly as large as that observed in the cognitive-behavior therapy condition.

It is worth highlighting one of the studies that was included in the Linden et al. (2007) meta-analysis. Blumenthal et al. (2005) conducted an RCT in which 134 adults with stable ischemic heart disease and exercise-induced myocardial ischemia were assigned to one of three conditions: (a) usual care; (b) usual care plus supervised aerobic exercise (35 minutes 3 times per week for 16 weeks); or (c) usual care plus weekly 1.5-hour stress management training for 16 weeks. What is unique to this study is the focus on effects of these differing stress reduction strategies on biological markers of cardiovascular risk in this population, rather than on cardiac or all-cause mortality at the end of 2 years. Although such hard outcome (i.e., mortality) evaluations are crucial, they are also expensive and rather time-consuming. Including dependent variables that are hypothesized markers of mechanisms culminating in negative cardiac disease events provides for more immediate assessments of the effects of psychosocial treatments.

Overall, results indicated that both stress reduction protocols, in comparison with the usual care only control, led to greater decreases in depression and general distress, as well as smaller reductions in left ventricular ejection fraction (a measure of myocardial performance) in response to mental stress testing. Additional biological benefits of stress reduction were found for myocardial wall motion abnormalities, flow-mediated dilation (a measure of arterial function), baroreflex sensitivity, and heart rate variability. Collectively, these results strongly suggest that for patients with stable ischemic heart disease, stress reduction strategies significantly impact both psychological and biological parameters associated with heart problems.

SUMMARY

Because of the large number of studies conducted during the past several decades designed to evaluate stress reduction efforts for individuals with cardiovascular disorders, we decided to present findings and conclusions of four major meta-analyses rather than describing myriad individual studies. In part because of the differing goals and methods of each of these meta-analyses, it appears that the major conclusions emanating from these reviews have not been consistent. However, with regard to attempts to identify potential moderators of treatment impact, Linden et al. (2007) found that not only was gender a potentially significant moderator (i.e., positive mortality benefits were found only for men), but that timing may also be a critical moderator of impact (i.e., treatment administered at least 2 months after an MI were more effective than if a program began sooner after such an event).

GENERAL SUMMARY AND CONCLUSION

A brief review of the literature on stress reduction across three differing chronic illnesses (i.e., cancer, diabetes, cardiovascular disease) revealed an increase in recognition of the importance of including such an approach within an overall treatment of the disease itself. Multiple types of interventions were identified as means to reduce disease-related stress, including various stress management strategies (e.g., PMR, guided imagery, biofeedback) and coping skills training protocols

(e.g., PST, CBT). It appears, however, that the majority of clinical trials incorporated multiple treatment components, rather than a singular strategy, making it difficult to determine which intervention is responsible for which positive effects. In addition, it should be noted that stress reduction attempts have somewhat differing goals dependent on the disease entity. More specifically, although one study described did find a positive effect of treatment on health outcome (i.e., increased length of survival) among cancer patients, typical stress reduction efforts for this population center around improvement of quality of life rather than on affecting ultimate physical health. However, because of the more direct influence that stress is hypothesized to have on the etiology and course of other chronic diseases, such as type 2 diabetes and cardiovascular disorders, stress reduction interventions have been evaluated with regard to their impact on both stress itself (both biological and psychological indices) and on health outcome (i.e., glucose levels, cardiac morbidity rates).

Both a review of individual studies as well as various meta-analyses suggested that, overall, psychosocial treatments designed to reduce stress are effective, both in terms of psychological outcomes (e.g., distress, negative affect) and a variety of biological parameters (e.g., heart rate variability, immune functioning). However, whereas the majority of studies and meta-analyses yielded positive effects, a sizable, albeit minority, group of studies found no effects due to psychological or stress management programs. Without minimizing the importance of these discrepancies, it may be expected that they will generate useful empirical questions that ultimately will enhance knowledge. Specifically, explication of inconsistent findings may lead to the identification and understanding of moderators of treatment outcome, including gender and other person factors, program characteristics (e.g., timing of intervention, length of treatment, individual treatments versus packages), matching strategies (e.g., matching treatment to patient and/or disease characteristics), and therapist characteristics (e.g., therapist competence) (see Nezu & Nezu, 2007b for a discussion of these and related issues).

It is also essential to recognize the importance of reducing stress as a legitimate target in and of itself. For example, decades of research have identified a strong link between depression and cardiovascular disease (Williams, 2008). This led to the implementation of the ENRICHD program, in which a psychosocial intervention was expected to exert a positive impact on mortality and morbidity rates. Disappointing results can be construed to indicate that stress reduction and other interventions designed to reduce negative affect may not be worthwhile, as they may not extend the life of either cancer or cardiac patients, or help to control diabetes. However, reducing stress, poor quality of life, depression, and anxiety all have value in their own right, and that value should not be ignored by focusing exclusively on ultimate physical health outcomes.

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35 Stress and Chronic Disease Management

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There is good reason to examine biological, behavioral, and subjective stress reactions in the context of chronic illness. Treatments for chronic illnesses such as asthma, coronary disease, congestive heart failure (CHF), and diabetes account for a significant portion of total health care dollars (Halverson, Sontheimer, & Duvall, 2007). Given the strong likelihood that chronic illnesses such as coronary disease and hypertension are, to some extent, consequences of life stress, avoidance and control of life stressors could positively affect the onset, progression, and outcome of these conditions. Furthermore, beyond direct effects on *disease* processes, emotional distress and depression symptoms are clearly implicated in the mismanagement of and nonadherence to treatment for multiple chronic conditions, such as diabetes (Hellhammer et al., 2009) and rheumatoid arthritis (RA) (Straub & Kalden, 2009), promoting *behavioral* processes that lead to more rapid disease progression. Adding to the enormous effect on health care expenditures, distress surrounding chronic illnesses and their management also creates untold costs in disruption of function, work, family roles, and relationships, and reductions in quality of life (Charlson & Peterson, 2002; Kilian, Matschinger, & Angermeyer, 2001).

Among physical diseases, chronic stress has been most strongly implicated in the development of hypertension and other cardiovascular diseases (Esler et al., 2008; Vitaliano et al., 2002) and, for acute stressors, the evidence is clearest regarding the onset of coronary events (Myers, Dewar, & Appleton, 1973; Tofler et al., 1990) and attacks of asthma (Lehrer, Isenberg, & Hochron, 1993). Acute stress is also linked to episodes of depression (Moos, Schutte, Brennan, & Moos, 2005), which is important as both clinical and subclinical levels of depression and anxiety are prevalent in many people with chronic conditions. Depending on the definition used, depression has been reported in 8–45% of patients with RA (Isik, Koca, Ozturk, & Mermi, 2007; Pincus, Griffith, Pearce, & Isenberg, 1996; Wright et al., 1998); 13–78% of those with CHF (Havranek, Ware, & Lowes, 1999; Koenig, 1998; Norra, Skobel, Arndt, & Schauerte, 2008); and 10–32% of those with diabetes (Adriaanse et al., 2008; Ali, Stone, Peters, Davies, & Khunti, 2006; Anderson, Freedland, Clouse, & Lustman, 2001; Fisher et al., 2007). Similarly, anxiety has been reported in 21–70% of patients with RA (El-Miedany & El Rasheed, 2002), 18–45% of those with CHF (York, Hassan, & Sheps, 2009), and 14–40% of those with diabetes (Grigsby, Anderson, Freedland, Clouse, & Lustman, 2002; Li et al., 2008; Mosaku, Kolawole, Mume, & Ikem, 2008).

In addition to their significance to public health, the relationships among stress, depression, and chronic disease pose a challenge for psychological theory. Chronic illnesses appear to be intimately involved in feedback systems that are both consequences and causes of emotional distress, including those involving symptoms of anxiety and depression. Thus, the relationship between chronic illness and distress provides a natural laboratory for developing detailed models regarding the biological, psychological, and behavioral aspects of the stress process. The value of such modeling is illustrated in recent work on the physiological processes by which surgically generated stress affects cell-mediated immunity (CMI) (Ben-Eliyahu, 2003). Studies on CMI indicate that psychological factors activate and sustain the stress-related hormonal cascade generated by surgery and suppress the CMI both in anticipation of surgery and afterwards, making an otherwise acute stressor chronic (Ben-Eliyahu, 2003). These studies reveal detailed dynamics of the endocrine and immune processes at the biological level and their correlation with psychological processes at the experiential and behavioral levels. Furthermore, the contrast between the biological and behavioral levels of description highlights the impoverished state of current models of the psychological stress process. This chapter addresses this deficit by providing detailed psychological models of the pathways from chronic illness to distress. Models such as these are needed to generate psychological interventions to improve management of both chronic illnesses and depressive symptoms by patients and their families.

Before we delve into these questions, it is useful to recognize that stress can be conceptualized in many different ways. Stress can refer to biological activation and/or dysregulation (such as may be associated with acute illness, injury, or chronic illness), exposures to life stressors

(e.g., demanding family, work, or health-related events and conditions), psychological consequences of stressful exposures (e.g., emotional distress arising from chronic illness and its management), and subclinical levels of mental disorders such as depression and anxiety. In this chapter, the terms stress and stressor refer to the causal agent of the stress response, whereas the term distress refers to the emotional consequences of the process that the agent sets in motion. Our primary focus is on distress manifested as symptoms of depression, fearfulness, and anxiety. We first briefly address how stress serves as an antecedent of chronic physical illness before moving on to our focus, an examination of pathways from chronic illness to distress. Following that, we describe how the Common-Sense Model (CSM) of self-management can fruitfully be used as a framework for generating hypotheses to understand, and for developing interventions to address, the pathways from chronic physical illness to emotional distress (Leventhal, Brissette, & Leventhal, 2003). Finally, we apply our analysis of the relationships between stress and illness to three chronic conditions: cardiovascular disease, diabetes, and RA.

STRESS AS AN ANTECEDENT OF CHRONIC PHYSICAL ILLNESS

Depression (Glassman, Bigger, & Gaffney, 2009; Mykletun et al., 2009), hostility (Everson et al., 1997), and anxiety predict physical health and mortality years and even decades after they are assessed (Charles, Gatz, Kato, & Pedersen, 2008). The most frequently documented relationships between stress and chronic disease are those in which chronic depression and hostility are associated with cardiovascular disease (see Bekkouche, chapter 28; Finan, chapter 16; this volume). While stress-related phenomena ranging from daily life events to anger to clinical depression can increase the risk of cardiovascular disease, the picture is less uniform for other chronic illnesses (Anderson, Bradley, Young, Mcdaniel, & Wise, 1985; Cohen, Janicki-Deverts, & Miller, 2007; Fauvel et al., 2003; Frasure-Smith, Lespérance, & Talajic, 1995; Kawachi, Sparrow, Spiro, Vokonas, & Weiss, 1996). For example, the evidence is less conclusive as to whether anxiety and depression increase the risk of incident hypertension (Deter, Micus, Wagner, Sharma, & Buchholz, 2006; Patten et al., 2008; Räikkönen, Matthews, & Kuller, 2001). Furthermore, there appears to be a relationship between work-related stress and diabetes as well as between family-related stress and asthma (Kozyrskyj et al., 2008; Kroenke et al., 2006), but the extent to which family stress is related to diabetes or to which work stress is related to asthma is unknown. It is important to note, however, that virtually all of these epidemiological studies treat depression and anxiety as unitary conditions or diseases, ignoring the pathways and variables linking distress to chronic physical conditions.

CHRONIC ILLNESS, CHRONIC ILLNESS MANAGEMENT, AND DISTRESS

As chronic illnesses are increasingly common with advancing age, and as older adults are an expanding proportion of the population, the comorbidity of distress with chronic illness is a massive problem for the future health care system. Furthermore, chronic conditions such as RA, cardiovascular disease (hypertension, CHF, myocardial infarction (MI)), diabetes, and depression are managed by patients and families in homes and communities. Thus, chronic illness management occupies both the bulk of medical practice and a substantial portion of a patient's daily life (Wagner et al., 2001). The aging of the population, as well as the assignment of virtually the entire disease management endeavor to the home environment, creates a critical issue for understanding how chronic illness relates to distress and for designing clinical interventions to modify the effects of emotional distress on home-based illness management. As stated earlier, it is known that symptoms of mental illness, depression in particular, are associated with nonadherence to recommended treatment (DiMatteo, Lepper, & Croghan, 2000). The consequences of nonadherence to treatment range from failure to control disease processes to frequent use of emergency services and hospitalization (Delea, Stanford, Hagiwara, & Stempel, 2008). These adverse health outcomes are especially concerning in older adults.

While distress is related to nonadherence to management regimens for physical illness, there is a dearth of treatments that effectively target both physical illness and distress. A substantial number of clinical trials have failed to show that treating distress, particularly symptoms of depression, improves chronic illness. Comprehensive reviews of the empirical literature indicate little or no benefit for cardiovascular disease outcomes with the treatment of depressive symptoms (Detweiler-Bedell, Friedman, Leventhal, Miller, & Leventhal, 2008; Thombs et al., 2008), and the outcome is equally negative for diabetes (Detweiler-Bedell et al., 2008; Katon, Lin, & Kroenke, 2007). In addition, effective treatment of chronic physical illnesses does not seem to improve depressive symptoms (Beers & Passman, 1990; Lorig, Gonzalez, & Ritter, 1999). The absence of observed benefits for one of these two targets, when treatment is directed at its presumably causally paired mate, is most likely due to failure to identify the pathways and factors linking chronic illness and distress. Studies that identify the variables in the pathways linking these conditions will enrich theory and allow us to focus treatment on both the specific disorder and the variables in the connecting pathway that would result in benefit to the linked disorder.

PSYCHOLOGICAL PATHWAYS FROM CHRONIC ILLNESS TO DISTRESS

Examination of the clinical trials targeting both depressive symptoms and a chronic physical illness, while failing to demonstrate a causal connection between the two, suggests that the trials are based on the assumption that a biological pathway links the two sides of the comorbidity equation. The chronic physical illness and symptoms of depression are treated as diseases connected to each other and initiated by common pathophysiological processes. If physiological factors alone were responsible for the association, effective treatment of cardiovascular disease and/or diabetes would affect depressive symptoms; likewise, effective treatment of depressive symptoms, or other emotional reactions that are physiological consequences of the disease, would automatically benefit their cardiovascular or diabetic mate. That treatment of one does not transfer to the other suggests that this simple biological model does not fit the data.

A central hypothesis underlying our CSM approach is that identifying processes generated by psychological factors requires that investigators examine the meaning of distress within the context of a chronic illness. Specifically, we must ask how specific types of emotional distress, including symptoms of depression, fear, anxiety, and anger, are embedded in the cognitive representations of their associated chronic physical conditions. The meanings of the emotional response (i.e., fears as expectations of specific threats, anxiety as a generalized indicator of inability to manage threat, and depression as an indicator of resignation and inability to control threat) are products of the perception of the disease, the perceived effects of self-management and medical procedures to control the disease, and the temporal expectations regarding when outcomes, from minor to disastrous, will occur. Once the psychological processes in these pathways are identified, treatment of either side of the equation (chronic physical illness and/or distress) can assure benefit to the other if treatment addresses the variables and behaviors in the causal pathway linking the two conditions.

Investigators have identified at least four sets of factors involved in pathways from chronic illness stressors to emotional distress, though detailed specifications of these factors and of the operative processes are lacking. First, distress often accompanies chronic conditions that elicit high levels of pain, severely compromise physical and mental function, and pose direct threats to life. Second, diagnosis and treatment appear to initiate a sequence of factors leading to emotional distress. Thus, depressive symptoms are more likely to be associated with diagnosed versus undiagnosed diabetes (Knol et al., 2007) and are more likely to be associated with treated than untreated diabetes (Golden & Carnethon, 2008; Golden et al., 2008). This may occur because newly diagnosed patients have worries about their future and concerns about how best to manage their illness. For example, patients managing heart failure who are concerned that medical care poses "a substantial economic burden" are more likely to report symptoms of depression (Havranek, Spertus, Masoudi, Jones, & Rumsfeld, 2004). Ambiguity about the cues indicating the onset, presence, and/or exacerbations of a chronic condition, and uncertainty about its amenability to management and control, are an additional set of diagnosis-related factors than can trigger distress.

A third trigger of distress involves patients' views of prescribed treatments and lifestyle behaviors. Patients may have concerns about the limited benefits of a treatment relative to its potential harms. Perceived harms can range from side effects, fears of addiction, and the expectation that medication for a given condition may interact adversely with medications for another comorbid condition (Barber, Parsons, Clifford, Darracott, & Horne, 2004).

Fourth, treatments can also disrupt social roles and relationships. Patients attempting to adhere to prescribed lifestyle and medication for diabetes may find they no longer have valued social roles in family gatherings, and have lower self-efficacy and self-worth, which appear to stimulate depressive symptoms (Vileikyte et al., 2009).

THE CSM: A DETAILED FRAMEWORK FOR LINKING CHRONIC PHYSICAL ILLNESS AND EMOTIONAL DISTRESS

The CSM describes the cognitive, affective, and behavioral processes involved in the ongoing management of chronic illnesses. More specifically, the CSM is designed to identify the processes by which various illness-related triggers (e.g., pain, symptom ambiguity, side effects) are related to underlying or implicit prototypes, that is, preexisting cognitive structures that shape the mental representation of changes in health status. Triggers may indicate deviations from the prototype of the healthy self and, if so, they may match and activate implicit prototypes of specific illness threats. The CSM is concerned with the cues that instigate motivation and initiate specific actions, the outcomes that are expected and perceived to be a product of these actions, and the perceptual environment or action plans that constrain and guide behavioral performance. By focusing on the cognitive framework generating action at the level of ongoing problem solving, the CSM can identify variables that define the pathways by which chronic physical conditions elicit affective reactions including specific fears and symptoms of anxiety and depression.

A large number of studies conducted within the CSM framework have used the Illness Perception Questionnaire (IPQ; Hagger & Orbell, 2003; Moss-Morris et al., 2002; Weinman, Petrie, Moss-Morris, & Horne, 1996) or its equivalent (Holcomb, Adams, & Ponder, 1983) to describe how patients and individuals at risk for illness frame or

represent threats to health. These instruments identify content domains that comprise illness representations: (1) the *identity* of the threat, in the form of experienced symptoms and functional changes and abstract labels that may correspond to these experiences; (2) its *timelines*, including expected or perceived rate of onset, temporal course and patterning, and duration; (3) *causes*, including a wide range of perceived antecedents, from genes and toxic exposures to stress, temperament, and religious/spiritual influences; (4) *consequences*, including subjective, physical, economic and social costs; and (5) *control*, or perceptions of the curability or manageability of the condition. Investigators have approached the conceptualization and measurement of the procedures or responses for disease management in a similar manner. For example, Horne and colleagues (Horne, Hankins, & Jenkins, 2001; Horne, Weinman, & Hankins, 1999) have developed four scales to assess beliefs in the perceived necessity of and the perceived concerns about both medications in general and the specific medications prescribed for one's own condition. The perceived consistency or coherence of the illness and treatment representations is measured in more recent versions of the IPQ (Moss-Morris et al., 2002). For example, one may query whether the procedure makes sense in relation to features of the representation of the illness (e.g., drinking something for a stomach problem, resting for a problem thought to drain energy). These well-validated measures assess many of the details involved in the ongoing management of chronic conditions and have proved effective for predicting adherence to treatment (Horne & Weinman, 1999).

Common measures of behavior and health outcomes often lack the specificity needed to define the elements of the feedback/control system in the CSM. They ignore the need to focus on the specific item(s) that are valid for predicting behavior involved in the feedback system of a specific patient. Yet, this is an approach that is critical for developing interventions to help the patient reshape behavior to improve control of a chronic condition, reduce long-term risk, and manage emotional distress. The CSM outlines a control system that can guide the development of interventions (Leventhal, 1970).

The comparison process is the core of the CSM when it is viewed as a control system for behavioral management of lifestyle and/or illness. The consideration and identification of the self as possibly, or definitely, ill involve a comparison between ongoing somatic sensations, current function, and any available objective signs (e.g., results of blood tests and blood pressure measurements) with the prototype of the healthy, normal self (see Kahneman & Miller, 1986, for a similar perspective). The contrasts experienced in these comparisons define the symptoms and functional deviations of illness. These comparisons and the many responses they initiate in a typical day are automatic and below awareness. Thus, if the automatic response to shift posture when there is back pain reduces or removes this deviation, the process stops. If the response does not remove the cues and/or if the cues intensify, the process enters awareness and recruits further thoughts and actions to form representations of the process underlying the experience and action.

Representations are hypotheses about the possible meaning of somatic sensations and functional changes and about operating characteristics of the processes by which they are generated and controlled. They are created from the fit of sensations and function to the features of prototypes (Gobet, 1998) that were formed during prior episodes of illness personally experienced, observed in others, or encountered in the media. Current experience is compared with features of underlying prototypes; the comparison occurs both simultaneously and sequentially. It is likely that the initial checks are conducted with prototypes of acute, benign conditions (e.g., the common cold, stomach upset, a rash, bruise, or cut), with more serious or personally relevant prototypes emerging as a function of the individual's history. The checks match to specific features within the five specific areas of the prototypes mentioned earlier: identity, timelines, causes, consequences, and control. Representations of the actions taken to manage a condition or reduce symptom burden also involve matching experience with prototypes and the comparison of pre- to post action experience. For example, prototypes for over-the-counter medications such as aspirin and acetaminophen are expected to achieve reductions and/or elimination of pain and distress (*identity*) in predictably short time frames (*timeline*).

Prototypes often do not fit ongoing experience in a given illness episode. For example, physicians may contribute to the creation of prototypic expectations for pharmacotherapies for control of chronic illnesses with insufficient attention to the time frames for experiencing changes in symptoms and function associated with both the benefits and risks of treatment. They also may fail to differentiate valid disease-related experiences from invalid expectations based on generalizations from treatments for acute conditions to treatments for chronic illnesses, or to address misinformation acquired from media and social exchanges. A stable management system will form only when the check process matches concrete experience with multiple features of a specific illness prototype, and when the treatment representation is consistent with the illness representation. When prior expectations of illness and treatment are inconsistent with posttreatment experience, the individual will likely be motivated to search for additional information, change behavior, seek input from others, and become emotionally distressed if the inconsistency is perceived as threatening.

Representations are dynamic, and can and will change in response to new information. They are especially likely to change when procedures to ameliorate initiating cues are inconsistent with and/or disconfirm a critical feature of the representation. For example, when headache pain localizes, worsens, and is not removed by aspirin, this disconfirms a stress hypothesis. The comparisons of symptoms and experience before and after performing a treatment procedure are critical

in establishing the coherence (Phillips, Leventhal, & Leventhal, 2010) or common-sense validity of both the illness and the treatment representations. Expectations for the how, when, and where of the procedure (i.e., was it performed correctly, at the right time of day, and in the right circumstances) define the criteria for evaluating its efficacy (i.e., which symptom or function will change, how is the change to be observed, and when should the observation be made). The greater the confidence in the procedure, the stronger is the implication of post action feedback about the validity of the representation of the condition. To illustrate, if surgery is perceived as the best cure for cancer, and the tumor is only partially removed and/or recurs after surgery, the obvious implication is that the tumor is intractable and deadly. High-level executive processes will begin at this point, including the selection of alternative prototypes and outcome targets such as pain management (Leventhal, Breland, Mora, & Leventhal, 2010).

COMMUNICATION AND THE INTERPERSONAL SIDE OF THE CSM

The checks that identify deviations from the norm and then compare and match these experiences to illness prototypes are as central to interpersonal communication as they are to the intrapersonal process involved in a patient making sense of his or her own experience. The checks are the focus of medical consultations; they are exposed when presenting a new complaint, conducting a review of systems, and assessing progress with the management of an ongoing problem. The practitioner's questions, "How are you feeling today?"; "What is bothering you?"; "Where does it hurt?"; "How long has it been going on?"; "What did you do?"; and "What happened when you did that?" define a process by which the practitioner accesses the patient's subjective experience and actions to gain information for generating hypotheses for the physical examination, additional tests, and treatment. Successful communication, a major issue for achieving good outcomes, requires information sharing. Further, creating and sharing treatment protocols require the use of language that addresses the experiences involved in comparing outcomes before and after specific actions: the how, when and where to act; and the how, when, and where to evaluate efficacy and to identify and respond to unexpected problems.

THE PATHWAYS TO EMOTIONAL DISTRESS: CSM PERSPECTIVE

The CSM provides a detailed psychological model of the pathways from chronic disease to distress. It emphasizes the need to identify the perceptions and cognitive and behavioral responses involved in the pathways connecting chronic illness to emotional distress. To apply the CSM in this manner, it is necessary to conceptualize the factors that may operate in these pathways and how they might function to create symptoms of distress in specific chronic conditions such as cardiovascular disorders, Type 2 diabetes, and RA.

These conditions differ in multiple ways: RA has the most salient subjective experience as well as greater subtleties of behavioral management; diabetes is a far quieter disease, with few subjective cues associated with elevations of blood glucose and a challenging array of experiences with the onset of comorbidities; and cardiovascular diseases vary greatly from the highly symptomatic (50–70% of MIs), to the symptomatic but confusing (CHF), to the symptom free (hypertension). The experience and interpretation of these disorders and the procedures for managing them differ with regard to cues for action, available self-regulatory responses, and perceived outcomes, and are each likely to be associated with particular types of emotional distress. They therefore provide a useful set of illustrations for how patients, clinicians, and investigators understand management of chronic conditions and associated emotional distress.

In addition to addressing specific pathways that lead individuals to form representations of chronic illness that may evoke distress reactions, it is important to identify the vulnerability factors that determine whether a patient will engage in behavior aimed at management of the disease, will experience emotional distress, or both. As neither a single trigger nor a single pathway is generally necessary or sufficient to produce an emotional response, there typically must be some vulnerability factor determining whether the outcome is a distress response. Negative affect arises when preexisting vulnerability and ongoing circumstances lead to a perceived threat to physical or psychological well-being. If illness puts the physical or psychological existence of the self at risk, it creates the conditions for anticipatory anxiety, specific fears, and depressive symptoms.

Features of illness and treatment representations (identity, timeline, causes, consequences, and control) set the groundwork for this process. For example, using the timeline prototype check to label a physical illness as chronic endows it as a lifetime feature of the self and creates the awareness that it may not be controllable. This has implications for an unknown, but potentially broad, array of harm and loss in the physical, psychological, and social domains. Specifically, a chronic disease label implies an internal, stable, potentially uncontrollable, and possibly global condition; these are key cognitive factors in the learned helplessness model of depression (Abramson, Alloy, & Metalsky, 1989). How the illness and management processes are experienced will determine whether the events surrounding management will confirm the validity of these perceptions of vulnerability. As noted earlier, vulnerability of the self is confirmed as a direct consequence of the ongoing process of checking deviations from the normal symptom-free self. The

check process is focused on the self, and failure to contain the effect of the symptomatic and functional disruptions caused by a permanent internally located disease means that the self is no longer what it was or hoped to be; it is damaged, trapped, and distressed. Confirming the vulnerability of self to a chronic physical disease elicits distress. This may begin with mild concerns and minor upsets as the patient masters some, but not all, problems in self-management. However, it often progresses through specific fears about the negative effects of specific interventions and the apparent course of the disease, and it can lead to more severe symptoms of anxiety and depression as severe doubts arise about containing the disease and avoiding its most negative outcome: destruction of the self. Although the initial response to diagnosis may be severe, it is this pathway involving problems with self-management and self-vulnerability that has the greatest implications for interventions to improve both illness management and distress. The CSM provides a way to address the management of a chronic condition in a framework that evaluates the patient's experience and areas of management that might lead to feelings of vulnerability. Because the development and evaluation of illness and treatment timelines takes time, and the progression from chronic physical illness to distress may be slow, it is quite possible that a patient may be unaware of the factors that have created the link between their chronic physical illness and distress. Recognition of this lack of awareness is critical to designing interventions to create the motivation to initiate, guide, and sustain the behaviors that are essential for effective management.

DISEASE-SPECIFIC EXAMPLES OF PSYCHOLOGICAL PATHWAYS TO DISTRESS

CARDIOVASCULAR DISEASE

Hypothesizing behavioral pathways from chronic cardiovascular conditions to emotional distress must take into account likely differences in the antecedents of different forms of distress and different components of these distress reactions. For example, the somatic, cognitive, and mood features of depression may have different antecedents and may have different consequences for behavior and coronary disease. Thus, both different distress responses as well as different components of a single distress response may be uniquely related to the following factors within the CSM: 1) ambiguities regarding the source and meaning of coronary symptoms (*cause, identity*); 2) labeling oneself as chronically ill (*timeline*); 3) unclear expectations as to how treatment will affect symptoms and function (*consequences*); and 4) inability to appraise the magnitude and meaning of treatment-generated changes in symptoms and function (*control*). Each of these factors and their combinations suggest different distress outcomes.

Uncertainty Regarding the Meaning and Controllability of Symptoms

Theory and data point to uncertainty and lack of control as factors in the ongoing process generating emotional distress and depression (Mishel, 1984; 1990). Patients with hypertension or CHF and those who have experienced MI face uncertainties in several areas. For example, they may have no way of monitoring their current or long-term risk using subjective events. With the exception of some MIs, neither symptoms nor moods are valid indicators of risk. There may be objective medical indicators, but no clear subjective or functional measures for monitoring chronic risk for hypertension, and unless patients are carefully educated, there is substantial ambiguity in monitoring cues for CHF (Horowitz, Rein, & Leventhal, 2004). For example, patients diagnosed with high blood pressure expect to experience symptoms as the label "hypertension" suggests: tension, stress, warm face, and beating heart (Baumann, Cameron, Zimmerman, & Leventhal, 1989; Blumhagen, 1980; Heurtin-Roberts, 1993). Symptoms are not, however, valid indicators of chronically elevated blood pressure (Baumann & Leventhal, 1985).

An early study showed that patients believed they could use symptoms to monitor their blood pressure. Specifically, 82% of the patients in ongoing treatment for high blood pressure believed that their symptoms were valid indicators of their blood pressure, but 92% also agreed that patients cannot monitor their blood pressure using symptoms (Meyer, Leventhal, & Gutmann, 1985). Patients who believed that treatment alleviated their symptoms reported higher levels of adherence and had better objective blood pressure control. Belief that symptoms were valid indicators of blood pressure had a different and adverse effect on treatment adherence for a group of patients who were recently diagnosed; new-to-treatment patients were more likely to drop out of treatment if they reported telling their doctor at baseline that they could rely on their symptoms to monitor blood pressure (Meyer et al., 1985). As physicians typically discount such claims, it is plausible to speculate that expressing this belief created a problem in communication between the patients and their practitioners, resulting in patients discontinuing treatment. A recent study of hypertension beliefs among African Americans highlights the role of symptom attribution in management; individuals who believed that hypertension was due to stress were more likely to pursue stress management techniques, whereas those who believed that hypertension was due to physiological and lifestyle factors were more likely to pursue lifestyle changes (Hekler et al., 2008).

Besides hypertension, qualitative data indicate that symptom ambiguity plays a substantial role in management and response to symptoms and functional changes for CHF. Contrasting interpretations of CHF symptoms by physicians and patients highlight the role of expertise in creating representations of the same condition. Symptoms of CHF, including swollen legs, breathlessness,

and a chronic timeline, are ambiguous for patients because they do not fit the common-sense prototype for a coronary event (Horowitz et al., 2004). In addition to being incompatible with the common-sense notion of coronary disease, both the symptoms and chronic nature of the functional difficulties are consistent with the perceptions and reality of aging, and CHF is common among older adults (Polidori, Mariani, Mecocci, & Nelles, 2006). Ambiguities such as these can set the stage for interpreting oneself as facing an experientially ill-defined chronic condition, exacerbations of which are difficult to predict or control. Furthermore, attributions of these experiences to age-related decline can lead to loss of hope about sustaining the physical and psychological self.

Although one might expect relatively little ambiguity in the interpretation and attribution of symptoms and functional changes during a heart attack, studies of patients with MI indicate that this is not the case. Patients reporting depressive symptoms delayed seeking care for an MI 7 hours longer than patients not reporting depressive symptoms (Bunde & Martin, 2006). This difference was largely accounted for by fatigue (reports of sleep disturbance also contributed but none of the items assessing depressive mood and depressive self appraisals were related to delay). It is unclear, therefore, if depression per se or the symptoms of the MI were responsible for the delay, and it is also unclear whether patients attributed these symptoms to a heart attack. That ambiguity in the interpretation of symptoms played a significant role in delay was strongly supported by clear evidence of misattributions; patients who attributed their symptoms to gastrointestinal distress were slow to seek care in contrast to the swift care-seeking by patients who experienced chest pain and sweating, symptoms that fit common-sense conceptions of heart attack (Horne, James, Petrie, Weinman, & Vincent, 2000). Contextual factors, in this case the patient's gender, can also create ambiguity for symptoms of MI for medical practitioners. It is well documented that female patients were less likely than male patients to be diagnosed and receive immediate needed treatment for MI (Hochman et al., 1999). Gender-based misattribution is the clear source of the delay (Martin et al., 2005).

These and other studies suggest that symptom experience and attributions are subject to a substantial degree of uncertainty that can serve as the basis for inappropriate decisions, poor self and professional management, and distress. However, it is doubtful that the fears activated during an MI and the misperceptions of symptoms and uncertainty that arise during the event are sufficient to generate longer term distress responses including hypervigilance and sustained symptoms of depression. An additional set of factors, including preexisting vulnerability to chronic distress, is likely essential for a longer term distress response. We hypothesize that the repeated experience of inconsistencies between one's own representation of cardiovascular disease and those of the physician and other authoritative sources can lead to concern and anxiety that may precede the onset of resignation and a sense of depression for some patients.

The Chronic Label: A Vulnerability Moderator

There is empirical support for the role of self-labeling in activation of emotional distress and behavioral response to cardiovascular disease risk. For example, anxiety and transiently elevated blood pressure have been found among patients who label themselves as hypertensive, whether they have clinical evidence of hypertension (Spruill et al., 2007). These effects were not related to patients' levels of trait anxiety; situational anxiety, apparently related to self-labeling, was associated with the blood pressure elevations. Patients were not on medication during the study. Although self-labeling was critical for the elicitation of cardiovascular-related emotional distress and white-coat hypertension in Spruill et al. (2007), the process was triggered by the clinical setting, which was responsible for the elicitation of a temporary state of distress.

Similar effects have been observed in patients who are extremely fearful of cardiopulmonary symptoms and check into emergency rooms complaining of chest pain; signs of coronary disease are absent on medical examination (Aikens, Zvolensky, & Eifert, 2001). The patients are focused on heart-related symptoms (e.g., "I pay attention to my heart" and "My racing heart wakes me up at night"), and avoidant of physical exertion, and they interpret these sensations as auguring a heart attack, responding with fear and care-seeking. Although the hypersensitivity to pain exhibited by these patients is related to anxiety (Aikens et al., 2001), it seems restricted to sensations that match a cardiac prototype, as they do not show hyper responsiveness to other types of pain stressors (Bradley, Richter, Scarinci, Haile, & Schan, 1992). The history that led to the formation and stability of the underlying conception of self as at risk for coronary disease is, however, unknown. It is also unclear whether specific environmental stressors activate the underlying sense of vulnerability that serves as the basis for the interpretive process that arouses cardiac fears and care-seeking. The findings, however, point to specific variables involved in a pathway from illness perceptions to distress.

TYPE II DIABETES

Diabetes management differs from management of conditions such as RA that have more salient symptoms; individuals cannot intuit their levels of glycosylated hemoglobin (HbA1c), an indicator of blood sugar control over a period of time. The CSM suggests ways of modeling both the detailed ground level processes involved in the moment to moment behavioral management of blood glucose and the higher level executive control system that addresses long-term management of diabetes.

Individuals managing diabetes are more likely to respond to the treatment regimen than symptoms; they may be distressed following a changed diet or exercise regimen or insulin prescription that does not appear to produce an immediate effect on objectively measured blood sugar. They also often feel uncertain about their ability to manage their condition (Peyrot & Rubin, 2007). That patients experience distress and report depressive symptoms is not surprising given that patients feel uncertain about their ability to manage their diabetes even when their HbA1c values are in normal range. The uncertainty arises in two points along the pathway between diabetes management and control. First, patients are often unclear as to how their specific actions affect their blood glucose; this reflects uncertainty at the ground level of management. Second, even if they monitor blood glucose regularly, they are unclear as to how specific blood glucose readings relate to physician-provided information about HbA1c levels (Peel, Douglas, & Lawton, 2007).

General stress reduction techniques, cognitive behavioral therapy (CBT), self-management education interventions aimed at simultaneously improving mental and physical function, and collaborative care for depression have been shown to moderately improve symptoms of depression as well as physical functioning (Glasgow, Boles, McKay, Feil, & Barrera, 2003; Lustman, Griffith, Freedland, Kissel, & Clouse, 1998; Rosenzweig et al., 2007; Williams et al., 2004). The improvements, however, do not always persist over time (Wing, Epstein, Nowalk, Koeske, & Hagg, 1985) nor do they translate into improved HbA1c levels (Glasgow et al., 2003; Steed et al., 2005; Williams et al., 2004). Furthermore, the interventions do not always produce a benefit over conventional treatment (Lane, McCaskill, Ross, Feinglos, & Surwit, 1993).

Most interventions targeting distress among diabetes patients focus on general stress reduction; they do not assess diabetes-specific distress. Interventions that highlight the correspondence between treatment regimen and diabetes control, and that explain the necessity of continuous control over diet and insulin, may reduce the uncertainty inherent in diabetes management, thereby reducing stress. The CSM provides a framework to structure CBT's emphasis on problem solving and changing harmful thought patterns. The control system features of the CSM indicate that management needs to focus on the effects of specific behaviors and not on diabetes in general. Patients need to test blood glucose before and after specific actions; comparisons before and after eating specific foods, doing specific physical activities, or some combination of eating specific foods and doing activities, provide evidence of the efficacy of these actions for controlling blood glucose if conducted at appropriate time points (Leventhal et al., 2010). These changes need to be related to the practitioners' marker for diabetes, HbA1c, giving patients a better understanding of the identity, causal features, and controllability of their condition. This also will give patients a better understanding of the features of effective behaviors (*identity*), when to assess effects (*timeline*), relative magnitude of changes (*control*), and an understanding of how behaviors affect blood glucose and HbA1c (elaboration of *causal factors* and *consequences*). This level of understanding integrates executive function (the questions one asks about self-management) with the experienced details at specific moments, and it links these details with interpersonal communications, the physicians' reports of HbA1c (Farmer et al., 2009). Associating the patient's change in behavior to the magnitude of change in HbA1c may make treatment regimens more meaningful and less distressing.

The factors in the pathway between diabetes and distress proposed by the CSM are visible in recent studies of adaptation to serious complications of advanced diabetes: peripheral neuropathy, foot ulcers and possibility of amputation. Both cross-sectional and longitudinal data show a substantial relationship between diabetic neuropathy and depressive symptoms (Vileikyte et al., 2009). Much of this relationship is accounted for by symptoms such as pain, loss of sensation, and unsteadiness; perceived self-efficacy of diabetes control; and disruption of social roles and relationships. Neuropathy could lead to distress if the symptoms are poorly understood or disruption of life roles is not expected by patients, and if practitioners do not communicate information about these symptoms and disruptions to patients. For example, practitioners did not recognize that unsteadiness due to loss of sensory feedback from the feet was strongly related to depressive symptoms and did not communicate this expectation to patients (Vileikyte et al., 2009). Patients also may be unclear that the reduction in pain and loss of feeling is a sign of disease progression rather than improvement.

In addition to understanding how diabetes symptoms lead to distress, more research needs to be done on the relationship between diagnosed versus undiagnosed diabetes and depression (Knol et al., 2007); it is unclear whether the chronic label of diabetes is itself distressing. Input from medical practitioners confirming the diagnosis and calling for lifestyle changes to lower HbA1c may have a substantial effect on an individual's daily life. These lifestyle changes could disrupt self-defining social roles, and information from internet searches that conflicts with medical advice may lead to adoption of alternative management procedures and worsening of disease symptoms and dysfunction; both can leave the individual patient in severe distress with nowhere to turn. The disruption of daily life activities due to disease and demands of disease management may deepen and enlarge upon evaluating the meaning of a chronic disease label, and this could trigger emotional distress and depression (Brown, 1995; Kleinman, 1988).

RHEUMATOID ARTHRITIS

Unlike the chronic conditions discussed earlier, there is no ambiguity for either the clinician or patient about whether RA has a chronic or episodic timeline; it is a cyclical, unpredictable disease characterized by flares and remissions that must be managed on a daily basis. RA has the most fully delineated behavioral pathways from disease to distress of the three diseases discussed here. It may generate distress related to the following factors within the CSM: uncertainty about the origin of the disease (*cause*); ambiguity regarding whether symptoms derive from the disease or medication side effects (*identity*); uncertainty regarding the long-term effect of the disease and treatment on symptoms and function (*consequences*); and lack of contingency between treatment and disease outcome and the challenge of managing a cyclical, dynamic disease (*control*). Some of the most widely reported sources of distress consist of RA management (i.e., medication side effects, lifestyle changes), fatigue, pain, functional impairment (Katz, 1998), uncertainty, potential deterioration, daily life interruption, and strain on relationships (Manne & Zautra, 1992). These major sources of distress can be broadly categorized into two related pathways: 1) symptom based and 2) uncertainty based.

Symptoms as Sources of Distress

Unlike both diabetes and cardiovascular disease, RA is a highly symptomatic illness, which has implications for the consequences, identity, and control dimensions of the CSM. Elevated pain and disability are associated with current depression as well as future incidence of anxiety and depression (Evers, Kraaimaat, Geenen, Jacobs, & Bijlsma, 2002; Wolfe & Hawley, 1993). Fatigue, pain, functional impairment and difficulties with RA disease management (e.g., treatment side effects, changes in lifestyle, delay between treatment initiation and disease change) are all anchored in the daily somatic experience of living with RA. Since the daily symptoms of RA can be very intense and disruptive, there are multiple (likely interacting) possible pathways to distress.

Pain is prevalent in RA and may be one of the primary symptom-based pathways to distress. Pain is unique in respect to other symptoms of RA, as it is emotionally activating (von Leupoldt et al., 2009; Zhang & Luo, 2009) and shares common neurobiological substrates with distress (Maletic & Raison, 2009). It is possible that the neural circuitry activated in response to the chronic pain of RA may itself prime individuals for experiencing depression. However, not all individuals experiencing RA-induced pain experience distress. Thus, while the experience of pain in and of itself may be sufficient to induce distress (Wolfe & Hawley, 1993), there are many additional pathways from pain to distress. Personality characteristics such as self-esteem and adjustment may introduce factors that mediate the association between pain and psychological well-being (Nagyova, Stewart, Macejova, van Dijk, & van den Heuvel, 2005).

The recognition of functional disability as a critical factor in the pathway from the experience of RA to distress is consistent with the suggestion that association of pain with distress may be mediated by functional limitations (James, Miller, Brown, & Weaver, 2005; Zyrianova et al., 2006). Indeed, increased functional disability is related to symptoms of depression independently of clinical indices of disease activity and pain (Margaretten et al., 2009). Functional impairments, whether assessed in comparison to prediagnosis or to quiet disease periods, may impinge upon the individual's sense of independence and self-worth and account for repeated findings that declining physical function is related to decreased physical and mental quality of life in RA (Kojima et al., 2009). The significance of the functional pathway is not unique to RA; physical disability and exposure to life event stress also have been associated with later development of depressive symptoms in individuals with multiple sclerosis (Aikens, Fischer, Namey, & Rudick, 1997), an autoimmune disease phenotypically similar to RA in its unpredictable, cyclical nature.

Data also indicate that functional disability may exert its effects on distress by disruption of social relationships (Fitzpatrick, Newman, Archer, & Shipley, 1991). Functional disability has been identified as a potential mediator in the pathway from pain to social withdrawal and distress (Zyrianova et al., 2006), where social withdrawal leads to feelings of loneliness, loss of self-worth, and depression. In contrast to the effects of withdrawal and loneliness as facilitators of distress, perceived social support has a direct relationship as a buffer of both anxiety and depression among individuals with RA (Zyrianova et al., 2006). Instrumental support is a superior buffer to depression than emotional support (Neugebauer & Katz, 2004). Individuals who experience more illness-related symptoms of RA also show greater distress in response to negative interpersonal interactions (Davis, Affleck, Zautra, & Tennen, 2006). While the investigators did not elucidate the mechanisms by which this occurred, one could hypothesize that the symptoms described (i.e., pain, tenderness, and fatigue) may have been difficult to control, leading to uncertainty, loss of function, and undermining the sense of independent self, which could then contribute to heightened reactivity to interpersonal conflict. When illness management in the lived environment is viewed as less controllable, depressive symptoms are more likely to occur (Chaney et al., 1996; Schiaffino & Revenson, 1992).

It must be noted that positive associations between illness and depressive symptoms may be attenuated with advancing age, indicating that the effect of illness and disability is more distressing earlier in life (Schnittker, 2005). This is consistent with the findings that those with newly diagnosed RA report more distress than those who have been living with their illness for an extended amount of time (Bailey & Nielsen, 1993), despite the fact

that the latter have more substantial functional disability. This also lends further credence to the notion that, when examining relationships between experiences with RA and distress, time from diagnosis should be included as a covariate. Fatigue, though less thoroughly studied than the other symptoms of RA, likely operates through similar pathways to distress (Mancuso, Rincon, Sayles, & Paget, 2006).

Despite much evidence supporting the notion that disease symptoms have a considerable influence on the manifestation of distress, other investigators have found a disconnect between functional impairment and psychological distress (Dickens & Creed, 2001). This has led to a strong interest in examining cognitive factors underlying vulnerabilities toward affective disturbance in RA and the examination of pathways involving uncertainty in disease course and control.

Uncertainty About Disease Course and Behavior–Outcome Noncontingency

Uncertainty in RA is related to symptoms, and it may mediate the relationships between RA symptoms and distress though this possibility remains little explored. Illness uncertainty comprises four basic elements that may be conceptualized using the CSM: 1) ambiguity about illness state (*cause, control*), 2) treatment complexity (*identity, control, duration of control*), 3) uncertainty about probability and seriousness of illness outcomes (*consequences*), and 4) perceived unpredictability of course (*consequences and time to negative outcomes*) (Mishel, 1984). RA is characterized by variability and unpredictability in disease course (Smith, Peck, & Ward, 1990), requiring a dynamic treatment strategy (Aletaha, Funovits, Keystone, & Smolen, 2007). Mishel has described a pathway whereby biological, psychological, and social factors act as antecedents to illness uncertainty, whereupon the appraisal of danger may lead to psychological distress if adaptive coping mechanisms are unavailable (Mishel, 1990). Individuals with RA who feel their disease to be less predictable report feeling a decreased sense of control over symptoms and disease course (Affleck, Tennen, Pfeiffer, & Fifield, 1987). The unpredictability of RA often leads to both a perceived and an actual behavior–outcome non contingency (Wagner, Chaney, Hommel, Andrews, & Jarvis, 2007) in which positive health behaviors may not directly influence disease course (Smith et al., 1990). This behavior–outcome non contingency, coupled with unpredictable disease course, may lead to uncertainty and searches for meaning. In both adults (Chaney et al., 2004) and children (Wagner et al., 2007) with rheumatic disease, negative attributions are associated with greater incidence of depressive symptoms. When behavior–illness relationships are unclear and individuals feel a lack of control, perceived lack of control may generalize to disease-unrelated events and further promote distress (Carpentier, Mullins, Wagner, Wolfe-Christensen, & Chaney, 2007). Thus, the uncertainties respecting what may happen and when it will happen that are produced by generalized perceptions of lack of control may push individuals with RA over a vulnerability threshold when they are exposed to non disease-related life stressors. These factors likely underlie data showing that a poor sense of coherence (i.e., belief in the predictability and manageability of the disease) contributes to depression in individuals with RA (Buchi et al., 1998), whereas high levels of self-mastery predict the absence of mood disturbance (Mangelli, Gribbin, Buchi, Allard, & Sensky, 2002), highlighting the importance of perceptions of control for adjustment to a chronic illness such as RA.

How Illness Representations May Lead to Distress in RA

A delineation of the elements of the negative illness self-schema found in depressed individuals with RA (Clemmey & Nicassio, 1997) may be informed by examining illness representations associated with distress, though few studies to date have investigated these pathways. Internal causal attributions have been associated with increased depressive symptoms in RA (Chaney et al., 2004; Schiaffino, Shawaryn, & Blum, 1998) and, in conjunction with stable and global attributes, have been shown to moderate the association between decreased sense of control and elevated depression (Schiaffino & Revenson, 1992), lending credence to a diathesis–stress model of RA. Strong illness identity and decreased controllability also have been associated with impaired social functioning (Scharloo et al., 1998), a known contributor to distress in RA patients. Recent-onset RA patients who were followed over 21 months demonstrated that beliefs about serious consequences of illness predicted increased levels of depression over and above the contributions of initial depression level, pain, disability, and active-coping strategies (Sharpe, Sensky, & Allard, 2001).

Only two studies have explored potential mediators in the relationship between illness representations and distress in RA patients. Although Scharloo and colleagues (1998) found that coping strategies did not mediate associations between illness representations and outcomes, others have found that avoidant and resigned coping partially mediated the association between identity and distress (Carlisle, John, Fife-Schaw, & Lloyd, 2005). One limitation of these studies is that they are cross-sectional, obviating the ability to establish causality. Moreover, cross-sectional designs do not capture the dynamic process of managing a fluctuating illness or the psychological ramifications of this challenge. A second relates to the measures of controllability. These measures often have poor internal reliability (Carlisle et al., 2005; Scharloo et al., 1998), likely due to the lack of discrimination between distinct aspects of control, such as control over disease course, symptoms, or treatment (i.e., individuals with RA may feel adequate control over treatment, but

very little control over disease course). Addressing these limitations and more fully delineating the relationship between illness representations and distress in RA may have important implications for developing and implementing interventions to target RA-related distress.

CONCLUSIONS

Despite the limitations of existing research, a picture of the behavioral pathways from disease to distress is beginning to emerge. For example, an unpredictable disease course in which positive health behaviors do not immediately affect symptoms may lead to perceived loss of control and uncertainty. This could then lead to feelings of threat, which, if no adequate coping mechanism exists, may leave an individual vulnerable to hopelessness and distress. We must delineate the processes by which illness and treatment representations related to chronic illness are formed through assessments of identity, timeline, causes, consequences, and control, as well as the steps involved in comparisons of symptom experience before and after treatments. In addition, it is important to recognize that while specific episodes may play a critical role in linking physical illness and distress, multiple experiences over lengthy time frames are likely involved in constructing and validating these pathways. The patient treated and/or interviewed in the clinic or research setting is unlikely to have in mind the myriad details of his/her history or be aware of the power of the connections that are identified by empirical research. Once we understand how the experience of illness and treatment can lead to feelings of distress, we can begin to design interventions at both the physical and emotional ends of the pathway, making visible the links between chronic illness and distress. Following this, we can implement behaviors to reduce the ambiguity of symptoms and their ability to generate distress, thereby improving patient outcomes.

Other models for improving health status, such as Wagner's chronic care model, speak in broad generalities (e.g., ". . . chronic disease interventions that positively affect patient well-being necessarily include systematic efforts to increase patients' knowledge, skills, and confidence to manage their condition") (Wagner et al., 2001, p. 67). Our hope is that practitioners can do a better job addressing emotional distress associated with chronic physical illness by incorporating a more detailed, CSM-like approach to the condition-specific processes of management and their corresponding sequelae into these larger chronic care frameworks. It is no surprise that diffuse strategies such as stress reduction interventions have inconsistent effects, if any. Though a disease-specific approach such as that proposed here may not yet provide a valid description of the variables and processes involved in the pathways by which living with a specific chronic illness can result in distress, we believe they offer an alternative to the current culture of repeated, large-scale clinical trials that offer limited insight to the solution of a seemingly intractable problem. Perhaps Weingarten et al. (2002) say it best: "It is ironic that disease management programmes are designed to reduce unexplained variations in care, yet there are large and unexplained variations in the design, development, and implementation of disease management programmes." The CSM provides a framework for systematically examining diseases and identifying specific targets for improved self-management and reduced distress.

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36 Acute Stress Responses in the Psychophysiological Laboratory

William Gerin

A great deal of epidemiological data provide support for a link between psychosocial stress—an admittedly ambiguous construct—and morbidity and all-cause mortality. However, the mechanisms by which environmental demands are implicated in the pathogenesis of diseases such as hypertension, coronary heart disease, diabetes, cancer, and others remain unclear. One method that is used to address this issue is to go into the psychophysiology laboratory to examine the effects of mental stress on markers of biological systems to study the nature of the dysregulations that may contribute to chronic diseases. This chapter will describe the laboratory procedures by which these experiments are accomplished.

Initially, such studies focused solely on the cardiovascular system, with heart rate and blood pressure as the most common outcome measures, and with some work involving serum catecholamines. A great advance seen in the past couple of decades has been the inclusion of a wider array of outcomes. This is crucial, as it is clear that many biological systems operate in concert as mediators of the observed associations between of stress and chronic illness. This has encouraged the development of interdisciplinary collaborations that are the lifeblood for the advancement of this field of study.

A BRIEF HISTORY OF THE PREDECESSORS TO MODERN LABORATORY-BASED MODELS

CANNON'S PIONEERING STUDIES OF "FIGHT OR FLIGHT" LAY THE FOUNDATION FOR ACUTE STRESS RESEARCH

Modern ideas regarding stress and its effects on the body date from the classic studies of the physiologist Walter Cannon (1932). Cannon (1923) first described the "fight or flight" response to threat, work that led to modern conceptualizations of the role of the environment in provoking perturbations in the biological systems of the body. Relevant to the present chapter, he concluded that we could learn about regulation and dysregulation by observing physiological processes at rest and under an emotional "load," that is, upon exposure to stress. Thus, his work anticipated the basic laboratory stress paradigm that is prevalent today.

Cannon showed the effects of emotional arousal—fear, in particular—on coordinated autonomic and neurohormonal activity, the latter notably involving adrenaline (epinephrine). Cannon identified the function of this process as preparation of the organism for a "fight or flight" response. This response involves a chain of biochemical reactions that follow threat perception and include activation of the sympathetic nervous system and stimulation of the adrenal medulla to secrete the catecholamines, epinephrine, and norepinepherine. This sympathetic adrenomedullary (SAM) activity triggers the peripheral physiological processes associated with the fight-or-flight response, including cardiovascular and respiratory changes that increase the supply of oxygen to the brain and muscles to mobilize the organism for action (Cannon, 1923). The sudden activation of these responses at the first sign of danger provides the basis for the study of physiological reactivity in response to acute laboratory stressors. These processes can provide a means of survival for the organism in the short term; however, they may have undesirable physiological consequences when sufficiently prolonged, frequent, or intense, and when provoked by threats for which vigorous behavioral and/or physical activity is not an option.

SELYE DESCRIBES THE GENERAL ADAPTATION SYNDROME

An important advance in the stress field occurred in the early 1950s, when Hans Selye (1950) put forward a model in which the term "stress" referred to the nonspecific elicitation of a physiological response by diverse noxious stimuli. Selye referred to that response as the General Adaptation Syndrome and characterized it as triphasic. In the initial *Alarm* phase, the mobilization of metabolic resources is initiated, which is marked by an increase in adrenal activity and other physiological changes. In the subsequent phases of *Resistance* and *Exhaustion*, the production of corticosteroids by the adrenal cortex first peaks

and then diminishes. These secretions serve protective functions through metabolic effects that include elevations in blood sugar levels and through downregulation of immune responses including inflammation of body tissue. If prolonged, undesirable health consequences follow. The influence of Selye's formulation provided a heuristic basis for the study of stress: One did not require a different model for each different environment-biology transaction; rather, a diverse range of environmental factors operate via the same biological channels, producing the perturbations described by Cannon and triggering a longer lasting hormonal response from the hypothalamic adrenocortical axis (HPA).

Taken together, the work of Cannon and Selye formed the foundation for the modern study of stress effects on biological dysregulation and health. However, because SAM is activated much more quickly than the HPA, and is reflected in end-organ activity that can be more easily measured (e.g., cardiovascular, electrodermal), the laboratory stress paradigm has focused on SAM responses to stress.

THE FIRST PUBLISHED "REACTIVITY" STUDY: HINES AND BROWN, 1932

In 1932, two physicians published findings that showed that, when exposed to a cold stimulus, hypertensive patients exhibited greater increases in blood pressure compared with normotensives, suggesting that blood pressure response to acute stress may be a risk factor for the later development of hypertension (Hines & Brown, 1932). The study is mentioned here not because of the cardiovascular health implications of their work, but rather because of the experimental design, which served as a forerunner for subsequent studies of stress and biological responses. Figure 36.1, which illustrates the design scheme, shows the three phases in the study: (1) baseline (rest), (2) presentation of the stressor, and (3) recovery. The stressor effect is represented as the difference between baseline and stress measurements. This laboratory model serves to this day as the most common means of assessing the effect of one or more stressors in producing observed changes in one or more physiological parameters.

This chapter is meant to address issues that generalize across biological systems. However, the application of the stress-response paradigm to all but a few physiological measures is a relatively recent development, and most of this research has focused on cardiovascular activity. Fewer studies have focused on serum measures of stress hormones such as catecholamines and, more recently, salivary-based measures, notably cortisol. However, reference to cardiovascular outcomes will be common in this chapter, as much of what we know from laboratory research was learned in studies of stressor effects on heart rate and blood pressure.

STRENGTHS AND WEAKNESSES OF LABORATORY RESEARCH

The selection of research environment and methods should always be dictated by the problem under study. An alternative to the laboratory is the field, notably, the research participant's natural environment, in which data from ambulatory monitoring of psychophysiological and self-report measures can be collected. Both venues have their strengths and weaknesses, and these are largely complementary. The major strength of the laboratory is, of course, the greater control it affords for implementing randomized experiments and for isolating the variables of interest from potentially confounding factors. It therefore allows stronger interpretations of results, particularly as regards causal inference. The great weakness of the laboratory concerns the limited generalizability of the results to (1) the real world and (2) other populations. In addition, in the laboratory, the participant is "forced" to confront the stressor being studied and must choose from a limited set of cognitive and behavioral response options, unlike in naturalistic settings, where the subject may use various strategies to avoid a stressor or to respond to its demands.

In contrast to the controlled laboratory environment, collecting measurements in the field provides a more representative sample of behavioral and biological responses, as the subjects self-select the situations in which they find themselves. Even in the field situation, however, the simple fact that the subject is aware that he or she is engaged in a research protocol, and is subject to the intrusion of the data collection methods, still places limitations on generalizability, albeit less so than in the laboratory. However, the main weakness of field research concerns the lack of experimental control relative to that which is possible in the laboratory. It is seldom possible to manipulate the naturalistic environment in a way that allows randomized field experiments concerning the biological effects of stress. Moreover, the real world is a noisy and distracting place, and it is almost always difficult or impossible to control extraneous influences; if they could be controlled, it would no longer be the natural environment. Unmeasured influences that have an impact on the dependent measures tend to enter the statistical model as unexplained variance, making it more difficult to detect systematic relationships.

It goes without saying that neither field nor laboratory-based research is generally superior; rather, each setting has its place in the elaboration of a model that ultimately may provide insight into the nature of stressor effects on mental and physical illness and may lead to interventions that serve to ameliorate those effects. We now turn to the main topic of this chapter, laboratory research methodology.

GENERAL ISSUES IN THE CONDUCT OF PSYCHOPHYSIOLOGICAL STRESS STUDIES

THE ASSESSMENT OF OUTCOME MEASURES IN THE LABORATORY

This chapter focuses on the independent rather than the dependent study variables; other chapters will go into detail concerning the specifics of different outcome measures. The laboratory milieu allows for the collection of a vast array of outcomes; however, the procedures associated with specific outcome measures do not, as a rule, change the essential experimental model. Rather, they call for adjustments to the timing and number of measurements that can be collected and to the interpretation of the resulting data.

SAMPLING RATES INFLUENCE THE EXPERIMENTAL PROTOCOL

Depending on which specific biological measurements you plan to sample, it may be possible to make multiple assessments *during* each experimental phase. In other cases, however, assessment might be restricted to only a few measurements within each phase. For example, several blood pressure measurements can be taken in a 10-minute period, and the mean value computed to represent the blood pressure level for that phase. In contrast, the number of repeat functional magnetic resonance imaging (fMRI) assessments that can be made during the course of any given experimental phase is constrained by practical and cost considerations.

BETWEEN-SUBJECTS AND WITHIN-SUBJECTS DESIGNS

Often, either of these designs will be appropriate for a particular research question. A within-subjects design is frequently deemed preferable, as it provides perfect control over within-subject factors that may influence the outcome (e.g., genetics, family history of illness), and therefore increases the statistical power to detect effects. However, the benefits of the within-subjects design may sometimes be outweighed by the disadvantages. One important issue that often arises in such studies concerns the possibility of habituation to the stressor, and to the laboratory situation in general, which may mitigate or lessen the subject's stressor response. Pilot testing is crucial to assess this possibility, and the task may have to be "tweaked" to prevent it from occurring. This may be accomplished by increasing the "dose" of the stressor (i.e., making the task progressively more difficult) or by using a different more than one form of the same stressor.

Conversely, a related issue concerns the degree of *carryover* of the effects of the first task (or experimental condition) that is administered on those of the second. We usually want the outcomes to be independent of each other and therefore usually must control for order effects by counterbalancing—having half the subjects exposed to task/condition A first, and then to task/condition B, and reversing the sequence for the other half of the subjects.

There may, however, be occasions when counterbalancing is not suffcient, for example, if one task tends to produce an overwhelming carryover effect that will obscure the effects of the second stressor. If one is using a task in which anger is aroused, and a second task, in the same session, in which the subjects is asked to count backwards by 13s, one may wish to always use the serial subtraction task first. If, having counterbalanced, we suspect an order effect, the dummy-coded order variable can be included in the statistical model as a means of assessing and potentially adjusting for its impact; however, it is desirable to avoid such effects altogether if possible. One way to do this if the tasks are given in separate sessions is to separate the sessions as much as possible in time, which will mitigate potential carryover effects. In this event, however, the researcher must be concerned about confounding factors that may arise between sessions, such as changes in medication regimen, physical activity, developmental changes, disease progression, effects of aging, and so on. The further apart the sessions, the more likely it is that such factors will arise.

THE LABORATORY MILIEU

Depending on their personalities and their previous experiences, research participants come into the laboratory with an amazing range of expectation, anxiety, hostility, excitement, and other characteristics that will influence their baseline and possibly their task levels of the outcome measure(s). When these influences are neither manipulated nor measured, they enter the statistical model as error variance. Therefore, it is important to be aware of these influences and to control them when possible.

Experimenter Characteristics

It is wise to be sensitive to the effect that constitutional characteristics of the experimenter or research assistants may have on the subject's psychological and biological states. For example, the results may be biased if a male rather than a female investigator is used, and the sex of the experimenter may interact with that of the subject. Resting affective and physiological variables may be affected, as well as physiological changes and recovery (i.e., post-stress return to pre-stress resting level of the dependent measure). A potential solution is to match so that a male experimenter sees male subjects, and a female experimenter sees female subjects; however, this may present other problems, such as increased "noise" in the administration of the measures. Similarly, race/ethnicity may have an effect. This is an unfortunate fact of our times,

but it must be addressed by the experimenter. Should same-race research assistants always be used? Or only in studies in which race/ethnicity is a factor? Unfortunately, these possible effects are almost universally unmeasured; it would be a problem if bias were allowed to creep into the results, but it is also a problem if potential research assistants are excluded based on their gender or race, or other characteristics that cannot be controlled. This is a fine line that the experimenter must walk; at the least, she or he should discuss the issue openly with the laboratory staff and research assistants.

There is also a more subtle issue that must be considered. Most researchers are careful to control the physical elements of the situation that may affect outcomes, for example, temperature, ambient noise, and lighting, but ignore another potential source of error, the social aspects of the laboratory setting. Attributes and behavior of research personnel who come in contact with subjects also may have a great effect on baseline measurements and possibly on stress responses.

Experimenter Behavior

In contrast to constitutional factors, some aspects of the experimenter or research assistants can be controlled. Mode of dress, for example, should be kept constant within and across conditions; even a shaven versus an unshaven research assistant might conceivably affect subjects in different ways, so it is up to the experimenter to use appropriate judgment as to which such factors need be controlled (blue jeans versus dress pants, for example, but not necessarily shoe color!). Then there are social factors other than physical appearance that may contribute to the results in an unintended way. To address this problem, carefully train your research assistants in the *concepts*—not merely the specific *behaviors*—you want them to enact. Thus, it is important that the experimenter treat each subject as much like all the others as possible. Moreover, the nature of these interactions should be as nonrandom as possible, and this can be accomplished by scripting, as much as possible, all the social interactions to which the subject will be exposed. The scripted lines should be recorded, and research assistants should learn the script.

Given that departures from the script are inevitable, and that the initial script must be considered a work in progress, the researcher must develop a manual of operations and log for every study. The manual should detail all behaviors (including the wording of instructions to the subjects and other relevant verbal behaviors) as they occur in sequence throughout the study. The manual should be revised at the outset of the study in pilot sessions, and throughout the actual study based on the observations of the research assistants and experimenters; such observations should be recorded in the log. The scenarios should be thoroughly rehearsed using research assistants as sham subjects. It is not only the words, but the *tone*, that must be held constant; human beings are exquisitely sensitive to nuance. These assertions are based not only on common sense but on data that have tested the effects of various social phenomena in the laboratory.

Here is an example from my own research. "Social support", in this experiment, was operationalized as the behavior of the experimenter while the subject gave an impromptu speech, with the experimenter making appropriate eye contact, nodding at appropriate times, and occasionally murmuring "that's true"; this was compared with a condition in which the experimenter behaved in a stereotypically "clinical" manner, providing little verbal or bodily feedback (Christenfeld & Gerin, 2000). Again, blood pressure reactivity was significantly greater in the "no support" condition. These results have clear implications for experimenter behavior and how it may influence subject behavior in an unintended manner.

The following section will briefly describe some of the social context issues you will need to consider.

Delivery of Instructions

One way to control differences between research assistants or between sessions is to use prerecorded instructions; thus, every subject hears exactly the same thing. The problem with this, however, concerns what it is you want to control: the objective reality (i.e., the words, the tone) or the subject's perception and understanding. We regard it as more important that each subject *understand* the instructions in the same manner, and that may require asking probe questions and providing an opportunity for the subject to ask questions. Unless the instructions are so straightforward that they cannot be interpreted differently by different persons ("when you hear the tone, press the red button"), I suggest training the research assistant to give instructions in a standardized manner, with feedback between subject and experimenter.

The Social Context

In the 1990s, the notion of "social-psychophysiological" research—studying the nature of social interactions in the psychophysiological laboratory—became established. As mentioned earlier, several studies addressed the question of the mechanisms by which "social support," which has been shown to have a substantive effect on morbidity and mortality, might operate to achieve this effect. The main thrust of the research was that the subject was exposed to stress, but in some conditions was alone and, in others, was accompanied by a friend or a friendly research confederate. In general, studies showed that when evaluation apprehension was not at issue (see next section), the presence of a supportive, friendly person had an attenuating effect on blood pressure and cortisol responsivity (Christenfeld et al., 1997). Although blood pressure cannot be used as a simple measure of emotional or stress-induced activation, it certainly is an indicator; thus, although you

may be studying different outcomes the cardiovascular effects shown in these studies suggest that other outcome parameters may be similarly affected.

In our laboratory designs, we now routinely script and control such behaviors, and our research assistants are carefully trained to act in a "clinical" manner, one that is not overly friendly or sympathetic, nor hostile and unsympathetic. *It is especially important to train research assistants that their own likes and dislikes, prejudices, or bad or good moods must not be allowed to influence the manner of interaction with any particular research subject.*

Evaluation Apprehension

The experiments that tested the effects of social support found, in general, that when compared with a control condition (in which no social support was provided), social support led to decreased cardiovascular arousal. However, not all studies have found this pattern of results; indeed, under some conditions, the presence of even a friendly observer led to a *larger* cardiovascular stress response than the control condition (Christenfeld & Gerin, 2000). In an attempt to explain these inconsistencies, Kamarck, Annuziato, & Amateau (1995) argued that reduced cardiovascular reactivity as a function of social support was most consistently observed when the study protocols were designed to reduce the *evaluative* nature of the stressor. They noted that studies that showed greater cardiovascular responsivity as a function of social support shared the following characteristics: (a) The supportive observer was in a position to observe task performance and (b) the supportive observer provided no verbal feedback to the participant during task performance. These studies emphasized the *evaluative* nature of the manipulation.

The subtle differences between the effects of social support and evaluation apprehension point to the importance of considering the nature of the social interactions that are programmed to occur during the laboratory session. An observer or experimenter who appears unfriendly may cause greater activation; however, a friendly observer may do the same if he or she is in a position to evaluate the subject's performance in response to the stressor challenge.

Demand Characteristics

"Demand characteristics" of the situation constitute a confound in the experimental design that occurs when research subjects modify their behavior in response to subtle cues—a higher status researcher, such as a physician, compared with a research assistant, for example—and in response to their own self-presentation styles and biases. One common cause of subjects responding to the demand characteristics of the situation concerns *evaluation apprehension* (see previous section), which may cause subjects to become overconcerned with achieving a good score (whatever that might be) rather than simply responding to the situation as presented.

Subjects have also been observed to enact certain "Roles," including the following:

- The "good subject": The subject forms an opinion about what the experimenter "wants," in terms of the results of the study, and tries to accommodate.
- The "bad subject": The subject forms an opinion about what the experimenter "wants," in terms of the results of the study, and tries to behave so as to undermine the study hypothesis. Subjects may come into the research laboratory with a degree of hostility, sometimes borne of anxiety, but also of other factors, such as "being forced" to participate for course credit.

Experimenter Expectancies

Perhaps the earliest to describe the effects of experimenter expectations on the behavior of the research subjects was Rosenthal (1994). He found evidence that when the experimenter or research assistant who was responsible for interacting with the subject was aware of the study hypothesis, or of the experimental condition to which a particular subject had been assigned, the results were stronger than when a single or double "blind" was implemented, in which neither subjects (see Demand Characteristics, earlier) nor the experimenter was aware of assignment. It is typically impractical, and sometimes impossible, to disguise the study hypothesis from the experimenter ("double-blind"), but it helps if it is concealed from the subject ("single-blind") which is often feasible.

Blinding is now a staple of experimental design whenever it is possible to implement. In the laboratory, the experimenter will usually necessarily know which condition a subject is in because he or she conducts the study protocol, which presumably differs depending on condition. This may not be true, however, in studies in which person variables are the focus, and no manipulation occurs, or when randomization to and creation of different experimental conditions can be computer programmed. In these cases, all participants are exposed to the identical protocol as regards experimenter behavior, and double-blinding is a greater possibility.

Other Possible Unwanted Influences

Human beings respond to subtle cues, some of which might never occur to the experimenter. In a recent experiment, we tested the effects of distraction—the display of colorful posters and interesting toys, compared with a "no-distraction condition" in which the subject sat in (the same) room, but with no distractions present—on blood pressure recovery following an anger-recall task. Angry thoughts were substantially decreased, and blood pressure recovery to pre-anger levels substantially increased, when distractions were present. Thus, even the physical

layout of the research milieu can have effects on behavior and physiology.

Presumably, with experience with these protocols, you will learn which factors matter and which do not; however, we regard it as wise to control these sorts of variables whenever possible and to be sensitive to others that you may have missed. Maintaining a log to record protocol deviations and equipment failures that may occur will allow better interpretation of data and can be crucial to the success of the experiment.

PHASES AND CHRONOLOGY IN A "TYPICAL" PSYCHOPHYSIOLOGICAL STRESS STUDY

PRE-SESSION INSTRUCTIONS AND CONTROLS

We would all like our research participants to enter the laboratory in as "pure" a state as possible, that is, one free of unwanted influences that may affect the subject's behavior and physiological measures. It is obvious, for example, that it would be desirable for the subject not to have had a couple of beers while waiting for the session to begin. This might not occur to the subject, however, so you should take pains to explain. What are the influences that you should be concerned with? Some generalize across most or all protocols and outcome measures, for example, alcohol or illicit drug use, prescription drug use depending on the nature of the drug (e.g., tranquilizers, mood elevators, beta-blockers). Some prohibitions may be determined by the particular outcome; for example, caffeine use will have a substantial effect on resting heart rate and should be avoided if heart rate is a study outcome. Also, hemodynamic shifts may occur after meals and reach their peak at around 2 hours postmeal. It is wise to schedule laboratory sessions at least 2 hours after the subject has eaten. (If it is too long a period, the subject may be hungry, a stressor itself, and even more problematic, may blame the experimenter!). Make sure to provide the research participant with a take-home list of items to avoid on the day—in some cases, on one or more days—prior to the experimental session. The specific time period should be noted; that is, if the experimenter wishes the subject to avoid food, caffeine, and nicotine use for 4 hours prior to the session, the subject should be given (or mailed) an appointment form. If the appointment is for, say, noon, the form should specify no caffeine (note on the form that tea and many carbonated beverages have caffeine in them) after 8 a.m.

When the subject arrives at the laboratory, one of the first things you will do will be to debrief the subject concerning these items. If it is important enough, and feasible, in some cases, biological tests may be used to ascertain compliance with the instructions; an example is the use of cotinine to assess nicotine usage over the previous week or so. To help elicit truthful statements, it is important not to appear punitive, but you must explain to the subject—beforehand—that these substances will make the study results meaningless. If any are used, request that the subject call and reschedule (if you decide to permit such) or, upon arrival at the laboratory, to let the experimenter know (again, offering to reschedule, if your protocol permits it, will make it easier for the subject to admit the noncompliance).

Another aspect of the pre-session protocol concerns person factors that may affect the scheduling of the session. In women, for example, hormone fluctuations across the menstrual cycle have profound effects on systemic hemodynamics and neurohormonal reactivity to stress. In the absence of urine tests confirming ovulation, the best way to ensure that menstrual cycle phase is controlled is to use the "day counting" method. By asking a woman to schedule her lab session within 5–7 days of the start of her period, you can be reasonably sure that she is in the early follicular phase, when estrogen and progesterone are at their lowest levels. Day counting is not effective for targeting the peak hormone response in the late luteal phase because many cycles, particularly in young women, are anovulatory (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999).

THE EXPERIMENTAL SESSION

The following procedures are common to most laboratory stress studies, but are not meant to be exhaustive. Additional procedures may be called for depending on which particular outcome measures you plan to use or the nature of your independent variable.

Adaptation

It is useful to allow the participant to acclimatize to the laboratory setting; simply being there may be highly stressful for some persons and may cause their baseline measurements to be elevated. During this period, the experimenter should take a few minutes to put the participant at ease. Like all parts of the protocol, this portion should be carefully scripted and piloted to ensure it has the desired effect.

Instructions

Next, the experimenter may describe the procedures and give instructions. Do this prior to the start of the baseline phase so that you do not have to interrupt the protocol at a later point, when it may prove distracting. If necessary, the instructions should request that the subject be careful not to move during the measurements.

Instrumentation

For those measures that will be taken *during* each of the phases, participants are instrumented prior to the start

of baseline. Explain what you are doing and why you are doing it; it will help the participant to relax.

Baseline

Most psychophysiological experiments begin with a baseline, or initial rest, period. This allows you to examine within-subject changes between baseline and task (and baseline and recovery). In most studies, the baseline involves resting quietly for a period of time appropriate for your measure. The baseline period for blood pressure measurement, for example, ranges from about 5 minutes to half an hour, whereas a longer baseline may be necessary if an intravenous (IV) line is used. Given the importance of the measures achieved during rest, a surprisingly scant literature has commented on specific procedures regarding the duration and content of the baseline period.

Obrist (1981) suggested assessing subjects' baseline levels and stress responses on different days. In support of this notion, we found in a recent study that resting blood pressure and heart rate measures taken on the day of the study procedures were significantly higher than those taken on the preceding day (Gerin et al., 2006). However, although assessing baseline and task measures on different days may provide more accurate estimates of the true resting level, this may not be feasible in many cases.

We suggest using distracting materials, such as magazines or even a relaxing video (for example, of an aquatic scene; nothing that will arouse the subject), to help him or her relax, unless there is a particular reason not to do this. Music, also, may help establish the baseline. Measurements are taken during or immediately following (depending on the specific measurement) the end of the baseline period and are thus considered reflective of the summary state of that phase on the dependent measure.

Finally, one must guard against reactivity to the measure itself. For example, insertion of an IV line or the first couple of blood pressure measurements taken with an inflating arm cuff may cause pain and fear, or alerting or orienting responses. If measuring blood pressure, it is common to discard the first few readings (the rule must be established a priori) for this reason.

Exposure to Stress

A stressor (we use this term generically, to refer to a challenging task, or a task designed to provoke an emotional response) is then presented. The duration of presentation tends to be brief, usually 2–5 minutes, although longer tasks (notably, the Trier Stress Task, described later in this chapter) have been used. As with baseline, measurements are taken during or immediately following (depending on the specific measurement) the end of the task period. The peak value is sometimes used, rather than the mean of the entire period.

SELECTION OF THE STRESSOR

The question of which particular stressor is best for a particular study should be based on what it is the researcher hopes to accomplish. Virtually all stressors are intended to increase the activation of one or more physiological measures; however, each task carries with it other effects as well. For example, a serial subtraction task—one of the most commonly used stressors—may, depending on how it is presented, elicit anger and frustration, as well as active coping. If it is desirable, given the purpose of your study, to arouse anger, then this may prove an appropriate stressor for your study. To help with your decision, the general properties of laboratory stressors are discussed next; subsequently, individual stressors will be classified on the basis of psychological and physiological considerations.

You must take several factors into account when deciding on a stressor.

Conceptuality

Does the task *conceptually* represent the situation you want to examine, in terms of both psychological and physiological aspects? This may be referred to as "ecological validity." In decades past, social psychologists have referred to "realism," defined as "generalizability to other settings." They also distinguished between *experimental realism* (are people involved/engaged in the same way as in the real-world situation of interest?) and *mundane realism* (does it merely *look like* the real world?). A third concept is that of *functional realism* (does the process being studied *function in the same manner* as it does in the real world?). Ensure that your task takes account of experimental and functional realism and does not get sidelined by undue concern for mundane realism.

Feasibility

Is the task feasible in terms of your equipment, your expertise, your time (and that, perhaps, of an assistant, or multiple confederates), your financial constraints, and your ability to obtain approval from your Institutional Review Board? No matter how scientifically appropriate the task, if you do not have the resources, and/or cannot get the approvals, consider alternative designs.

Psychometric Properties

Is the task well supported in terms of its reliability (preferably test-retest) and its validity (e.g., does an "anger-provocation" manipulation produce significant increases in self-reported anger)? You are staking your entire experiment on the selection of the task. Make sure that there is evidence that the task manipulates what it is *supposed* to manipulate (e.g., is the commonly used serial-subtraction task manipulating anxiety or active coping?). You may

find that some tasks confound the variable of interest with other factors not included in your model. For example, arm movements during the stressor may affect some measurements.

Precedent

Has the task been used by others in the field for similar purposes? Note which pitfalls may accompany a particular task and what sorts of studies the task has been used in.

TASK DOMAINS AND SPECIFIC TASKS

Classification of stressors is complex and controversial. Any particular stimulus is likely to be classifiable in more than one domain, and very little has been published in this regard. A researcher may wish, for example, to manipulate the feedback the subject receives about his or her performance on the task, and a variety of tasks would serve for that purpose. Serial subtraction, for example, could be used. However, serial subtraction also contains a social component. It is usually the research participant performing and the experimenter observing; but might the experimenter's behavior be interpreted by the subject as evaluative? And does it appear to the subject that her or his performance is being assessed by the experimenter as subpar? By what standard? In accordance with the subject's skin color or style of dress? One can see that the effects of the simple serial subtraction task may not be so simple to interpret.

The following is not intended to be an exhaustive listing of stressor tasks. Rather, it is offered to provide a broad guide to task selection based on conceptual characteristics of study requirements.

Active Coping

Paul Obrist described one model of the psychological properties of stress tasks and the hemodynamic pathways by which a particular stressor may increase blood pressure (Kirschbaum et al., 1999). Obrist hypothesized that certain tasks may be thought of as "active coping" tasks—that is, challenges that in the eyes of the subject can be overcome by the subject's efforts and abilities. "Mental arithmetic" is an example of an active coping task. A "passive coping" task, on the other hand, is one in which the subject perceives that exercising his or her efforts will not affect the outcome. Watching a stressful film is an example. What makes this typology significant is that there is some evidence that responses to active coping tasks tend to be centrally mediated, culminating in increased cardiac output produced by stimulation of β-adrenergic receptors; in contrast, responses to passive stressors tend to be mediated in the periphery, culminating in increased total peripheral resistance produced through α-adrenergic pathways. Although these biological mediators are specific to the cardiovascular system, the concept of active and passive coping may be applicable to other biological systems as well.

Active coping tasks are ones that provide a linkage between one's efforts and abilities, and the resultant outcomes; thus, in an active coping task, trying harder should result in a better performance. Examples of tasks that are thought to embody active coping include serial subtraction and tasks that involve the persuasion of one or more other persons by use of a speech or argument. However, although the active coping formulation provides a useful heuristic, it is not so straightforward: For example, some tasks, such as the cold pressor, are mediated by both α- and β-adrenergic pathways.

Emotional Arousal

Many researchers focus on the arousal of an emotional state, as a means of examining the accompanying physiological activity. The most common emotion to be manipulated in this way is anger, although some researchers have focused on anxiety. There are several ways to arouse anger. The anger-recall task (Ironson et al., 1992) is a relatively simple procedure in which the experimenter asks the subject to think about, and discuss, a situation in which he or she had become very angry. The task consistently has been shown to raise blood pressure, heart rate, self-reported anger, and angry thoughts. A second means of anger arousal is through the use of the Type A Structured Interview, an instrument that was originally devised by Rosenman (1978). The interview consists of a standardized series of questions posed to participants in a challenging and, at times, brisk manner, aimed at eliciting Type A behaviors including impatience and hostility. Serial subtraction, or other forms of mental arithmetic, may be used to evoke anger as well. The task may be presented in a way that is harassing to the subject ("can't you go any faster than that?") and that causes anger and resentment that outlast the task itself (Glynn, Christenfeld, & Gerin, 2002). Other tasks that involve an evaluation component can be modified in a similar manner.

Social Interaction and Speech Tasks

Although a great deal of the stress we tend to experience comes from our interactions with others, and social psychologists have been engaging in research involving social interaction in the laboratory since the early 1900s, it is only within the past 20 years that stress psychophysiologists have begun to make use of this method. Many interesting questions can be asked using this paradigm: What are the person dimensions—race, sex, emotional supportiveness, hostility, and so forth—that affect physiological outcomes in social interactions? What situational attributes—the presence of another person, the status difference between the subject and an observer, and so forth—tend to exacerbate, or attenuate, the stressfulness of particular social interactions?

A relatively simple social interaction that may be modeled in the laboratory involves public speaking, an activity that is stressful for many people. For example, several researchers have examined the effects of the supportive versus nonsupportive demeanor of the observer. A different type of design concerns structured, but real, interactions between persons. For example, Smith and Gallo (1999) have used a marital interaction situation, in which a married couple discusses their problems. This is a good example of a way to increase the external validity of the laboratory situation.

In making use of true social interactions, which are unscripted, the researcher sacrifices a degree of experimental control, as not all interactions will take the same form. However, the tradeoff for additional external validity is often profitable.

The Trier Social Stress Test

The Trier Social Stress Test (TSST) was initially developed to evaluate effects of psychosocial stress on cortisol activity in a laboratory setting (Kirschbaum, Pirke, & Hellhammer, 1993). Because the time course of a change in cortisol secretion is relatively slow—a measurement may reflect the state of the body 15–20 minutes earlier—the researcher has to pay particular attention to the timing of the task and the measurements. Moreover, for a stressor to have a substantial effect on cortisol, it must persist for a longer time than is required by other measures. The TSST was designed to address these concerns. The 20-minute test comprises two stressors, conducted in front of a panel of judges: an impromptu speech in which the participant explains why she or he had been caught shoplifting, and mental arithmetic.

The Cold Pressor

Historically, the cold pressor was the first task used in a published study of stressor effects on cardiovascular reactivity (Hines & Brown, 1932) and was then used in virtually every such study until the late 1950s. The cold pressor is problematic, as mentioned earlier, as it is not clear what processes mediate its effects. Psychologically, it involves pain experience, the perception of cold, and the challenge to endure aversive stimulation. In hemodynamic terms, the task is "mixed," in that it produces both central (cardiac output) and peripheral (total peripheral resistance) effects.

GENERAL METHODOLOGICAL ISSUES

USE OF MORE THAN ONE STRESSOR WITHIN A SINGLE SESSION

Much of the foregoing discussion assumes that the researcher is administering one stressor during the laboratory session; however, you may want to use more than one task, or multiple repeats of one task, within a single session. For one thing, it may be more efficient and less costly, as it eliminates the need for the subject to come back for additional sessions. Alternatively, you may find yourself studying a research question that calls for a comparison across two or more tasks (for example, you might be interested in knowing the extent to which responses to two different tasks are correlated, with both possibly tapping the same or a similar underlying dimension).

You must consider the following: Is the parameter in which you are interested subject to elevation over the duration of the session and across its different phases? The mean resting blood pressure, for example, tends to rise following the offset of each preceding stressor. This is information that can be captured if one uses a recovery phase (in fact, the recovery phase for Stressor 1 also may serve as the baseline for Stressor 2). If, on the other hand, your measures tend to return to resting levels immediately following the termination of a stressor, you can use your initial baseline measurement for multiple stressors. (This is also true of Obrist's suggestion that baseline be assessed on a separate day.) However, if you suspect that the effect of the stressor may be sustained even after the stressor has ended, you must use a new baseline period from which to assess the change for Stressor 2.

Similarly, you must consider the question of habituation to the stressor, and the issue of counterbalancing, as was considered in an earlier section in this chapter.

There are two general frameworks to consider when using multiple stressors (whether within a single session or over more than one session). First, you may consider the individual stress tasks to each represent one facet of a broader construct—a useful example here concerns the underlying dimension of *active coping*, discussed earlier. Both mental arithmetic and the speech task are considered to be tapping this dimension. In such a case, using both tasks would be likely to increase the reliability of your measures, as presumably your effects can be taken as the mean score of the different tasks.

However, to the extent that you believe that two different tasks elicit physiological changes that represent *different* dimensions, you would not expect them to correlate highly; instead, you are probably looking for mean differences *between* the measures obtained during the two tasks.

Intertask Baseline

In the event you decide to use more than one task within a single session, you must decide whether or not to use a rest period to separate them. If you are using more than one task because you want a longer exposure duration, as the Trier tasks were designed for, you will not want to use an intertask baseline between them. If, however, you plan to use multiple stressors for the unique information each may provide, we suggest you use a separate baseline period for each of the tasks. Try to spread apart the tasks

temporally as much as possible, within the limits of the duration of the session.

Returning, now, to the question of whether to use multiple tasks within a single session: If you have reason to be concerned about carryover or habituation effects from one to the other (if you do not know whether they exist, we suggest you collect pilot data to find out), you might consider the following: (1) having the subjects come for a separate laboratory visit for each task you intend to use or (2) switching to a between-subjects design, in which subjects are randomly assigned to be exposed to one or the other of the tasks, which, in this instance, would be thought of as "conditions."

WHAT IS THE "CORRECT" SAMPLING INTERVAL?

This is a meaningless question when asked across different types of measurements, because the answer will depend to a great extent on the biological parameter of interest. Some measurements can be taken only once, usually at the end of each phase of the study, because of timing constraints (how long does the measurement take?) or expense (e.g., echocardiogram, fMRI). Others may be assessed continuously (e.g., electrocardiogram) or intermittently (e.g., biomarkers derived from blood specimens, blood pressure) during the study phase.

A second determinant of the frequency of the sampling interval concerns preplanned events that occur during the session; examples include the onset of a stressor or signals that provide feedback regarding task performance. You must "position" your measurement, if this is possible for the measure you propose to use, to capture the physiological changes occurring in response to these events. Thus, if your stressor period is 5 minutes, and you are planning to sample blood pressure once every 3 minutes, you might prefer that the first measurement taken during the task phase occurs at 2 minutes (by which time the stressor presumably would have had a chance to engage the subject) and again at 5 minutes. If instead you were to record the initial blood pressure reading at the *third* minute into the stressor, it would only be possible to collect one measurement.

MEASUREMENT RELIABILITY

A particular measurement is useful only to the extent that it is reliable (changes little from measurement to measurement when conditions remain constant) and valid (measures what it is intended to measure). For physiological variables, a major concern is reliability of measurement. If values vary a great deal from one occasion to the next without any intervention between measurements, that indicates that a given score substantially reflects extraneous influences (which increase measurement error), and little of the "true" score, compared with a measurement that is temporally stable (Gerin, Pieper, Marchese, & Pickering, 1993).

Consider the following: A stress researcher interested in a marker of immune function takes a measurement following a 20-minute baseline, and then following a 5-minute stressor, and computes a change score. The researcher repeats this process under precisely the same conditions (even the same experimenter) 1 year later (long enough that all effects of the first session have dissipated) and finds a test-retest correlation of 0.80. (Test-retest reliability is assessed usually as a Pearson or intraclass correlation or under Generalizability Theory, which allows the inclusion of relevant dimensions that may affect stability over time [Gerin, Christenfeld, & Pieper, 1996].) Such a correlation would, for this dimension over this relatively long period of time, indicate fairly high stability over time. The greater the correlation, the more "true score" resides in the individual's score and the less error. A score with poor measurement reliability—whether used as an independent or dependent variable—will increase the likelihood that you will miss a predicted significant relationship in your data.

Reliability may be augmented using a variety of strategies. More measurements will usually increase the reliability of the measure. Thus, by lengthening the duration of a phase of the experimental session, the number of measurements you can take is increased, thereby enhancing reliability. This can usually be done more easily for the baseline period than for the stressor period.

However, as discussed previously, not all measurements can be repeated during or following a particular phase. Some measures themselves are reactive; some are too expensive; some take too long, or are too distracting to the subject, or are (undesirably) invasive. However, the measure may still have poor reliability. Another strategy must therefore be considered. Some measurements can be repeated over sessions or days, rather than within a phase of a single session. For example, the assessment of vasodilation using brachial artery ultrasound cannot easily be performed more than once within an experimental phase. However, test-retest reliability for this method can be poor, as this method is dependent on the skill of the technician. One way to address the problem is to repeat the sessions over more than one day, yielding more than one measurement that can be averaged. Other problems do arise, including the possibility of habituation, or stressor carryover, over sessions, but this may be the only way to increase the reliability of your measure.

Finally, there are often multiple ways to obtain the same, or a conceptually similar, measure. Check the literature for the most accepted measure of a given construct—this applies to all measurements, paper-and-pencil and biological measurements alike.

DURATION OF STRESSOR EXPOSURE

A tradeoff exists between the advantages of a longer duration task, say one lasting 15 minutes, and the additional burden you place on your subject. In terms of

measurement reliability, discussed earlier, a longer duration allows a greater number of intermittent measurements to be taken and a longer sample of continuous measures. It may also provide greater ability to observe patterns of changes within the course of the stressor, something that would be more difficult in tasks of briefer duration. Finally, as discussed previously, depending on what you are measuring, it may allow the collection of additional measurements to increase the reliability of the measure (as distinct from the use of multiple measurements taken during different tasks/conditions that are conceived as independent). However, many standardized stressors do not lend themselves to extended durations. For example, the cold pressor cannot be longer than a few minutes for obvious reasons. Similarly, it would be difficult to have a subject engage in serial subtraction for longer than a few minutes.

Apart from the increased number of measurements it allows, another determinant of task duration concerns the particular measure being taken. Thus, blood pressure regulation is immediately responsive to one's reactions to the environment; however, cortisol, often measured from salivary measures, takes about 15 to 20 minutes to respond to stress. Because you cannot precisely specify the time lag for each individual subject, you need a longer task duration if cortisol is your outcome, to ensure that each subject's cortisol level—presumably measured at a prespecified interval of perhaps 20 minutes—is indeed reflecting the subject's response to the stressor. The Trier stressor, described earlier, was developed partially for this reason. On the other hand, if blood pressure is your measure of interest, the task duration can be considerably briefer because of the small latency between stress and response.

For some outcomes, such as an echocardiogram, or brachial artery ultrasound for the measurement of flow-mediated dilation, the foregoing discussion may be irrelevant: The measurement takes a certain amount of time to complete, and multiple measurements are just not feasible.

STATISTICAL CONSIDERATIONS

"Reactivity" refers to the change that occurs in a physiological or psychological parameter as a result of exposure to stress, in any of its various forms. As such, it has classically been measured as a simple change score: the mean of the measurements taken during the stressor less the mean of the measurements taken during baseline. A change score is easily interpretable; a change of zero means that the stressor had no effect on whatever was being measured; a change value of, say, +10 indicates that the subject responded to the stressor with a 10-point increase. However, change scores bring hidden perils, and it would be wise to study the basic statistical theory that explains the *why* of those perils (Vickers & Altman, 2001).

There are several other methods that are used, although less frequently than simple change scores: (1) repeated measures designs, in which baseline and stressor levels are treated as two levels of a single factor; (2) analysis of covariance, in which baseline levels are used as covariates; and (3) residualized change scores. Which of these is "correct" remains one of the controversial issues in this field (Altman & Matthews, 1996).

TYPE I ERROR

Psychophysiological experiments provide many opportunities to take advantage of chance. Every additional outcome you measure for which you do not have a strong, a priori hypothesis adds to the experiment-wise error rate. For example, blood pressure is often measured as both systolic and diastolic pressure, with each outcome treated in a separate analysis; the Type I error rate in that instance is almost *double* what is reported because, there seldom are instances in which differential results are predicted for these two measures. Even more problematic is the use of impedance measures of hemodynamic patterning; several measurements are frequently examined, including stroke volume, cardiac output, total peripheral resistance, and pre-ejection period. However, all these measures tend to be highly intercorrelated, and as a result, the likelihood that some significant effects may occur by chance increases dramatically.

There are several methods that provide protection against Type I error. The strongest is to use only outcome measures that are based on specific hypotheses. However, often this is impractical, and it may be that different, albeit correlated, outcomes represent different aspects of the same construct and therefore must be considered simultaneously.

Another method is the Bonferroni correction, but this is a very conservative technique. There are, however, other *post hoc* tests that may be used, assuming the omnibus test is significant. Another method is to use a multivariate analysis in which two or more outcome measures that presumably tap the same dimension are included in the same model; as with *post hoc* tests, if the omnibus test is significant, the analyses for the individual measures may be interpreted (Vickers & Altman, 2001).

ASSESSMENT OF POSTSTRESS RECOVERY

If the parameter you are measuring tends to return to its resting level immediately following the termination of the stressor, measurement of recovery becomes irrelevant. However, this is not true of many physiological measures; a degree of carryover of the effect of the stressor will often exist. In this event, you may want to include a poststress rest period in your protocol (Figure 36.1) as a means of evaluating recovery of the parameter from the stress-induced levels. Assessment of recovery—a dynamic

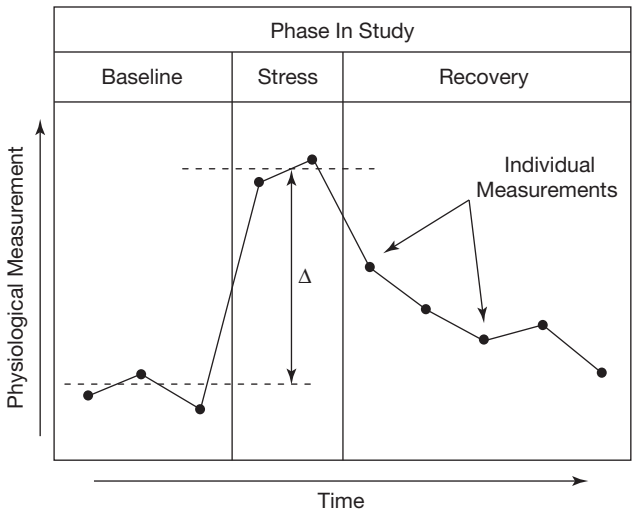

Figure 36.1 ■ Schematic representation of a typical psychophysiological stress study protocol.

state—presents methodological and statistical challenges mostly avoided in the measurement of baseline and task levels, which are usually regarded as stable (see discussion in the following section). For measurements that can only be taken a single time, at the end of the phase, assessment of recovery is fairly straightforward. However, as with baseline, when measurements that are taken during the recovery period are used, the correct measure is unclear. Unlike the case of baseline and task phases, there is little agreement about how to assess recovery. A common method is to select a point during the recovery phase and measure the parameter at that point; thus, one might conclude that at 5 minutes into the recovery period, subjects in group A had recovered an average of 60% of their task values, compared with subjects in Group A, who had recovered only 30%. However, this method ignores a great deal of the information—it may be that it is the decline observed earlier or later in the period that is important, for example—and does not benefit from multiple measurements (see section Measurement Reliability).

Alternatives to time to recovery include calculating area under the curve, obtaining poststress measurements at arbitrary intervals, computing change scores from poststress levels and baseline levels, and using curve-fitting estimates. The advantages and disadvantages of each of these approaches are discussed in detail with respect to blood pressure measurement in a review by Linden, Earle, Gerin, and Christenfeld (1997). In addition, Christenfeld, Glynn, and Gerin (2000) and Llabre, Spitzer, Siegel, Saab, and Schneiderman (2004) have published statistical models designed to assess recovery from stress.

MANIPULATION CHECKS/PROBE MEASURES

Throughout the experimental session, you may want to take measurements—"probes"—that will help you to interpret your data by serving as checks to see that your manipulation is indeed effective for its intended purpose. For example, if one is examining the effect of an anger-induction task, compared with a nonemotional control condition, it would be wise to ask the subjects, at some point in the protocol, how angry they had become. This will help you to understand why you may have null results and may provide the means for post hoc analyses that will at least serve as pilot data for the next study—for example, you may want to separately analyze data for subjects who actually did report higher levels of anger. This type of analysis also may anticipate the queries that referees are likely to have during the peer review process.

Often, probes are directed at psychological states. It is crucial that the experimenter understand the effect that the task is having on research participants. It may be substantial, but not necessarily in the way the researcher had hoped. Here is an example. Earlier, we discussed the subtle overlap in conditions that create perceived social support (which may attenuate stressor effects) and evaluation apprehension (which may increase stressor effects). In the event that overlap was allowed to creep into the experimental design, some subjects might report feeling emotionally supported, others might report experiencing evaluation apprehension, all owing to the identical manipulation. Without subjective reports to shed light on the results, this study might be written off by the researcher as unsuccessful, which would miss the point.

When and how to ask probe questions also is a delicate business. The report itself should be given as close to the relevant time period as possible (e.g., at the end of the stressor) and yet should not influence other measures. The wording of the question should be as neutral as possible and should not point to an expectation on the part of the researcher. For example, the phrasing "how angry do you feel at this moment?" differs only subtly from "do you feel any anger at this moment?" but may produce a bias to report—or to avoid reporting—anger. It is also best to keep such measures as brief as possible. For instance, if the researcher is interested in the degree of anxiety being experienced following the stressor, she or he might administer a one-item anxiety measure with a Likert-type scale; this is probably less reliable and less valid than a multi-item measure, but the latter may simply be too intrusive for the purpose at hand.

SUMMARY AND CONCLUSION

Although it has advanced markedly in terms of the types of physiological parameters and patterns that are examined during rest, stress, and recovery, the format of the reactivity study has changed very little since the original foray by Hines and Brown in 1932. In a sense, these are simple studies to conduct, as they are quite straightforward in many respects. One can determine the effect of

any number of variables on the degree of physiological response and recovery. The far greater challenge, however, is to design studies that help place the responsivity and recovery models in the larger picture, detailing the precise manner in which acute life stressors and their psychological and physiological effects can, over time, influence the etiology and pathogenesis of chronic disease.

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37 Cardiovascular Measures in Stress Research: Methodological, Analytic, and Inferential Issues

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Stress and physiological reactivity are intertwined concepts. Existing definitions of stress are many and varied despite the fact that stress has been a mainstay in psychological research for at least half a century. Stress research can be identified, however, by common themes that have consistently emerged in both human and animal literatures. Arguably, the most common theme is that stress resulting from some discrete event or environmental condition is accompanied by a physiological response. The primary focus of this chapter is a set of methodological issues surrounding the assessment of such physiological responses, most particularly cardiovascular responses, in the context of stress research.

The prominent role of physiological responses in stress research can be traced to famed Harvard physiologist Walter Cannon. Advancing prior work on homeostasis by Bernard (1974), Cannon (1939) popularized the notion of the "fight-or-flight" response, a set of en masse physiological changes resulting from sympathetic excitation and serving to maintain or restore an organism's homeostatic balance. Following the ground work established by Cannon's enquiry into the fight-or-flight response, Selye (1956) made clearer the link between persistent long-term activation of a physiological response to a stressor and risk of physical disease, further intertwining stress and physiological responses. Cannon based much of his work within the context of manifest or inferred psychological processes (e.g., induced emotional states such as fear or anger) and envisioned the physiological change as a direct result of said psychological state, whereas Selye operationalized stress solely in terms of physiological change, effectively eliminating subjective experience, as well as any psychological processes occurring within the organism. Although it may be attractive to some to define stress solely in terms of physiological responses, this can result in something of a slippery slope in which any physiological change, no matter how innocuous, might be unrealistically interpreted as an objective marker of stress. In later sections, we will describe a number of other factors requiring careful consideration if stress is to be validly inferred from observed physiological change.

Our discussion will be limited primarily to methodological issues involved in the assessment of physiological change, although we recognize that modern stress research takes care to analyze psychological processes, such as appraisal, that translate events into stressors of variable potency (Lazarus, 1966). We will remain relatively neutral with regard to preference for any particular model of stress. The choice not to tailor our discussion to a particular stress model should not limit the applicability of the issues addressed in this chapter; rather, researchers should feel free to insert intervening variables or individual differences of interest as they see fit. Likewise, although this chapter will focus on cardiovascular measures, it is our hope that many of the topics, particularly in the more analytic sections, will apply equally well to other physiological response systems employed in stress research (e.g., endocrine and immunological).

The content of the chapter is divided into largely independent sections that roughly mirror the research process. The coverage is obviously not exhaustive; our aim was to highlight three groups of salient issues—experimental design, analytic, and inferential—that researchers are likely to encounter when incorporating physiological measures in the context of stress research. The coverage of experimental design issues begins with variable selection, including the increasingly popular approach of assessing cardiac autonomic control. A basic coverage of the advantages and drawbacks of ambulatory recording is then addressed followed by a discussion of issues related to adequate sampling and processing of physiological measures to insure accurate characterization of physiological responses. The importance of resting or baseline periods is then highlighted, as is the potentially useful, though still somewhat understudied, recovery periods following stress exposure. A number of analytic issues are then addressed, including the potential utility of data aggregation techniques and a caution against the dichotomization of continuous variables. Multivariate statistics as well as causal modeling of physiological variables are also discussed as potentially useful analytic tools. Issues regarding inferences based on physiological measures

are then addressed. Specifically, researchers are urged to give careful consideration to cooccurring, and potentially confounding, psychological processes and cautioned against generalizing measures of autonomic function beyond the organ system from which they are recorded. Finally, the emerging literature placing cardiovascular measures at the heart of models of organismic regulation is briefly reviewed. Readers wishing to delve more deeply into these topics are referred to the recently published *Handbook of Psychophysiology* (Cacioppo, Tassinary, & Berntson, 2007).

EXPERIMENTAL DESIGN ISSUES

VARIABLE SELECTION

A number of practical and theoretical factors must be considered during the early stages of study design when measures of cardiovascular physiology are selected. Practical considerations, such as participant burden, expense, or recording environment, may limit from the outset the list of viable options. Ultimately, decisions should be made in the context of the theoretical framework and methodological constraints inherent to the study at hand.

Perhaps the simplest motivation for selecting a given measure is clinical interest. For example, a researcher interested in the effects of stress on the development hypertension may naturally gravitate toward the measurement of blood pressure. Chest pain, angina, or its physiological signature, S-T segment depression in the electrocardiogram, might be an essential dependent variable in the study of cardiac patients.

More typically, cardiovascular stress response variables are chosen based on prior stress research. As such, historical precedent often plays a large role in the determination of what cardiovascular measures will be used. For example, a well-established cardiovascular reactivity literature now exists based largely on individual differences in blood pressure and heart rate reactivity and represents the largest body of work incorporating cardiovascular measures in the stress domain (Matthews et al., 1986; Turner, 1994; Turner, Sherwood, & Light, 1992). Researchers wishing to replicate and extend that work may naturally choose those measures so as to be able to compare their findings directly to the existing literature. However, it warrants mentioning that the notion of cardiovascular reactivity has been extended to include a host of additional measures of cardiovascular function beyond heart rate and blood pressure (Cacioppo, Uchino, & Berntson, 1994; Friedman & Thayer, 1998; Sloan et al., 2001; Vella & Friedman, 2007). These measures, such as stroke volume derived from the impedance cardiograph (Sherwood et al., 1990), resemble the invasive measurements made by cardiologists and can be useful for this reason. A more typical reason for incorporating these measures is a desire to understand the underlying autonomic influences that induce different patterns of cardiovascular stress responses.

The shift toward investigating the autonomic underpinnings of physiological changes has been driven largely by advances in analytic methods and measurement techniques, as well as increased availability of recording equipment. These advances in the measurement of autonomic influences on the heart have allowed researchers to inform the generation and refinement of theoretical models through more precise knowledge regarding the aspects of the nervous system involved in a manifest physiological change. For example, a change in blood pressure can be due to an increase in cardiac force or an increase in peripheral resistance. Use of impedance cardiography permits a separation of these two factors.

This point has been elaborated fully in considering autonomic control of the heart. As is the case with most organs of the body, the heart is dually innervated, meaning both the sympathetic and parasympathetic branches of the autonomic nervous system (ANS) exert regulatory control over end organ function. Despite the long-held view that the relationship between the sympathetic and parasympathetic branches of the ANS is entirely antagonistic, modern research has shown that the sympathetic and parasympathetic branches of the ANS do not always function in this often-presumed reciprocal fashion but can be simultaneously active or inactive at any given time (Berntson, Cacioppo, & Quigley, 1993; Berntson, Cacioppo, Quigley, & Fabro, 1994). If the two branches of the ANS fail to show a consistent relationship with one another, the implication is that dually innervated organs such as the heart cannot be adequately characterized by a single continuum extending from sympathetic dominance on the one extreme to parasympathetic dominance on the other. The simultaneous recording of measures reflecting activity in both branches of the ANS, thus describing a two-dimensional "autonomic space" (Berntson et al., 1993), allows for the most complete description of autonomic activity underlying manifest physiology and captures the full range of the potential modes of autonomic control (e.g., sympathetic–parasympathetic coactivation). Using this perspective, investigators have recently shown that one pattern of cardiovascular response is related to myocardial infarction and another to diabetes (Berntson, Norman, Hawkley, & Cacioppo, 2008).

Prior stress research has largely focused on the sympathetic nervous systems and its activating role, but parasympathetic activation has powerful effects on the heart that interest many as a potential "brake" on sympathetic activation. Inferring activation or inhibition of parasympathetic effects on the heart has increasingly relied on the measurement of heart rate variability. Since the application of spectral analysis by Akselrod et al. (1981) as a specific means to tease apart the various components of variability present in cardiac rate, the analysis of heart rate variability has received widespread use. Although numerous time- and frequency-domain

analytic techniques can be used to quantify the variability present in the interbeat interval time series (Friedman, Allen, Christie, & Santucci, 2002), spectral analysis remains the most popular and, through either parametric or nonparametric methods, affords the most detailed parsing of frequency components. Regardless of the type of spectral technique used, the end result is a power spectra depicting the variance attributed to various frequencies. A power spectra derived from 1 minute of resting heart rate data is depicted in Figure 37.1. The interbeat interval time series, the time between successive R-spikes in the electrocardiogram, is displayed in panel A, and its power spectra, showing the power or variance present in the time series as a function of frequency, is displayed in panel B. The result of such heart rate variability analysis derived from healthy individuals typically contains a number of identifiable power bands, two of which are of particular relevance to the present discussion. The first is a faster, high-frequency (HF) component (0.15–0.4 Hz) reflecting variance in heart rate linked to respiration at normal respiratory rates (Saul, 1990). This component of heart rate variability is mediated solely by parasympathetic influences carried to the sinoatrial node via the vagus nerve. Accordingly, spectral power in the HF band, alternately referred to as respiratory sinus arrhythmia or cardiac vagal control, has become a commonly used index of parasympathetic control of the heart. The second relevant band is the slower, low-frequency (LF) band (0.04–0.15 Hz) believed to represent baroreceptor-mediated regulation of blood pressure. The autonomic underpinnings of the LF band are believed to be largely sympathetic, though there is debate regarding the extent to which vagally mediated variability is also present (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). For this reason, some have employed the ratio of LF to HF power as an index of sympathovagal balance (Berntson et al., 1997; Malik & Camm, 1990; Malliani, Lombardi, Pagani, & Cerutti, 1990; Stein, Bosner, Kleiger, & Conger, 1994; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996).

Whereas respiratory sinus arrhythmia is a widely used index of parasympathetic control of the heart, noninvasive measures of sympathetic cardiac control can be acquired through the study of systolic time intervals obtained by means of impedance cardiography. Sympathetic activation has been classically associated with stress, most notably as already mentioned in the work of Walter Cannon on bodily regulation supporting fight-or-flight behavior in response to physical emergencies. As such, indicators of sympathetic cardiac control are of particular interest in the study of stress physiology. As implied by the name, systolic time intervals provide information regarding the left ventricular ejection phase of the cardiac cycle. Myocardial contractility, the force with which the heart contracts, is of particular interest because it is largely under sympathetic control. Though the vagus does have an inhibitory effect on the contractile force of both the atria and ventricles, the effects on the ventricular myocardium are far less pronounced (Berne & Levy, 2001; Levy & Pappano, 1994). Thus, variations in systolic time intervals provide information as to the left ventricle's contractile force and serve as putative indicators of sympathetic cardiac control. Specifically, pre-ejection period (PEP), the period of isovolumic contraction extending from the onset of left ventricular contraction to the opening of the aortic valve, decreases under increased sympathetic drive. That is, as sympathetically driven contractility increases, the pressure required to open the aortic valve is reached more quickly, and PEP is shortened (Newlin & Levenson, 1979; Sherwood et al., 1990). Example impedance cardiograph, more precisely the so-called *dZ/dt* or derivative of the impedance signal, and electrocardiograph (ECG) waveforms used to derive systolic time intervals are illustrated in Figure 37.2. The onset of contraction is identified by the Q-wave of the ECG and the opening of the aortic valve by the B-point or the onset of the rapid upswing in *dZ/dt* that occurs with the ejection of blood from the left ventricle. A second systolic interval, left ventricular ejection time, is also depicted,

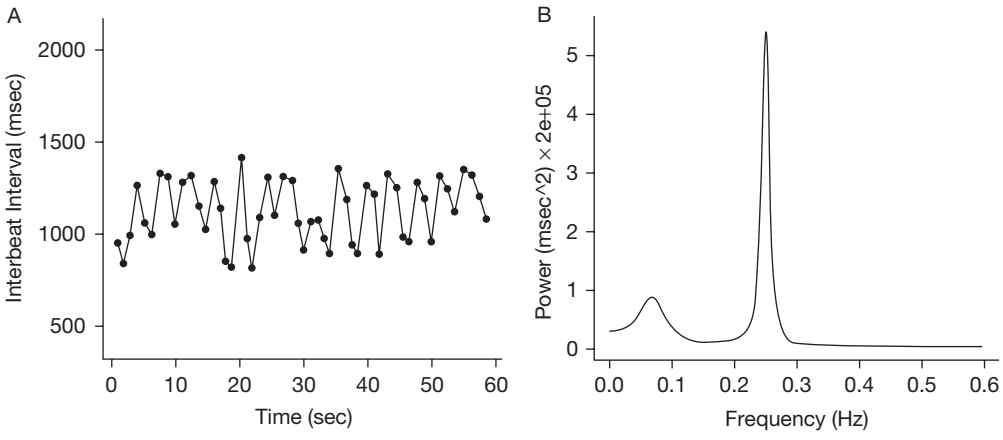

Figure 37.1 ■ A power spectra derived from 1 minute of resting heart rate. Spectral analysis of beat-to-beat variability in interbeat intervals (Panel A) yields power spectra (Panel B) with identifiable power bands corresponding to low and high frequency activity associated with different sources of autonomic influence on heart rate (see text for details).

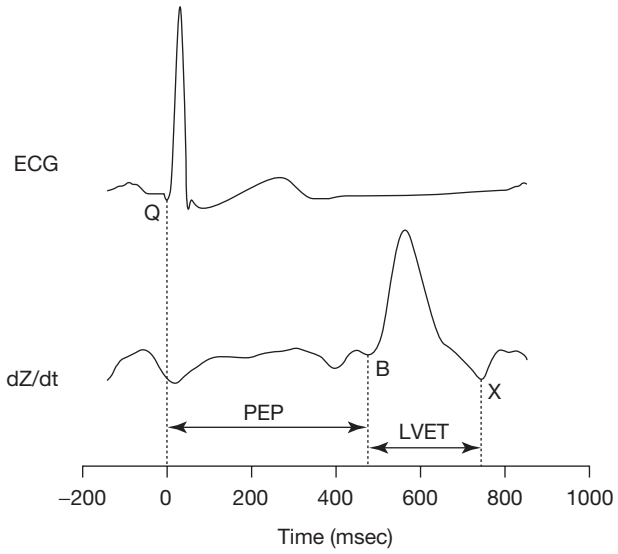

Figure 37.2 ■ The electrocardiograph (ECG) and impedance cardiograph (dZ/dt or derivative of the impedance signal) waveforms used to derive systolic time intervals including the pre-ejection period (PEP) and left ventricular ejection time (LVET) (see text for details).

though this measure is less widely used. Confirming the validity of PEP as a noninvasive measure of sympathetic cardiac control, Cacioppo et al. (1994) conducted a study involving both single and double autonomic blockade in humans and concluded that PEP reflects sympathetic but not parasympathetic influences on the heart.

Overall, a variety of methods for assessing cardiovascular function exists. Variables should be carefully selected with particular attention paid to the feasibility of assessment and to applicable theoretical frameworks. Measurement of vagal and sympathetic outflow can be used to provide important information about the autonomic underpinnings of the stress response. As such, there are many variables to consider when designing an experimental study of stress.

AMBULATORY VERSUS LABORATORY RECORDINGS

The setting in which the recordings will occur is perhaps the most fundamental factor to be considered and is driven largely by the nature of the stress in which the experimenter is interested. Is the stressor under investigation some standardized laboratory task (e.g., mental arithmetic) taking place in a well-controlled laboratory environment, or is it naturally occurring events taking place in the subject's normal environment (e.g., high demand in the workplace)? In either of these environments, a rich array of physiological measures can be recorded and each has its respective advantages and disadvantages. Whereas the more traditional laboratory setting provides a greater degree of experimental control and, perhaps, the broadest range of physiological measures to choose from, field work involving ambulatory recording of physiological function arguably offers greater ecological validity. The opportunity for real life data collection comes at a cost, though, as the natural environment is fraught with potential sources of recording noise such as excessive movement or poor electrode contact. More importantly, various behaviors not necessarily related to stress threaten to confound the interpretation of physiological measures, such as posture changes or caffeine and nicotine consumption, as well as increased metabolic demand due to normal body movements throughout the day. In many cases, these latter, behavioral factors may be partially accounted for by entering them as covariates in the analysis stage of the experiment. For example, hourly or daily self-reported caffeine, nicotine, and alcohol consumption, as well posture and levels of physical activity, are routinely used as covariates in ambulatory studies (Kamarck & Janicki, 2008). More objective estimates of gross motor movements can also be derived from accelerometer recordings. As a means to control for potential confounds of metabolic demand, others have used ambulatory recordings of respiration to calculate the so-called additional heart rate, that is, heart rate above what would be expected due to metabolic demand as estimated by respiratory parameters (Obrist, Black, & Brener, 1981; Wilhelm & Roth, 1998). In more severe cases, however, factors such as movement artifact might obscure the signal of interest altogether, rendering sections of recordings unusable. Until recent decades, the measures employed in ambulatory work were limited by the availability of ambulatory equipment, though there is a trend toward increasing availability of suitable portable equipment and most researchers would be hard pressed to find more than a few cardiovascular or respiratory measures that cannot be measured to some degree in ambulatory settings.

SAMPLING RATE AND RESPONSE CHARACTERIZATION

Upon presentation of a stressor, a cardiovascular response occurs, but how is this defined? The response develops over time and may well be influenced by the state of the cardiovascular system just prior to the stressor. Thus, when considering the collection and processing of cardiovascular measures, it is often helpful to first view the recorded data as a physiological time series, i.e., a series of data points each representing some index of cardiovascular physiology at a discrete point in time. Although time series are typically assumed to have a uniform sampling rate, the frequency with which a given variable is measured (e.g., once a second), this is not always the case with physiological time series. Such time series often measure parameters of irregularly occurring events. For example, the force with which the heart contracts during a single cardiac cycle and the time elapsed between successive

beats both measure aspects of an event that occurs at varying intervals (i.e., the heart beat). An irregular sampling rate may also be due to measures or recording techniques that require variable amounts of time per data point, such as blood pressure measurement via traditional auscultatory or oscillometric methods. Because of the nonuniform sampling rate, it might be more appropriate to refer to such physiological recordings as event series, though the term time series is more widely used, and will suffice here, so long as its use is not assumed to imply a uniform sampling rate. Perhaps the most advantageous effect of adopting the view of cardiovascular data as physiological time series is that it serves to remind us that the physiological response of interest is essentially a time-varying phenomenon that must be adequately sampled and the data processed in such a way as to allow for accurate response characterization. By response characterization we refer to the ability of the recorded data to reconstruct the physiological response of interest accurately.

Although sampling rate is often discussed in relation to frequency-domain time series analyses like those often used to derive heart rate variability power values discussed above (e.g., Gottman, 1990; Lyons, 2004; Warner, 1998), it is equally relevant in a discussion of adequate response characterization. Without an adequate sampling rate, the experimenter may be unable to sufficiently capture the meaningful variance comprising the physiological response of interest. For example, a researcher wishing to examine individual differences in blood pressure reactivity in response to a stressful public speaking task that is 6 minutes in duration may choose to record blood pressure at 3-minute intervals (i.e., at the end of the third and sixth minute). Naturally, the data will allow the researcher to distinguish between subjects with differing blood pressures at the midpoint and end of the task, but no information exists in the recorded data regarding potentially meaningful response characteristics such as rapid changes in blood pressure during the first minute. The sampling rate could be simply too slow to characterize such rapid changes in physiology, and as a result, the researcher may miss potentially meaningful stress-related physiological change. This example is depicted graphically in Figure 37.3 in which a hypothetical blood pressure response curve is sampled at 1- and 3-minute intervals. Note how the two sampling rates result in markedly different response characterizations, specifically how poorly the slower sampling rate is able to reconstruct the first half of the response curve. Continuous (e.g., Fin-a-pres) or semicontinuous (e.g., Vasotrac) blood pressure sampling devices could be used to sample more frequently if such rapid changes are of primary interest to the stress researcher.

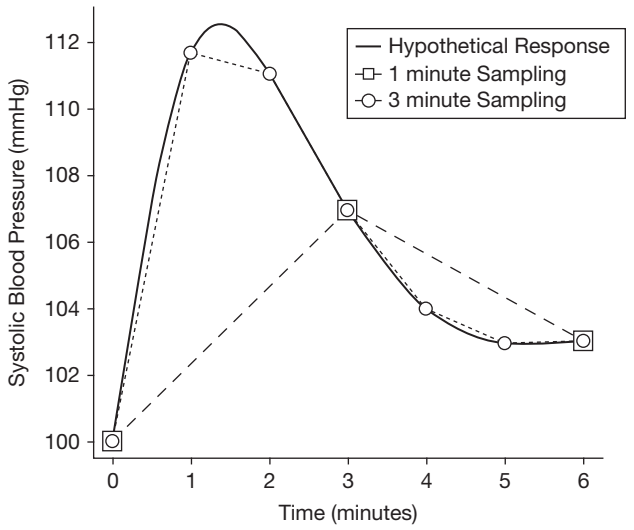

Figure 37.3 ■ A hypothetical blood pressure response curve sampled at 1- and 3-minute intervals results in markedly different response characterizations, with the slower sampling rate providing a poor reconstruction of the first half of the response curve.

The notion of adequate sampling rate is very naturally extended to include early stages of data processing, first and foremost being the size of data epochs into which recordings are typically divided. As a first step of data processing, researchers routinely segment their continuously or intermittently recorded data into smaller, equal length time periods, or epochs. In the same sense that inadequate sampling rates can cause rapidly changing or short-lived physiological responses to be poorly characterized, epoch sizes that are too large can likewise obscure meaningful features of the physiological response. For example, it is known that heart rate recovery following physical or psychological stressors exhibits a rapid and sizeable rebound within the first minute following the cessation of the stressor (Cole, Blackstone, Pashkow, Snader, & Lauer, 1999; Mezzacappa, Kelsey, Katkin, & Sloan, 2001). Figure 37.4 depicts the average heart rate response of 60 subjects prior to, during, and following an orthostatic challenge (i.e., 3 minutes each seated, standing, and seated), which results in a characteristic heart rate acceleration upon standing and can be viewed as a simple physical manipulation to assess heart rate responsivity. Heart rate was derived from a continuously recorded electrocardiogram and averaged across both 30- and 60-second epochs. Although the initial seated and standing periods appear to be characterized equally well by the two epoch durations, the magnitude of the heart rate rebound during the first minute of recovery (highlighted in gray) is drastically underestimated (by 40%) when the longer epoch lengths are used.

The argument can be made that slow sampling rates represent a greater risk than excessively long epochs, as the latter can typically be remedied by reprocessing the data with shorter epochs, whereas nothing can be done to increase the sampling rate after the data has been collected; however, reprocessing data of even modest sample sizes and record lengths can represent significant time investment, and our experience suggests that the further one proceeds down a given data processing stream, the less likely reprocessing with a different

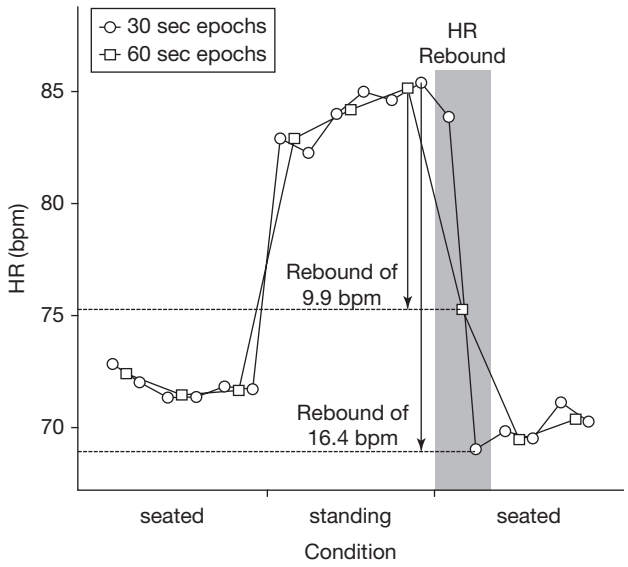

Figure 37.4 ■ The average heart rate response of 60 subjects prior to, during, and following an orthostatic challenge resulting in a characteristic heart rate acceleration upon standing. Whereas the initial seated and standing periods appear to be characterized equally well by either 30 or 60 second epochs, the magnitude of the heart rate rebound during the first minute of recovery (highlighted in gray) is drastically underestimated (by 40%) when the 60 second epochs are used.

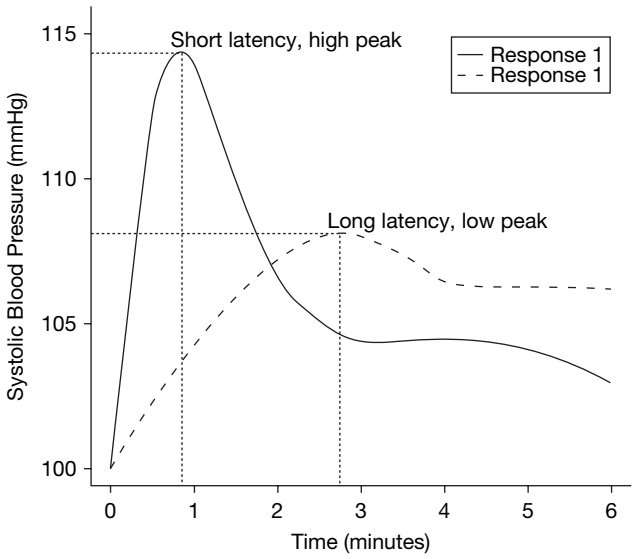

Figure 37.5 ■ Two hypothetical blood pressure response curves with identical mean responses when averaged across the entire recording period but with markedly different peak responses and latency to peak responses.

epoch length becomes. Although various measures of cardiac function may have inherent sampling rates (e.g., blood pressure sampling rates can be limited by equipment restrictions) or may require longer epoch lengths due to signal-processing limitations (e.g., impedance cardiography waveforms are often averaged across multiple cardiac cycles to improve signal to noise ratios), it is generally wise to employ as short an epoch as reasonably possible so as to yield the greatest resolution in the reconstructed response. Note that the unfortunately common practice of simply averaging across the entire duration of a task is analogous to creating a single large epoch, yields the poorest temporal resolution possible, and affords the researcher the fewest options with regard to response characteristics.

Essentially, any characteristic by which individuals might vary in terms of their physiological responses can serve as a useful source of variability in relation to some stressor. Although the mean response is arguably the most commonly used characteristic for cardiovascular measures, other characteristics such as magnitude of maximal response or latency to maximal response may prove to be more informative. For example, Figure 37.5 depicts two hypothetical blood pressure response curves with identical mean responses when averaged across the entire recording period, but markedly different peak responses and latency to peak responses. Use of such measures must be tempered by the possibility that these "extreme" values may have occurred by chance and on retest may regress toward the mean response level. A potentially useful alternative metric less commonly employed in the cardiovascular reactivity literature is area-under-the-curve (AUC). This measure summarizes the information present in the physiological time series by integrating the serial data points of the response curve over time. Pruessner, Kirschbaum, Meinlschmid, and Hellhammer (2003) provide a highly readable discussion of the formulas used in the calculation of both absolute AUC and AUC quantified relative to some reference value such as baseline readings, and Kario et al. (2002) illustrate how such AUC indices can be used to characterize physiological responses. For an additional detailed and mathematically rigorous framework for the quantification of time-varying physiological data, see the discussion of waveform moment analysis by Dorfman and Cacioppo (1990).

On the whole, stress researchers wishing to incorporate physiological responses must ensure that their measures of choice are sampled at a rate that sufficiently captures the physiological response of interest. Similar attention should be paid to preserve the temporal resolution of the response at the data-processing stage via the selection of appropriately small data epochs. It is also prudent to consider how the physiological response of interest can best be characterized through summary measures that allow for the capture of the within- and between-subjects variability present in stress reactivity.

BASELINE ASSESSMENT

One of the most ubiquitous characteristics of psychophysiological studies conducted in laboratory settings is the

baseline recording. Serving as a comparison condition between a participant's engaged and nonengaged physiological state, baseline recordings play a key role in the analysis of physiological change. Two realizations bear upon the importance of baseline recordings. First is the fact that a successful outcome of a study typically hinges on finding that the physiology of the engaged state differs significantly from the physiology of the nonengaged state. Second, which we feel less often fully appreciated, is the fact that the nonengaged state contributes half the variability to this key statistical comparison. For these reasons, the baseline recording conditions should receive the same careful attention to reliability and validity as would the recording from the primary experimental manipulation (i.e., the stressor itself).

Various terms are employed in the literature to label the nonengaged state (e.g., physiological baseline and rest period). We suggested a variant of assessing the nonengaged state that introduced another term, the "vanilla baseline" (Jennings, Kamarck, Stewart, Eddy, & Johnson, 1992). The rationale for the vanilla baseline suggested that a comparison condition was required that had all the aspects of the engaged condition except for the specific process manipulated in the experiment. Contrast this with the fairly common practice of instructing subjects to simply "relax" while baseline recordings are acquired. Such resting baselines do provide a comparison condition, but it is unclear what different participants are in fact doing when they "do nothing." Between-subject variability during the nonengaged period may well increase if some participants do simply relax with little mental activity and others become agitated wondering about the upcoming or preceding experimental period (Jorgensen & Houston, 1989). Our particular version of vanilla baseline asked participants to become engaged in the minimally demanding and presumably minimally stressful task of observing large colored squares on a computer screen that changed colors every few seconds. The participant had merely to count how many times a particular color occurred. The physiological recordings taken during this vanilla baseline condition were then compared with an engaged condition consisting of a cognitive task involving color identification (i.e., the Stroop task; Kamarck et al., 1992). The vanilla baseline performed well in a major epidemiological study of the relationship of cardiovascular responses to stress and heart disease, but we know of no data specifically on whether the test–retest value of reactivity measures based on a vanilla baseline is superior to that based on "resting" baselines (Jennings et al., 2004; Kamarck & Lovallo, 2003).

The nonengaged state should ideally be tailored to the experimental condition to which it will be compared. In the case above, challenging tasks were designed to engage the participants and our vanilla baseline was designed to be nonchallenging while containing many of the elements of our challenging tasks. Our variant of the vanilla baseline may not be ideal for other experimental situations. For example, if the experimental manipulation was recall or imagery of some stressful situation, an appropriate vanilla baseline might be mental imagery of mundane nonstressful moments. Indeed, the simple resting baseline may be appropriate for some questions. We might wish to study the transition from rest to engagement per se. An unfocused relaxed state would be then compared with the reaction when the participant is simply asked "Are you ready to complete the rest of the experiment?" Even so, it might be argued that care should be taken to ensure the induction of an unfocused relaxed state. Various approaches have been employed as a means to induce something of a uniform relaxed state, such as specific relaxation instruction, "easy-listening" music, or relaxing video clips. Obrist et al.'s (1981) early work examining baselines collected on experimental and control days illustrates the importance how resting baselines collected in different way can influence one's results (see also Hastrup, 1986).

One issue that arises when creating a vanilla baseline is the tendency for subjects to find them rather boring. Indeed, in our initial study, a substantial percentage of our participants reported that they would rather have a simple quiet rest period rather than our vanilla baseline task. Although we would continue to argue for the superiority of the vanilla baseline format on the basis of more powerful comparisons with experimental conditions, validity might be threatened if participants truly find the vanilla task truly aversive. As is often the case, pilot testing of your nonengaging condition will likely be required to ensure its suitability.

Another methodological decision to be made regarding baseline recordings is their length. In addition to the near certain presence of individual differences in the time required to reach a stable nonengaged state, different physiological measures may require different amounts of time to reach a truly steady state. Early (and likely current) literature was characterized by substantial variability in baseline period length (Hastrup, 1986). Our work, partially reported by Kamarck and coworkers (Kamarck, Jennings, Stewart, & Eddy, 1993; Kamarck et al., 1992; Kamarck & Lovallo, 2003) clearly suggested that relatively brief (e.g., 5 minutes) nonengaged periods permitted a stabilization of heart rate, but that blood pressure typically required longer periods, often 10–15 minutes.

Despite these problems, some control over your nonengaged periods can be achieved by crafting the engaged and nonengaged periods to isolate the influence of your variable of interest and by minimizing irrelevant individual differences influencing the nonengaged state. In addition to the considerations already discussed, basic factors typically controlled in psychophysiological experiments are the prestudy state of the participants. Most typically, we ask participants to abstain from alcohol and nonrequired drugs for 24 hours and to abstain from heavy

exercise, heavy meals, caffeine, and nicotine for 3 hours or more, prior to participating in an experimental session. Some participant samples require more elaborate screening for various medications that can alter physiological function. Care must also be taken to uniformly reassure participants about the experiment and their safety and to provide uniform and clear instruction about the nonengaged period.

CONSIDERATION OF RECOVERY

Physiological change during the period following stressor exposure, so-called recovery, serves as yet another manner in which cardiovascular measures can detect individual differences in the context of stress research. One would expect that greater stress and possibly disease risk is indicated by the individual showing a more sustained physiological response to stress that fails to return promptly to baseline. Individual differences in recovery have been viewed by many to be particularly meaningful with regard to the effects of stress on the development of physical disease and are believed by some to be at least as important as cardiovascular responding that takes place in the presence of a stressor (Schwartz et al., 2003). Prominent review articles have repeatedly called for greater attention to physiological recovery processes (e.g., Linden, Earle, Gerin, & Christenfeld, 1997; Linden, Gerin, & Davidson, 2003); however, it remains somewhat understudied.

The previous recommendation to consider cardiovascular responses as physiological time series likewise applies to investigations of recovery periods. Numerous characteristics of the recovery curve can be derived, including (a) the latency to recover to prestressor levels, (b) the degree to which a variable returns to prestressor level at the end of a specified period of time, and (c) the degree to which a variable changes from its maximal response during the stressor, again after a specified period of time (Haynes, Gannon, Orimoto, O'Brien, & Brandt, 1991). Unlike studying stress reactivity, where the onset and duration of the stressor can be strictly controlled by the experimenter, recovery is largely driven by factors internal to the individual. The lack of experimental control inherent to the study of recovery results in a number of measurement complications. The truth of the matter is that even during extended time periods, some subjects may exhibit very little recovery, much less return to prestressor levels (Linden et al., 1997). Failure to recover makes measures such as latency to recover problematic as the experimenter is left with choosing between recording a missing data point and entering the maximum time allowed (i.e., the duration of the recovery period), which has the undesirable side effect of creating an artificial ceiling. Application of AUC methods, as discussed in the earlier section on response characterization, can also be applied as a means to quantify recovery processes (Linden et al., 1997). An additional analytic tool that has been particularly applied to the study of recovery is the fitting of curves to the available data points. The general strategy of the curve-fitting approach amounts to estimating a nonlinear model separately for each subject's data using the successive levels of the variable of interest as the dependent measure and the corresponding times as the independent measure. The coefficients resulting from each subject's recovery curves are then used in subsequent analyses and interpreted according to the nature of the fitted model. Data suggests the curve-fitting approach may prove more reliable at estimating individual differences in recovery than simpler methods such as latency to recover or recovery change scores (Christenfeld, Glynn, & Gerin, 2000). For examples of modeling recovery via curve-fitting, see Llabre, Spitzer, Siegel, Saab, and Schneiderman (2004), in which latent growth curve modeling was employed within a structural equation modeling framework, or the summary statistic approach using nonlinear logistic functions used by Christenfeld et al. (2000).

Regardless of the manner in which recovery processes are quantified, it is important to realize the fact that stress reactivity does not occur in lockstep fashion with stress exposure. Rather, physiological recovery is a dynamic process and can serve as a rich source of individual variability for the stress researcher.

ANALYTIC ISSUES

DATA AGGREGATION

How many cardiovascular responses to stress should be collected? There are extensive discussions in the personality literature regarding the benefits of aggregating across multiple observations drawn from single subjects (for reviews, see Epstein, 1979, 1980; Epstein & O'Brien, 1985). Foremost among these benefits is the reduction in random error that accompanies aggregation, ultimately resulting in a more reliable estimate of an individual's typical behavior. Examples of the dramatic increases in reliability observed with aggregation were illustrated in a series of four studies in which a wide array of behaviors (e.g., positive and negative affectivity, physiological measures such as heart rate, and various social behaviors) were collected on consecutive days for a number of weeks. Reliability coefficients were calculated by correlating odd and even days averaged across an increasing number of observations. Practically every variable investigated exhibited a similar pattern of increasing reliability, typically beginning below 0.30 with only 1 or 2 days to 0.80 or even 0.90 when aggregation was extended across an increasing number of observations (Epstein, 1979, 1980).

Despite its potential utility, the aggregation approach has not received widespread use in psychophysiological

research. Commenting on the lack of aggregation in psychology in general, Epstein (Epstein, 1980, p. 798) stated the following:

> It is a well-known principle in test construction that a number of different items which individually have low reliability and validity can be combined into a composite scale which has high reliability and validity. Unfortunately, this principle is often forgotten when items consist of behavior in laboratory or real-life situations rather than responses to paper-and-pencil tests.

This is not to say the aggregation approach has gone entirely unused in psychophysiology and related disciplines. Aggregation has been employed in behavioral medicine research to markedly improve the test–retest reliability of cardiovascular reactivity measures (for reviews, see Kamarck, 1992; Manuck, 1994; Manuck, Kamarck, Kasprowicz, & Waldstein, 1993).

An additional point that merits discussion regarding the aggregation strategy is the need for standardization, both within- and between-subjects, of data prior to aggregation. This serves to ensure that the resulting aggregate accurately reflects within-subject tendencies across tasks. Such standardization is necessary for two specific reasons. First, it is readily acknowledged that individuals vary markedly in both the magnitude and range of physiological reactivity. Such between-subject differences represent a source of error when the topic of interest is the pattern of responding within subjects. Standardization of observations drawn from a single subject by means of a *z*-transform serves to remove irrelevant between-subject variance by forcing each subject's distribution of observations to a mean of zero and a standard deviation of one while still maintaining the integrity of the subject's unique response pattern across tasks. This approach has received widespread use in experimental designs involving multiple measurements (e.g., Jaccard & Wan, 1993) and has been employed in psychophysiological research to account for differences between subjects in overall level of physiological responses such as evoked potentials (Allen, 2002) and skin conductance (Ben-Shakhar, 1985).

The second reason for standardization is the fact that when variables are aggregated in the absence of standardization, they are effectively weighted by their standard deviations such that variables having larger standard deviations have a greater impact upon the resulting aggregate than do variables with smaller standard deviations (Stevens & Aleamoni, 1986). Following standardization, again with a simple *z*-transformation, variables are unit-weighted with respect to their standard deviations and thus contribute equally to the resulting aggregate. This technique has been employed in numerous psychophysiological studies involving aggregation of measures across tasks (e.g., Kamarck et al., 1993; Kamarck et al., 1992), and though the rationale is not always expressly stated, the purpose of standardization in those investigations is to ensure equal weighting of the various component tasks in the final aggregate. Thus, though not a uniform practice in the stress research field, data aggregation is a methodological tool that may enhance the reliability of physiological recordings.

ANALYSIS OF CONTINUOUS VARIABLES

Many of the variables of interest in stress research, be they some physiological response characteristic or an individual difference (e.g., hostility), represent continuous dimensions rather than typologies or classes. Patently ignoring the inherent distribution of such variables, continuous measures are routinely dichotomized in behavioral research. The practice of dichotomization at arbitrary cut points (e.g., the mean or median) has garnered much criticism by methodologists, and there are literally decades of warnings to the contrary. The practice of dichotomization appears to be less common when physiological measures are treated as dependent measures and is more often used to create physiologically based independent measures (e.g., comparing disease risk in "hot' vs. "cold" reactors). In one of its most widely cited criticisms, Cohen (1983) shows that the dichotomization of one variable in a bivariate normal pair results in a 36% reduction in explained variance, and the dichotomization of both variables results in a 60% decrease. Cohen (1983) goes on to equate the decrease in explained variance to a reduction in statistical power "equivalent to discarding one-third to two-thirds of the sample" (p. 253). Subsequent investigations using Monte Carlo methods have illustrated the increased likelihood of Type II errors (concluding that a difference is absent when in fact it is present) when one member of a bivariate pair of variables is dichotomized (MacCallum, Zhang, Preacher, & Rucker, 2002). In addition to the underestimation of the strength of relationships and the loss of statistical power resulting from dichotomization, there is also evidence that when both members of bivariate pairs of independent variables are dichotomized the risk of spurious statistical significance can be quite high, thus increasing the probability of Type I error (Maxwell & Delaney, 1993). Although these arguments against the dichotomization of continuous variables are generated from a largely analytic perspective, they extend to aspects of experimental design as well. At all stages of the research process, from planning to subject recruitment to final analysis, the treatment of continuous variables in a categorical fashion can be viewed as a loss of potentially meaningful information.

The rational for dichotomizing continuous variables is rarely clear, though presumably it is frequently motivated by the desire to analyze the data within an analysis of variance (ANOVA) framework. Our general recommendation in such instances is to instead employ multiple regression to analyze data, using continuous variables in their natural state. Though ANOVA and multiple regression have traditionally been viewed as distinct analytic approaches, ANOVA can actually be viewed as a

special case of multiple regression (Cohen & Cohen, 1983; Pedhazur, 1997). Multiple regression has the added benefit of being applicable to designs involving continuous and/or categorical independent variables and their interactions, as well as the ability to characterize higher order curvilinear effects (e.g., quadratic). On the whole, any data that can be analyzed by ANOVA can be analyzed by multiple regression, though the reverse is not the case.

UTILITY OF MULTIVARIATE STATISTICS

Although, the use of multivariate statistics in studies involving physiological change is completely existent, their use is typically limited. One application is in the service of data reduction by means of procedures such as factor analysis. Another application is the use of multivariate ANOVA (MANOVA) as an attempt to justify subsequent univariate analyses and ostensibly control accumulation of Type I error across multiple comparisons, though the practice is considered ill advised by some (Huberty & Morris, 1989). Beyond these somewhat common uses, the judicious application of multivariate statistics can provide a great deal of information regarding the coordination of multiple response variables and have the potential to significantly inform theoretical models of stress-related physiological change. For example, when the goal is to detect or describe patterns of physiological responding, multivariate tools are almost certainly required because univariate tests (e.g., *t* tests and ANOVA) are insensitive to the coordination of multiple response variables.

One area where these multivariate techniques have proven useful is the study of autonomic specificity of emotion, where the goal has been to determine whether patterned activity within the ANS could reliably distinguish between different affective states. Both the predictive and descriptive applications of discriminant analysis (Huberty, 1994), the former commonly referred to as pattern classification analysis, have proved useful in the study of autonomic changes related to affect (Christie & Friedman, 2004; Kreibig, Wilhelm, Roth, & Gross, 2007; Nyklicek, Thayer, & Van Doornen, 1997; Rainville, Bechara, Naqvi, & Damasio, 2006). Briefly, predictive discriminant analysis involves the generation of classification functions, linear or nonlinear combinations of predictor variables, for each level of some categorical grouping variable (e.g., stimulus condition, gender, and ethnicity). Individual cases are then "blindly" assigned to levels of the grouping variable based upon an input vector of predictor variables. The success of the classification functions, which is taken as evidence of patterned activity distinguishing between groups, is evaluated by testing the percentage of correct classifications against chance levels using a standardized normal test statistic (Huberty, 1994). The descriptive application of discriminant analysis involves the generation of a smaller number of discriminant rather than classification functions and is used to identify dimensions that maximally separate groups in multivariate space. Once identified, the discriminant functions, again, linear combinations of the response variables, permit the computation of group centroids (multivariate group means) that can be plotted against the functions as a means to facilitate interpretation and labeling of the discriminant functions (Huberty, 1994). Considering that the levels of the grouping variable are typically believed to differ in meaningful ways, knowledge of the manner in which they are (or are not) separated within the multivariate space defined by a given set of variables can be quite useful in the context of theory building (e.g., Christie & Friedman, 2004).

Both types of discriminant analysis involve the coordination of multiple variables in relation to some categorical grouping variable. If such a grouping variable does not naturally exist, a researcher might use a technique like cluster analysis to determine if homogenous subgroups are present based upon similarities across multiple response variables (Lorr, 1983). An application of cluster analysis by Allen, Boquet, & Shelley (1991) determined the extent to which individuals' patterned responses to a series of laboratory tasks either were consistent with the group mean response or were largely idiosyncratic. Results suggested that on the whole, subjects exhibited patterns of response that were at least qualitatively similar to the response patterns suggested by the overall mean scores, though this differed somewhat as a function of task. Another application of multivariate statistics employed within- and between-subject variants of factor analysis called chain P-technique to extensively describe individuals' physiological responses by reducing a host of cardiovascular variables into a smaller number of composite factors (Friedman & Santucci, 2003). Results suggested that individual differences in cardiovascular responses can be characterized in terms of both complexity (i.e., the number of factors) and the relative magnitude (i.e., percent variance explained). These are but a few examples of the manner in which multivariate techniques like pattern classification, discriminant function analysis, cluster analysis, and factor analysis might be employed to describe the underlying structure in the data. The presence or absence of patterned physiology in response to a given stressor, the manner in which variables combine to discriminate between groups (e.g., gender) or stimulus conditions (e.g., engaged vs. nonengaged states), or the degree to which subjects exhibit similar or dissimilar response patterns are all inherently multivariate questions and require the appropriate statistical tools.

CAUSAL MODELING OF PHYSIOLOGICAL VARIABLES

A natural extension of the increased multivariate focus advocated above is the description of causal relationships among cardiovascular measures, specifically among indicators that provide information regarding

sympathetic or parasympathetic cardiac control. As discussed in an earlier section, research giving rise to the notion of autonomic space suggests that the sympathetic and parasympathetic branches of the ANS are at least capable of operating largely independently of one another (Berntson et al., 1993; Berntson et al., 1994). A separate line of research involving both invasive nerve stimulation and recording in animals (Levy, 1984; Levy & Zieske, 1969) and noninvasive recording of cardiac autonomic control in humans (Uijtdehaage & Thayer, 2000) has illustrated a complex pattern of interaction between sympathetic and parasympathetic control of heart rate that has been called accentuated antagonism. That is, sympathetic influences have a smaller effect on the heart when parasympathetic influence is simultaneously high than when parasympathetic influence is low. Likewise, parasympathetic influences become progressively more pronounced as sympathetic activity increases. These and other findings have been taken as evidence that parasympathetic influences play the dominant role in the control of cardiac physiology. It is likewise known that parasympathetic influences dominate resting cardiac function (Howard, Gaebelein, Galosy, & Obrist, 1975) and that physiological stress responses are typically in the form of a shift from parasympathetic to sympathetic dominance. However, as the notion of autonomic space suggests, the degree to which the shift toward sympathetic dominance might be driven by withdrawal of parasympathetic influences or simply represents a relatively independent change within the two branches of the ANS remains an empirical question. The answer to this essentially causal question—"Does one branch of the ANS bear greater responsibility for stress-related physiological change?"—would almost certainly have significant theoretical implications in the study of stress, but it has received little attention.

The notion of describing causal relationships among simultaneously recorded time series emerged from the econometrics literature (see Granger, 1969 for the seminal paper in the area) and has been applied to a diverse array of topics ranging from climatology (Mosedale, Stephenson, Collins, & Mills, 2006) to neurophysiology (Pereda, Quiroga, & Bhattacharya, 2005). Despite this, the application of causal modeling has been limited primarily to the physics, physiology, and biomedical engineering literatures with only very recent application to measures of cardiovascular physiology (e.g., Faes, Nollo, & Chon, 2008; Faes, Widesott, Del Greco, Antolini, & Nollo, 2006; Porta et al., 2002). The major approach to causal analysis between two time series is based on whether the prediction of one series can be improved by incorporating information regarding the other. More specifically, if the variance explained by an autoregressive model of the first time series is significantly increased through inclusion of prior measurements of the second series, then the second time series is said to have causal influence on the first (Granger, 1969).

Although causal modeling of physiological time series has not yet been used in the context of stress research, these analytic tools have the potential to significantly advance our knowledge regarding the interrelationships among multiple variables of interest. For example, as was mentioned earlier, changes in blood pressure can be attributed to alterations in any of the physiological parameters that give rise to blood pressure (e.g., increased contractile force of the myocardium or increased resistance in peripheral vasculature). If data regarding each of these parameters are available, causal modeling of the sort described above might be used to identify the underlying determinants of an observed change in blood pressure beyond what might be described by simple correlational analysis. Likewise, the interplay between the sympathetic and parasympathetic branches in controlling cardiac physiology is characterized by complex interactions (e.g., accentuated antagonism) and the possibility for largely independent function (e.g., two-dimensional autonomic space). Although the physiological stress response is typically characterized as a shift from parasympathetic to sympathetic dominance, the complex interrelationship between the two branches makes it difficult to conclusively state whether the shift to sympathetic dominance is due to increased sympathetic control, decreased parasympathetic control, or both. Given the apparent predominance of parasympathetic influences over cardiac control, it is a distinct possibility that the traditional notion of the sympathetic stress response could be illustrated to be largely driven by causal changes in parasympathetic control.

INFERENTIAL ISSUES

CONSIDERATION OF CONFOUNDING PROCESSES

Interpretation of physiological responses would be simplified if we could assume that stress uniformly induced the response. Changes in cardiac and vascular function, however, arise from a multitude of causes other than psychological stress, and valid interpretation requires recognition of these multiple causes. A basic example is change in posture. As mentioned earlier, moving from a seated to standing position results in a transient drop in blood pressure that in turn induces an increase in heart rate (orthostatic reflex). Interpreting the heart rate acceleration as a marker of stress, at least in the traditional notion of stress reactivity, would be misleading. Of course, standing when faced with a stressor might be a realistic response to stress, but standing occurs frequently in the absence of stress and alterations in heart rate due to postural change can confound the interpretation of heart rate in the context of stress research. Subtler threats to the validity of interpretation are changes in muscle tension, movement, and vocal effort (e.g., Tomaka, Blascovich, & Swart, 1994). The coupling between respiration and heart

rate has been discussed above and again suggests that changes in respiratory rate and depth are potential factors that could confound the cardiovascular response to stress. Note how common stress tasks, such as requiring a subject to verbally defend him or herself against a hypothetical shoplifting charge, might readily result in differences between individuals in cardiovascular reactions due in part to respiratory and motor differences rather than to the stress of the speech challenge, per se.

A potentially more interesting concern is that the psychological response to stress itself engages multiple response systems. Stress theorists, such as Richard Lazarus (Lazarus, 1966), have noted that stress likely involves factors such as vigilance toward threat, threat evaluation, selection and activation of coping responses, anxiety related to threat, and affect appropriate to the coping response. Do all of these processes induce the same "stress" response? It seems equally plausible that a different response may be generated by each of these states. Most strikingly, attentive vigilance has been shown to induce a slowing of heart rate even under psychologically arousing conditions (Lacey & Lacey, 1974). Different forms of attentive and cognitive processing have been shown to induce cardiovascular reactions, largely in the absence of apparent stress or affect (for an exhaustive review, see Jennings & Coles, 1991). Emotional responses themselves have also been posited to develop over time, with initial reactions of vigilance and environmental evaluation inducing clearly different cardiovascular responses than later reactions to the arousal and valence qualities of an affective stimulus (Bradley & Lang, 2007). Different emotions also appear to elicit different cardiovascular responses (Gross & Levenson, 1993; Mauss, Levenson, McCarter, Wilhelm, & Gross, 2005), although arguments continue about whether we can determine specific emotions solely from the pattern of change across autonomically controlled response systems. There appear to be many physiological responses within the complex of reactions that are called the stress response.

In sum, given the many sources of physiological change and the complexity of the stress response, physiological changes must be interpreted within the context of the environmental and individual characteristics present during the response. Ideally, investigators should approach the subject of physiological change with a conceptual model of the specific processes (e.g., expression of anger and a resulting physiological response such as increased blood pressure). Research can then be designed to isolate the factor of interest, at least to some degree, and control for other possible factors influencing the cardiovascular response.

INTERPRETATION OF AUTONOMIC INDICATORS

One unfortunately persistent trend in research involving physiological measures is the habit of interpreting measures taken from one physiological system, cardiovascular or otherwise, as indicative of some global bodily state. This practice is often performed under the guise of measuring "physiological arousal," which, presumably, signifies a state of bodily sympathetic predominance. Numerous criticisms of the very notion of physiological arousal exist, perhaps the most commonly cited of which is that the various peripheral, central, and behavioral measures presumed to index arousal fail to consistently covary with one another (Lacey, 1967). The traditional notion that the sympathetic branch of the ANS is involved in predominantly widespread or global physiological adjustments, whereas the parasympathetic branch acts in a more targeted or focal fashion, has likely served to prolong the use of physiological measures as indices of arousal.

The opinion regarding the differing degree of specificity of the two branches of the ANS has persisted for nearly a century and was so heavily influenced by the writings of Walter Cannon (e.g., Cannon, 1915) that it served as a primary tenant of what came to be known by some as Cannon's Functional Doctrine (e.g., Wang, Holst, & Powley, 1995). Although there are a number of structural and neurochemical differences between the two ANS branches, the supposed difference in their ratios of pre- to postganglionic efferent fibers, often referred to as anatomical divergence, was identified as the primary cause for their purported differences in specificity of action or functional divergence (Fulton, 1938). Specifically, the sympathetic branch was described as having greater divergence (i.e., a lower ratio of pre- to postganglionic fibers) resulting in a greater functional divergence. By contrast, the parasympathetic branch was described as having a much lesser degree of anatomical and, thus, functional divergence.

In light of modern research on the anatomical and functional specificity of the ANS, the supposed differences in the divergence of sympathetic and parasympathetic fibers and function are now viewed as drastic overgeneralizations of a small number of flawed neuroanatomical studies. For example, two of the most influential early studies that supporting the notion of differing divergence between the sympathetic and parasympathetic branches were based on extremely limited neuroanatomical sampling because they examined only a single ganglion from each autonomic branch (Billingsley & Ranson, 1918; Wolf, 1941). More complete explorations of autonomic anatomy have since shown that the two branches of the ANS have broad and largely overlapping ranges of pre- to postganglionic fiber ratios and also have demonstrated marked differences across species and within individuals of the same species (Wang et al., 1995). Perhaps most relevant to the present point regarding the interpretation of cardiovascular measures is that even the sympathetic system, the once presumed monolithic effector of physiological arousal, actually operates with a great deal of functional divergence and organ specificity, allowing for a rich patterning of autonomic states in support of behavior and homeostatic reflexes

(Morrison, 2001). One consequence of the realization that both branches of the ANS show a high degree of anatomical and functional divergence is that no physiological measure, no matter how clear its autonomic underpinnings might be, should be taken as an index of autonomic state elsewhere in the body, much less throughout the body as a whole.

NEW DIRECTIONS IN INTEGRATED PHYSIOLOGICAL ASSESSMENT

Although the primary focus of this chapter has been to review a range issues related to the use of cardiovascular measures in the context of stress research, we would remiss if we failed to comment upon the growing literature that places cardiovascular measures at the center of models linking organismic dysregulation and poor health. In particular, measures of heart rate variability, serving as an index of cardiac vagal control, have proved to be predictive of the integrity of a host of the body's regulatory systems. In addition to itself being predictive of poor health outcomes (e.g., Kleiger, Miller, Bigger, & Moss, 1987; Thayer & Lane, 2007), decreased cardiac vagal control has been associated with impaired glucose regulation and diabetes risk (e.g., Liao et al., 1995; Singh et al., 2000), impaired regulation of the hypothalamic–pituitary–adrenal axis (e.g., Thayer, Hall, Sollers, & Fischer, 2006), and immune dysfunction and excessive inflammation (e.g., Janszky et al., 2004; Marsland et al., 2007; Sajadieh et al., 2004; Sloan et al., 2007). The observed relationship between cardiac vagal control and a host of the bodies' regulatory systems and the growing evidence that measures of cardiac vagal control may serve as indicators of inhibitory drive from the central nervous system (Thayer & Lane, 2000) has led to a realization of the importance of inhibitory processes in the regulation of allostatic systems (for a more extensive review of this literature, see Thayer & Sternberg, 2006).

CONCLUSION

Cardiovascular reactions to stress are an integral component of stress research. Evidence now exists showing that these reactions are important predictors of health outcomes. Given this, it becomes important to understand both the physiological and psychological processes underlying cardiovascular reactions. We have discussed techniques for inferring sympathetic and parasympathetic control of cardiovascular responses as well as providing guidelines for the scoring and analysis of cardiovascular measures. We have further urged investigators to relate specific psychological and physiological processes rather than using any general arousal/activation concept. Success in this endeavor will undoubtedly lead to central mechanisms triggered by different forms of stress and triggering not only cardiovascular responses but also immune and endocrine responses.

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38 Neuroendocrine Measures

Ulf Lundberg

INTRODUCTION

Hormones and neural signals are important means of communication between the brain and the rest of the body. Of particular importance is communication between nerves and the endocrine systems (i.e., neuroendocrine activity). The brain sends signals to the body, but the body also sends information to the brain. This means that the brain can regulate activity in the body according to various external demands but also in relation to internal conditions in the body. Thus, psychological, psychosocial, and physical conditions as perceived by the individual are reflected in biological processes, many of which can be measured.

Hormones released into the bloodstream from endocrine glands in the brain, or due to neural stimulation, circulate until they reach specific receptors in the body, through which they act upon various organs and functions. One example of this is the hypothalamic–pituitary–adrenocortical (HPA) axis. The hypothalamus and the hippocampal formation in the brain secrete hormones, which start a cascade of events that in humans ends in the release of cortisol from the adrenal cortex. Another example is the sympathetic adrenal medullary (SAM) system, where the sympathetic nervous system (SNS) stimulates the adrenal medulla to secrete the two catecholamines, epinephrine and norepinephrine. Norepinephrine is also a transmitter substance in SNS. The HPA and SAM systems regulate and influence a number of important bodily functions in response to stress in humans and animals. Examples of such functions are the cardiovascular, gastrointestinal, musculoskeletal, and immune systems. Consequently, epinephrine, norepinephrine, and cortisol are considered the most important "stress hormones," although a number of other hormones are also influenced by stress, but are usually not considered stress hormones.

The amount of stress hormones secreted depends greatly upon the intensity of the stimulation. However, the response of the target organ also depends on the number and sensitivity of the receptors, which may change in response to the intensity and duration of the exposure. Chronic or repeated stress may cause changes in regulatory mechanisms and attenuate or enhance the response of the target organs (Sapolsky, 1998; Rosmond & Björntorp, 2000; McEwen & Lasley, 2002). Thus, measurements of stress hormones such as epinephrine, norepinephrine, and cortisol reflect the intensity of acute stress exposure rather well, whereas the relation between chronic stress exposure and stress hormone levels is more complex.

The stress responses mediated by neuroendocrine activity play an important role by mobilizing resources in the individual that protect the body and increase the individual's ability to cope with various demands (McEwen, 1998; Sapolsky, 1998). These systems have developed slowly during evolution and have contributed to animal and human survival. From a biological perspective, the modern human being is about a hundred thousand years old. It is reasonable to assume that the environmental conditions of so long ago were somewhat different than the challenges humans face today. This could be one reason for bodily responses that have been protective and contributed to survival for thousands of years to cause damage and health problems today under certain conditions. Activity in the two most important stress systems not only serves as a biomarker of stress, but these hormones also form a link between psychosocial stress exposure and various stress-related health problems. As the SAM system and the HPA axis control the most important biological stress responses and have been investigated extensively, this chapter aims to summarize important aspects of measurement of activity in these systems and their role in health. However, it is important to keep in mind that a number of other neuroendocrine functions are also influenced by stress, directly or indirectly, due to factors such as compensatory mechanisms. Examples include the secretion of sex hormones (testosterone, estrogens), growth hormones, and prolactin, to name a few.

RESPONSES TO ACUTE AND CHRONIC STRESS

In an acute stress situation, such as an immediate physical threat, a number of bodily functions are activated by an increase in stress hormone secretion. Heart rate and

blood pressure increase rapidly in response to sympathetic stimulation and elevated catecholamine levels. This means that oxygen, and energy in terms of glucose and lipids, can be transported more efficiently to the working muscles and the brain. There is also a redistribution of blood from the gastrointestinal system, the inner organs, and the skin, in favor of the more important needs of other parts of the body in this acute situation. Glucose and lipids are released from deposits in the liver. The stress hormones also increase coagulability of the blood and reduce pain sensitivity, which decreases bleeding in the case of a wound and makes it possible for the individual to continue to struggle for survival without being hampered by pain. In addition, certain immune functions are activated, protecting the body against microorganisms and contributing to more rapid healing of wounds. An acute increase in the secretion of stress hormones also has mental consequences, in terms of more focused attention on the immediate threat, widening of the pupils, and a better memory of how this threatening situation came about. By remembering how he or she came to be exposed to the threat, the individual has a better chance of avoiding similar threats in the future. It can be seen from this brief description that the series of events that follow increased secretion of stress hormones contributes to protection and survival in a number of different ways.

If the individual is exposed to repeated or chronic stress, or if the stress is extremely intense, regulatory mechanisms may be influenced and some responses may change character and even function in a manner opposite to what happens in response to acute stress. For example, during chronic stress, the immune functions become impaired, memory functions deteriorate, pain sensitivity increases, and performance efficiency is reduced. There is, of course, no sharp line between acute and chronic stress exposure. It is difficult to specify a priori a defining transition point between the two. Moreover, certain stressors combine features of both acute and chronic stress. For example, exposure to the same acute environmental stressor may recur on a chronic basis, or chronic episodes of psychological re-exposure may occur as a consequence of recurrent intrusive thoughts about an acute stressor experienced in the past. Nonetheless, there are cases that are usefully viewed as chronic in which a gradual change takes place over time with stressor exposure of sufficient duration.. The speed of this process may vary considerably due to individual factors such as lifestyle and other stress-reducing or stress-enhancing factors, and in relation to the intensity, frequency, and duration of stress exposure, and the opportunities for rest and recovery.

THE SAM SYSTEM

Sympathetic arousal and catecholamine secretion have been of central interest and importance in stress research since the beginning of the 20th century. Numerous animal and human experiments have illustrated the active defense reaction and the"emergency function" of the adrenal medulla, which increase the organism's chances of survival through "fight-or-flight." Secretion of the catecholamines is regulated by mental influence (from the cortex) on the hypothalamus in the central nervous system, which activates the SAM system. However, bodily responses may also occur without conscious awareness of the threat. For example, activation of amygdala has been registered in response to subliminal stimulation (Liddell et al., 2005). This very rapid "alarm system" is probably of importance for survival in dangerous environments.

Generally, the SAM system is activated when the individual is challenged in his or her control of the environment, and this defense reaction prepares the body for vigorous behavioral activity. The catecholamines do not pass the blood–brain barrier but exert their effects peripherally. In modern society, elevated catecholamine levels are probably more often caused by threats of a social or mental nature than a physical one. As a consequence, bodily responses such as elevated blood pressure and heart rate, high blood lipid levels, and increased blood coagulability are likely to have harmful rather than protective effects, particularly on the cardiovascular system.

The catecholamines also influence the individual's mental and cognitive capacity. In summary, performance efficiency and mental well-being can be described as an inverted-U function of the intensity of stress. Under low or moderate levels of stress and arousal, a further increase in catecholamine output is associated with improved performance, whereas under conditions of very intense stress, additional increases in catecholamine output may cause deterioration in mental functioning and disorganized behavior. The optimal level of performance is located at higher stress levels for simple and routine tasks compared with more complex ones, and varies between individuals depending on personality characteristics, mental state, and so on.

Mental stress is a very potent stimulator of epinephrine output, whereas norepinephrine, as both adrenal hormone and neurotransmitter, and having an important role in blood pressure homeostasis, is more closely associated with physical activity and demands as well as body posture. This means that epinephrine levels may be elevated not only by actual exposure to a stressor but also by the anticipation of future stressful events, as well as by rumination over previously experienced stressful events. In this way, in contrast to animals (Sapolsky, 1998), humans may be exposed to high levels of stress hormones and their concomitant effects on other physiological functions, such as blood pressure, heart rate, muscle tension, and lipolysis, for long periods of time. This may cause a long-lasting imbalance between activation (catabolic processes) and rest/recovery (anabolic processes).

Numerous studies from laboratory experiments as well as natural settings illustrate the sensitivity of the catecholamines to various physical, psychological,

and psychosocial conditions in humans and animals. Catecholamine activation is also known to interact with the other major neuroendocrine stress system, namely the HPA axis and the secretion of cortisol, and form an integrated stress response, which seems to potentiate several health risks including coronary heart disease. Negative emotional stimulation activates, through higher brain centers, the secretion of both catecholamines and cortisol. High epinephrine levels seem to enhance the HPA response and low levels seem to diminish it, and the corticotrophin-releasing factor (CRF), which activates the HPA axis, also seems to stimulate sympathetic outflow.

Lasting elevated catecholamine levels are thought to contribute to the development of atherosclerosis and to predispose individuals to myocardial ischemia. The following mechanisms have been suggested and supported by research: Psychosocial stress will cause an increase in blood pressure and heart rate as well as a release of energy in terms of glucose and free fatty acids into the bloodstream. Frequent or chronic elevation of blood pressure will contribute to structural changes in the arteries, for example, in the coronaries supplying blood to the heart itself (myocardium). High blood pressure will lead to thicker and stiffer walls of the blood vessels and a smaller diameter (lumen) will reduce the blood flow, which will, due to higher vascular resistance, increase the blood pressure even more. A high heart rate and elevated blood pressure may cause damage to the inner walls (endothelium) of the blood vessels, particularly where a vessel branches off. Fatty acids will be built into the walls at these places in the blood vessels and form foam cells in the intima (atherosclerosis). The high level of blood lipids during stress will enhance the atherosclerotic process. A narrowing of the coronary arteries due to thicker walls and atherosclerosis will reduce blood flow to the myocardium. The individual will feel pain (angina) when exposed to physical and mental effort requiring more energy and oxygen to the heart than the blood vessel can transport. Blood clotting (coagulation) will be promoted during stress and, in combination with atherosclerosis, will further increase the risk of a myocardial infarction, that is, a complete obstruction of the blood flow to parts of the heart muscle. Furthermore, atherosclerotic arteries have been found to respond paradoxically to stressful demands by vasoconstriction rather than vasodilation (Harris & Matthews, 2004), thereby further diminishing blood flow to the myocardium.

THE HPA AXIS

The HPA axis is also activated by signals from the brain, via the hypothalamus and the hippocampal formation. The pituitary responds to hormonal signaling by CRF and starts to secrete adrenocorticotropic hormone (ACTH) into the circulation, stimulating the adrenal cortex to secrete cortisol. It takes about 30 minutes after exposure to a stressful situation for the cortisol level to reach its peak. Cortisol affects cellular metabolism and has an important role in controlling the immune system, for example, exerting anti-inflammatory effects. Activity of the HPA system will mobilize energy and prepare the organism for sustained stress exposure.

Whereas sympathetic arousal is viewed as an active "defense reaction" (fight-or-flight), activation of the HPA axis has been characterized as a "defeat reaction" (Henry, 1992). In species living in relatively stable social hierarchies, subordination has been linked to activation of the HPA axis (cortisol or hydrocortisone in primates and corticosterone in rodents) (Sapolsky, 2005). It has been suggested that the HPA axis is influenced by social position in humans as well (Lupien, King, Meaney, & McEwen, 2000), but the SAM system is also likely to be involved (Sapolsky, 2005). Recently, Cohen, Doyle and Baum (2006) demonstrated higher cortisol and epinephrine levels in individuals with low socioeconomic status (SES), defined by income and education, compared with intermediate and high SES individuals. Similar findings have previously been reported for children (Lupien, King, Meaney, & McEwen, 2001), but discrepant results have also been found (Kristenson, Eriksen, Sluiter, Starke, & Ursin, 2004).

Dysregulation or hyperactivity of the HPA axis may contribute to a number of health problems (Sapolsky, 1998). High cortisol levels cause an accumulation of surplus fat in the central region of the body, due to the high density of cortisol receptors on the fat cells there. This is an important energy resource, but free fatty acids are readily released from visceral fat deposits, and this increases the risk of cardiovascular disorders when the energy is not needed for physical activity. This effect of cortisol is very obvious in Cushing's syndrome, a disease characterized by excessive cortisol levels. This causes symptoms such as accumulation of abdominal fat, thinning legs and arms, and a round face. Cortisol also reduces the secretion of anabolic hormones, such as sex and growth hormones, which further contributes to a redistribution of fat to the abdomen (Björntorp, 1996; Steptoe, Kunz-Ebrecht, Brydon, & Wardle, 2004). The role of sex hormones is illustrated in menopause, in which the most important reason for abdominal fat accumulation and thinner hips and thighs in women is the lack of estrogen production. In men, the secretion of testosterone decreases gradually with age, which means that the male and female body shape becomes more similar later in life.

High cortisol levels also increase insulin resistance and contribute to Type 2 diabetes, despite normal or elevated insulin levels. High lipid levels, high blood pressure, and abdominal fat accumulation are key components of the "metabolic syndrome," a condition associated with coronary heart disease and Type 2 diabetes (Rader, 2007), although its designation as a "syndrome" has been questioned (Kahn, Buse, Ferrannini, & Stern, 2005). Moreover, long-term hyperactivity of the HPA axis impairs the immune system and thus increases the risk

of infections (Cohen, 2005) and delays healing processes (Kiecolt-Glaser, Marucha, Malarkey, Mercado, & Glaser, 1995). In addition, high cortisol levels cause memory impairment (episodic memory) through degeneration (dendritic atrophy) of the hippocampal formation in the brain (Sapolsky, 1996). It has also been suggested that cortisol mediates the effect of the intrauterine environment on adult circulatory disease, but evidence is contradictory (Koupil et al., 2005). Dysregulation of the HPA axis and inadequate or blunted responses may induce compensatory overactivity in other systems (McEwen, 1998).

ASSESSMENT OF CATECHOLAMINES

Assessment of catecholamines can be made from blood (usually plasma) as well as urine. A small but relatively constant fraction of the circulating levels of epinephrine and norepinephrine in the blood is excreted into the urine. In general, results from studies based on blood and urine samples are highly consistent, showing significant positive relationships between changes in urinary and plasma catecholamines in response to stress (Åkerstedt et al., 1983).

Blood levels of catecholamines change rapidly (within a minute) in response to stress exposure. Thus, plasma catecholamine levels readily reflect acute stress responses during exposure to short-term stress and have been used extensively in laboratory and animal research. To obtain representative measures of circulating levels of catecholamines in the blood for longer periods of time, frequent sampling using an indwelling catheter is necessary, a technique usually not feasible, for example, in the study of everyday stress. Other problems associated with venipuncture are that norepinephrine concentrations vary between sampling sites because of differences in regional blood flow and reuptake by the nerve endings, and that blood sampling itself may cause increased levels of epinephrine secretion.

The advantages of urinary measurements in the study of people in their natural settings are that they do not interfere with the participant's normal habits and environment and that they cause no harm or pain to the individual. In addition, they provide temporally integrated measurements, which are more relevant in the study of the psychosocial stress associated with many actual life conditions. The measurement of urinary catecholamines is based on the time between urine sampling. Using voluntary voiding, the normal period between urine sampling is 2–3 hours, which means that urinary catecholamines are preferable for the study of relatively long time periods compared with the study of acute laboratory stressors lasting only for several minutes. A typical procedure for studying long-term stress could involve taking urine samples at regular intervals lasting for 24 hours, a number of days, or several weeks (e.g., Cohen et al., 2006).

The amount of urinary catecholamines excreted during a particular period of time can be determined by the concentration of the sample multiplied by the total urine volume. Thus, in the study of urinary catecholamines, the total volume of the sample has to be measured after voiding. In addition, the pH level of the urine should be adjusted to about 3.0 (using acid) to prevent the catecholamines from deteriorating. The acidified urine sample should then be kept frozen (–18°C) until it is analyzed. In cases in which the time between voidings of urine is unknown or the total volume of the sample has not been properly measured, the catecholamine concentration can be related to a reference substance such as creatinine, which is thought to be secreted at a constant rate.

ASSESSMENT OF CORTISOL

Cortisol can also be measured in blood and urine, as well as in saliva. The advantages and disadvantages of using blood and urine measurements are the same as for the catecholamines. For example, blood sampling represents momentary values but may cause stress responses. For urine measurements, time between sampling and total urine volume have to be determined. Cortisol measurement in saliva has many positive features. It serves as a reliable marker of HPA activity in humans and reflects free and physiologically active cortisol. Samples can be obtained within relatively short periods of time, often using a specially manufactured cotton roll stored in a plastic tube (Salivette) that is placed in the mouth for 1–2 minutes. Salivary cortisol is independent of saliva flow, and samples can be kept at room temperature for up to 3 weeks without deterioration (Garde & Hansen, 2005). This makes it possible to ship test tubes containing saliva to a remote laboratory for cortisol analysis.

Recently, methods for determining cortisol in human hair follicles have been described (Ito et al., 2005). This is of potential great interest and importance, making it possible to study cortisol levels retrospectively depending on the length of the hair. As hair grows about 1 cm per month, cortisol levels 4–5 months before the measurements can be determined in 5 cm of hair. This opens new possibilities for studying causal relationships in cross-sectional studies. If this turns out to be a reliable and valid method for measuring cortisol at different earlier points of time, the antecedents of certain slowly developing stress-related conditions, such as occupational burnout, can be investigated.

METHODOLOGICAL CONSIDERATIONS

The catecholamines and cortisol have a pronounced circadian pattern, which has to be taken into consideration in the study of responses to stress. This can be complicated

by the fact that behavioral activity also follows a daily pattern, and can therefore confound the acquisition and interpretation of measures, especially in the case of catecholamines. Under normal night-sleep/day-wake conditions, the catecholamines follow a sinusoidal curve, peaking in the middle of the day and reaching their lowest levels during night sleep. Cortisol levels reach their peak early in the morning, with a sharp decline during morning hours, followed by a small peak after lunch, further reduced secretion in the afternoon, a relatively stable low level in the evening, and a very low level during the night until the individual is about to wake up. Cortisol levels increase rapidly just before the individual awakens. In most individuals, the salivary cortisol awaking response (CAR) is characterized by an increase in cortisol during the first 30 minutes after the individual awakens, followed by a decrease in secretion (Kirschbaum & Hellhammer, 2007; Lundberg & Hellström, 2002). Time of awakening does not seem to matter greatly for CAR, as long as it is regular. If the individual wakes up a few hours earlier than normal, for example, with the help of an alarm clock, the CAR response may be attenuated or disappear completely.

The circadian rhythm of epinephrine remains relatively stable, even during several nights of sleep deprivation, whereas norepinephrine is more influenced by the amount of physical activity (Åkerstedt & Fröberg, 1979). Variations in shift work (Karlson et al., 2006) and frequent east–west flights will disturb the normal circadian rhythm and produce a "flattened" curve of catecholamine and cortisol secretion as well as problems staying alert and sleep disturbances. Consistent changes in the sleep/wake pattern, for example, habitual night work or east–west traveling over 12 time zones, will completely reverse the circadian rhythm of the catecholamines within about a week. Other (nonpsychological) factors that may influence catecholamine and cortisol secretion are the intake of caffeine (e.g., coffee), alcohol, and nicotine (e.g., cigarette smoking), certain medications (e.g., beta blockers, diuretics), and heavy physical exercise.

Epinephrine secretion is particularly sensitive to novel stimulation and stress associated with anticipation. Exposure to the laboratory and the experimental equipment to be used in a study may induce as high or even higher epinephrine levels in the subject than the actual laboratory stressors. This means that catecholamine levels before an experiment usually cannot be used as baselines. The anticipation and novelty effects can be reduced or eliminated by inviting the subject to the laboratory before the experiment to become familiar with the methods of measurement and the equipment to be used. Similarly, at the workplace, the stress induced by the investigation *per se* can be avoided by performing measurements (e.g., urine or saliva sampling) one or several days before the actual data collection to familiarize the participants with all aspects of the study.

In the study of stress and stress hormones, the influence of confounders has to be controlled by requesting that the participants refrain from smoking, drinking coffee, and so on, or by controlling the effects on these hormones by asking the participants to consume the same amount of cigarettes and coffee in the control condition as in the experimental situation. Small or moderate seasonal variations in stress hormones (Hansen, Garde, & Skovgaard, 2001), as well as variations during the menstrual cycle (Abplanalp et al., 1977; Mills et al., 1996), have been reported. However, it is unclear as to what extent sex hormone and mood changes during the menstrual cycle contribute to the variation in stress hormone levels (Davydov, Shapiro, Goldstein, & Chicz-DeMet, 2005). Kudielka and Kirschbaum (2003) concluded that CAR is influenced by health status and awakening time but not by menstrual cycle phase. However, in an earlier study (Kirschbaum, Kudielka, Gaab, Schommer, & Hellhammer, 1999) the same authors reported an effect of the menstrual cycle on salivary cortisol.

Norepinephrine and cortisol levels have also been found to increase somewhat with age (Deane, Chummun, & Prashad, 2002). As related to weight, children have higher levels than adults, but as related to body surface area, the excretion rates are relatively stable from the first years of life into adulthood. Individual variations in baseline levels are pronounced but relatively stable over time. For instance, the highest epinephrine level may be 10 times greater than the lowest one in a random sample of people. For cortisol, even greater interindividual differences have been seen. This variation is likely to be related to individual differences in renal clearance, body weight, and other biological factors, but psychological and psychosocial differences in stress exposure between individuals with high and low baseline catecholamine levels have also been reported (Lundberg, 1984). There are no "normal" levels of catecholamines or cortisol and no established clinical "risk" limits, but clearly pathological levels can be found in association with, for example, pituitary tumors (e.g., Cushing's syndrome). The distribution of cortisol levels (and sometimes also catecholamine levels) in a normal population is usually skewed, and to create a more normal distribution for statistical analysis a logarithmic transformation can be necessary (Cohen et al., 2006).

As a means of reducing the influence of circadian rhythms and individual differences in baseline levels, it is generally recommended that the individual's response to stressful conditions be compared with his or her corresponding baseline level. The two measurements have to be obtained at the same time of day, which means that they must be taken on separate days. By studying the relative change from baseline, rather than absolute levels, the variation between individuals is considerably reduced and statistical power is increased without having to increase the sample size.

Reliable baseline or rest levels can be obtained in situations in which the individual is alone and able to relax completely. In an experimental study this can be achieved by inviting subjects to come to the laboratory

after the experimental session and making sure that they are confident that they will not be exposed to any kind of stressor. To help the subject relax, a quiet environment, light entertainment with music and/or suitable reading material, as well as relaxation training can be used. In studying stress in natural settings, such as the work environment, baseline levels can be obtained by giving the worker a paid day off from work. He or she is then instructed to relax alone at home and avoid any activity that might contribute to stress, such as shopping, cleaning, taking care of children, and performing heavy physical exercise.

Cortisol levels are influenced by certain forms of medication influencing the HPA axis, for example, the intake of corticosteroids (e.g., cortisone), as well as by physical exercise and cigarette smoking. A moderate intake of alcohol does not seem to have any noticeable effects on salivary cortisol (Pruessner et al., 1997), but earlier studies based on urinary cortisol have shown significant increases in cortisol in response to alcohol consumption (Myrsten, Lamble, Frankenhaeuser, & Lundberg, 1979). A possible explanation for these inconsistencies is the amount of alcohol consumed and the conditions under which the studies were performed, for example, whether food intake was allowed or if the participants were exposed to mental stress. Another possible explanation is the effect that alcohol has on the amount of urine excreted (diuresis). A high diuresis or urine volume induced by alcohol intake may contribute to a greater output of urinary cortisol but not necessarily increase blood or saliva levels.

WHAT CAN WE LEARN FROM CATECHOLAMINE MEASUREMENTS?

Epinephrine levels are significantly elevated by overstimulation as well as understimulation, compared with more optimal environmental conditions (Frankenhaeuser, Nordheden, Myrsten, & Post, 1971). This means that work overload, a very high work pace, too much responsibility and role conflicts, as well as simple, monotonous, and repetitive jobs, or lack of meaningful activities (e.g., unemployment, sick leave) may contribute to elevated epinephrine levels. However, as first demonstrated by Levi (1965), epinephrine output reflects the intensity of stress rather than its emotional valence. Intensive pleasant stimulation, such as watching a funny movie, may induce elevated epinephrine levels just as unpleasant stimulation. On a group level, there is usually a strong correlation between the intensity of perceived stress and the epinephrine output (reviewed by Lundberg, 1984).

Epinephrine is very sensitive to mental stress, whereas norepinephrine mainly reflects physical activity and body posture. As a consequence, stress induced by white-collar work (Frankenhaeuser et al., 1989; Lundberg & Frankenhaeuser, 1999) is reflected in elevated epinephrine levels, whereas manual work on an assembly line (Lundberg, Granqvist, Hansson, Magnusson, & Wallin, 1989) or at a checkout counter at a supermarket (Lundberg et al., 1999) is associated with both elevated epinephrine and norepinephrine excretion. In normal daily work, mean eprinephrine levels are elevated about 50–100% compared to non-work days. However, individual differences are pronounced. In response to more intensive stressors, such as public defense of a doctoral dissertation (Johansson, Collins, & Collins, 1983) and childbirth (Alehagen, Wijma, Lundberg, & Wijma, 2005), epinephrine levels may rise 5–10 times above the rest level at the same time of the day.

In conclusion, the catecholamines provide sensitive and reliable measures of psychosocial and physical stress, and data are relatively easy to interpret. Epinephrine secretion from the adrenal medulla reflects the mental arousal induced by various psychosocial conditions, positive as well as negative. Norepinephrine levels, emanating mainly from sympathetic nerve endings, increase in response to physical demands such as manual work, body posture, and physical activity.

WHAT CAN WE LEARN FROM CORTISOL MEASUREMENTS?

Measurement of cortisol in saliva is very convenient and has been used in a great number of studies. A standardized stressor, the Trier Social Stress Test or TSST, has been developed to challenge the HPA axis under controlled conditions (Kirschbaum & Hellhammer, 1989, 2007). However, interpretation of cortisol responses is generally much more complicated than catecholamine responses, and results from different studies are not always consistent.

Daily routine work does not seem to influence cortisol levels greatly (Lundberg, 2005; Pollard, 1995). By contrast, emotionally intense stress combined with physical demands, like that found in parachute jumpers (Ursin, Baade, & Levine, 1978) and women during childbirth (Alehagen, Wijma, Lundberg, Melin, & Wijma, 2001), is associated with a very pronounced increase in cortisol secretion. However, with less consistent results, cortisol secretion has also been related to various work conditions, personality characteristics, mental states such as depression, chronic fatigue, burnout, mood (positive and negative), and SES.

Childbirth has the distinction of being one of the most commonly occurring of those life experiences that are marked by high levels of both physical and psychological stress. Alehagen et al. (2005) measured salivary cortisol and perceived pain and fear in 55 women during childbirth. At the end of labor (full opening of the uterus), mean cortisol levels increased by about 11 times the corresponding level during pregnancy. At the same time, pain and fear ratings reached a peak. Women receiving epidural anesthesia during labor reported less pain and

fear and had an attenuated cortisol response of about 5–6 times the pregnancy level.

With regard to work conditions, Schlotz, Hellhammer, Schultz, and Stone (2004) measured CAR on 6 consecutive days and found that chronic work overload was associated with a stronger increase and higher mean levels of cortisol on weekdays but not on weekend days. Hansen, Persson, Garde, Karlson and Ørbæck (2006) compared diurnal profiles of salivary cortisol on workdays among 40 male construction workers and 118 white-collar workers and found that physically demanding construction work was associated with increased cortisol excretion compared with white-collar work. Klumb, Hoppmann and Staats (2006) examined paid and unpaid work in 52 dual-earner couples with at least one child under 5 years of age and found that more paid work by the individual and his or her spouse tended to be associated with increased cortisol levels, whereas more unpaid work by the spouse was associated with lower cortisol in the individual. Lundberg and Hellström (2002) compared morning cortisol levels in women with different amounts of paid work and found that women regularly working more than 50 hours per week had cortisol levels on the weekend that were twice as high as those of women working less than 50 hours. However, Persson, Ørbæck, Kecklund and Åkerstedt (2006) found that male construction workers who willingly worked 84 hours in 1 week did not differ in cortisol levels from those working 40 hours.

Other research has focused on workers with potentially stressful social characteristics or job situations. For example, Huebner and Davis (2005) investigated 73 gay and bisexual men. They found that being open about their sexual orientation at the workplace was associated with negative affect and higher cortisol levels at work compared with corresponding levels at home. Threat of unemployment, which may have been a factor contributing to the findings of Huebner and Davis (2005), has been linked directly to elevated cortisol levels (Grossi, Åhs, & Lundberg, 1998).

Evidence that personality may influence cortisol reactivity comes from a recent study by Wirtz et al. (2007). Salivary cortisol responses to TSST were examined in 50 middle-aged men. Perfectionism, assessed by the German Version of the Frost Multidimensional Perfectionism Scale, was significantly related to area under the total response curve, a measure of overall hormone concentration.. Overcommitment, a work-related orientation measured by the widely used Effort-Reward-Imbalance Questionnaire, was significantly related to higher morning cortisol response in 197 working men and women from the Whitehall II study (Steptoe, Siegrist, Kirschbaum, & Marmot, 2004).

Depression was examined as a predictor of cortisol activity in a study of 1109 very low-income women reported by Burke, Fernald, Gertler, and Adler (2005). In response to a naturalistic psychological stressor (unexpected arrival of a team of researchers), women with depressive symptoms showed a blunted cortisol response. Chronic exposure to psychosocial stress has also been linked to an attenuated cortisol response (Kristenson et al., 1998). However, Diego et al. (2006) found that 98 women exhibiting psychological distress during pregnancy exhibited elevated cortisol levels during midgestation and lower fetal weight. Similarly, Nierop, Bratsikas, Zimmermann and Ehlert (2006) found that 57 pregnant women developing postpartum depressive symptoms had higher cortisol reactivity to TSST during pregnancy.

Cohen and colleagues have examined SES as a predictor of cortisol activity. Cohen, Schwarz et al. (2006) measured cortisol at wake-up, after 45 min, 2.5 hours, 8 hours, and 12 hours in 781 individuals and found that lower SES (income, education) and being black were associated with a flatter diurnal rhythm (higher evening levels of cortisol). In another study, discussed earlier in this chapter, Cohen, Doyle and Baum (2006) reported that low SES (again based on income and education) was associated with significantly higher 24-hour cortisol and epinephrine levels, compared with individuals with intermediate and high SES.

In some earlier studies, burnout, chronic fatigue, and posttraumatic stress disorder were associated with very low cortisol levels (hypocortisolism) (Yehuda et al., 1996; Pruessner, Hellhammer, & Kirschbaum, 1999), but more recent findings have not always been in agreement (Sonnentag, 2006). For example, Di Giorgio, Hudson, Jerjes and Cleare (2005) found reduced ACTH secretion (full circadian cycle) in 15 patients with chronic fatigue syndrome compared with 10 healthy controls, but no differences were found in cortisol levels. Söderström, Ekstedt and Åkerstedt (2006) found that 9 individuals with high burnout scores had higher awakening cortisol during the workday than during the weekend compared with 11 individuals with low scores. Mommersteeg, Heijnen, Kavelaars and van Doornen (2006) investigated 56 persons with burnout and 38 healthy controls and found that the burnout group showed an increased production of the anti-inflammatory cytokine interleukin-10, but found no differences in cortisol after wake-up. Langelaan, Bakker, Schaufeli, van Rhenen and van Rhenen (2006) compared 29 burned-out, 33 work-engaged, and 26 healthy reference managers in the CAR. Cortisol levels were higher on workdays but did not differ between the groups. However, the work-engaged group showed stronger cortisol suppression in response to the dexamethasone suppression test. Low preoperative cortisol did not predict chronic fatigue syndrome after surgery in 161 patients undergoing selective surgery (Rubin, Hotopf, Papadopoulos, & Cleare, 2005).

Sleep quality has also received attention in research concerning influences on cortisol activity. Microarousals during sleep were found to be associated with elevated cortisol in the morning on a subsequent working day in 10 men and 14 women (Ekstedt, Åkerstedt, & Söderström, 2004), and Gustafsson, Lindfors, Aronsson and Lundberg (2008) found that white-collar workers who did not feel recovered in the morning had higher cortisol levels during the workday compared with those who felt recovered.

These findings take on added significance when one considers that poor sleep quality can at times reflect psychological stress or psychological disorder.

Positive influences that are potential modulators of the effects of stressors have also been studied in research on cortisol activity. Beck, Cesario, Yousefi, and Enamoto (1999) found reduced cortisol levels after choral singing. Khalfa, Bella, Roy, Peretz and Lupien. (2003) compared the effects of relaxing music to those of silence during recovery from a psychologically stressful task in 24 students. The data show that in the presence of music, the salivary cortisol level ceased to increase after the stressor, whereas in silence it continued to increase for 30 minutes. Grewen, Girdler, Amico and Light (2005) found that greater self-reported partner support was related to higher plasma oxytocin in men and women (38 couples, 20–49 years of age) but no consistent relationship was found for cortisol. However, warm contact with their partner (e.g., holding hands) was followed by lower cortisol in both women and men. Hoppman and Klumb (2006) found that goal-furthering activities were associated with positive mood and decreased secretion of cortisol. Steptoe, Brydon and Kunz-Ebrecht (2005) studied financial strain over 3 years in 160 men and women (47–59 years) and found that the CAR was lower in men who reported improved financial strain. Lindfors and Lundberg (2002) and Evans et al. (2007) found that positive psychological well-being was associated with lower cortisol levels in men and women. In an earlier study of 5-year-olds (30 boys and 30 girls) (Lundberg, Westermark, & Rasch, 1993), stimulating activities at a day care center (e.g., interacting with other children, playing games, running, climbing) were associated with reduced urinary cortisol during the day, compared with corresponding home levels. At the same time, activities at the day care center were associated with significantly elevated blood pressure, heart rate, and catecholamine levels, suggesting a dissociation between the response of the SAM system and the HPA axis under the conditions of this study.

In conclusion, there is strong evidence that a very high workload, overcommitment, and perfectionism are related to elevated cortisol secretion. This is likely a normal response by the body to a high demand, which, from a short-term perspective, helps the individual cope and is generally not associated with health problems. However, construction workers willingly working 84 hours in 1 week by their own will did not differ in cortisol levels from those working 40 hours (Persson et al., 2006). This indicates that under some conditions even 1 week of high workload does not influence cortisol levels. Depressive mood, negative affect, and poor sleep are generally related to elevated cortisol levels, but findings are not quite consistent as a blunted cortisol response was related to depression in one study (Burke, Fernald, Gertler, & Adler, 2005). This could be explained by a "flatter" diurnal cortisol curve in depressive patients due to elevated evening levels, as demonstrated earlier by Sachar (1975). In contrast to acute or short-term activation, chronic overactivity or dysregulation of the HPA axis is related to several health problems. Studies on the relation between cortisol and burnout/chronic fatigue are not quite consistent, whereas the relation between positive mood and decreased or even suppressed secretion of cortisol is supported by several studies.

There are several possible explanations for the inconsistent findings with regard to burnout. Cortisol levels on awakening and the CAR are very important indicators. A methodological problem associated with these measures is compliance with the time schedule for saliva sampling among the participants. Because of the rapid changes in cortisol levels in the morning, deviations from the time schedule may have serious consequences on the results and conclusions. Kudielka, Hawkley, Adam and Cacioppo (2007) investigated compliance with ambulatory saliva sampling in the Chicago Health, Ageing and Social Relations Study in participants 50–67 years of age using an electronic monitoring device that recorded the timing of saliva collection. Nonadherence had a significant effect on the CAR, producing a lower level at the first measure, showing that individuals had already passed the morning peak. As noncompliance is likely related to personality and environmental conditions, this could introduce systematic bias into the results.

Another reason for the inconsistent results is that the CAR varies over time in the same individual. Carlsson Eek et al. (2006) explored intraindividual stability of morning cortisol in 75 women and 67 men during 3 workdays and 1 weekend day. Saliva samples were obtained at wake-up, after 30 min and 8 hours, and at 9 pm, and the awakening response was found to be very unstable in single individuals. However, other studies have shown that repeated measurements of morning cortisol under strict control of awakening time seem to indicate rather reliable patterns of HPA activity (Pruessner et al., 1997).

Different measures, such as the magnitude of the response and the pattern of response over time, may give different results (Fekedulegn et al., 2007). The CAR and the difference between morning and evening levels have been of particular interest (Clow, Thorn, Evans, & Hucklebridge, 2004; Gunnar & Vazquez, 2001), but the meaning of changes in these dynamic responses is not clear. Another possible explanation for the inconsistent findings is that chronic stress conditions may have certain effects initially, for example, hypercortisolism (elevated cortisol levels), whereas long-term exposure to stress may cause dysregulation and changes in receptor sensitivity and the release of hormones, possibly leading to hypocortisolism. Depending on the duration of chronic stress exposure and individual differences, results may differ (cf. Rosmond & Björntorp, 2000). The only way to investigate such changes in reactivity pattern over time is with longitudinal studies with repeated measurements, or through the use of hair follicles if this turns out to be a reliable indicator of preexisting cortisol levels.

GENDER DIFFERENCES

Up until 1970, almost all stress studies were performed on men or male animals. However, when gender differences were studied in the early 1970s, men were found to be consistently more responsive to experimental stress than women by showing greater elevations in epinephrine output (Frankenhaeuser, 1983). Although women performed as well or, more often, even better than men on the various stress tests used in the experiments, their epinephrine secretion did not increase much. During more intense (e.g., examination) stress, women's epinephrine output was found to increase significantly, but still to a lesser extent than that of men in the same situation. Studies investigating the influence of estrogen and testosterone on women's catecholamine responses did not support a significant role of sex hormones in catecholamine output (Collins et al., 1982; Lundberg, Hanson, Eneroth, Frankenhaeuser, & Hagenfeldt, 1984; Lundberg et al., 1983).

A possible explanation for these gender differences is that the performance tasks used to induce stress in the laboratory were less challenging to women than to men. In keeping with this, it was found that emotional stress associated with accompanying a 3-year-old to the hospital had a more pronounced effect on the catecholamine levels of mothers than fathers (Lundberg, de Château, Winberg, & Frankenhaeuser, 1981). The importance of gender roles is also illustrated by the fact that women in male-dominated occupations and lines of education seem to respond to performance stress with epinephrine responses similar to those of their male colleagues (Collins & Frankenhaeuser 1978). Recent studies comparing men and women matched for education and occupational levels show similar catecholamine responses to job stress in women as in men, but women's stress levels seem to remain elevated after work also (Frankenhaeuser et al., 1989; Lundberg & Frankenhaeuser, 1999). However, Deane et al. (2002) found lower catecholamine and cortisol levels in female premenopausal nurses compared to male nurses. Although the possible influence of biological factors such as sex hormones on catecholamine responses cannot be excluded, it seems as if psychological factors and gender role patterns are generally more important than biological differences for the variation in catecholamine responses between men and women.

In men, a significant positive correlation is usually found between perceived stress and performance, on the one hand, and catecholamine responses at work, on the other. The more intense or frequent the stress exposure at work, the higher the catecholamine output. In women, however, corresponding relationships are more inconsistent. Stress exposure and catecholamine levels at work seem to "spill over" into nonwork situations. Women with high catecholamine levels at work tend to have high catecholamine levels after work, and women exposed to elevated work stress (e.g., by working overtime) have elevated catecholamine secretion in the evening or during the weekend at home. A likely explanation for this is that there is a greater interaction between the stress from paid employment and that from unpaid work at home for women than there is for men. These gender-related circumstances have to be taken into consideration in the study of women's stress and workload (for a review, see Lundberg, 1996).

Gender differences have also been reported for cortisol. Kirschbaum, Wust and Hellhammer (1992) examined sex differences in cortisol responses to psychological stress (TSST) and to bicycle ergometry until exhaustion. Men had a more pronounced increase in cortisol to psychological stress, but no gender differences were found after bicycle ergometry. It was concluded that the observed sex difference does not reflect an overall lower responsiveness in women, but that sex differences in cognitive and/or emotional responses to psychosocial stress may influence cortisol secretion. Kunz-Ebrecht, Kirschbaum, Marmot and Steptoe (2004) measured CAR on workdays and weekends and found that anticipation of the working day is associated with an enhanced cortisol response, which was larger in women than in men. However, cortisol on awakening did not differ between women and men. Ennes, Kelly and Lambeert (2001) measured urinary cortisol during anticipation of a psychological stressor (academic examination) and found that men making a challenge appraisal had a significant increase in cortisol excretion, whereas women had a decrease. Treatment with an antidepressant noradrenergic compound (reboxetine) induced a significant increase in cortisol in male but not female volunteers (Tse & Bond, 2005).

In summary, gender differences in cortisol, like in catecholamines, seem to depend largely on environmental circumstances, emotional responses, and type of stress exposure.

CONCLUSION

Epinephrine is very sensitive to behavioral, emotional, and cognitive stimulation, and the magnitude of the response seems to be closely related to the intensity of perceived stress regardless of its emotional valence. Norepinephrine is more sensitive to physical demands and body posture. The catecholamines may thus serve as objective indicators of the intensity of mental and physical stress an individual is exposed to. This is generally an appropriate response contributing to protection and survival. However, under certain conditions, such as chronic activation without enough time for rest and recovery, these responses also play an important role in the development of several health problems and, thus, create a link between stress and disease. To obtain valid and reliable measurements, strict control of possible confounders is necessary at all stages of the process—informing and preparing the subjects, determining baselines, collecting,

preparing and storing the samples, performing the hormone assays, and so on.

Cortisol seems to habituate to repeated moderate levels of stress, such as ordinary work. However, chronic high workload, intense emotional stress, pain, and lack of control seem to have a significant effect on cortisol levels. With regard to the effects of chronic stress on the HPA axis, data suggest that a dysregulation may occur. From a short-term perspective, stressful psychosocial conditions seem to create overactivity in this system, without any negative health consequences. Chronic stress, however, may be followed by elevated baseline (and afternoon levels) and an attenuated response to acute stress (Kristenson et al., 1998) and relatively low morning levels (Clow et al., 2004), conditions that are associated with a number of health problems. Pleasant emotional conditions and psychological well-being seem to be rather consistently related to reduced cortisol levels.

Gender differences have been found for stress responses in catecholamine and cortisol output. These seem to depend greatly on psychological factors. Variation within groups of men and women is greater than mean differences between the sexes.

In conclusion, catecholamines are reliable and sensitive indicators of mental and physical arousal. By contrast, the relation between psychosocial conditions, mental states, and cortisol, is more complex. The study of differences in stress hormone levels will likely continue to inform research on stress-related mental and physical disorders. However, greater focus on dysregulation of the neuroendocrine stress systems, involving alterations in circadian rhythms and in other response patterns, would seem to be a more promising approach. Examination of neuroendocrine activity evoked by psychological responses to environmental stressors has been and will remain a key focus in research on human adaptation.

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39 Neuroimaging Methods in Human Stress Science

Peter J. Gianaros and Mary-Frances O'Connor

Life stress can be a gateway to ill health among vulnerable individuals. This stress-related vulnerability is determined by genetic, biobehavioral, and environmental factors that interact over the lifespan to influence individual risk trajectories. Broadly stated, human neuroimaging technology makes available methodological approaches and conceptual frameworks that enable researchers to explicate the neurobiological pathways by which stress-related processes affect health and well-being throughout life. This chapter highlights some of these approaches and frameworks for stress researchers with limited backgrounds in neuroscience, neuroanatomy, and neuroimaging. It focuses specifically on functional and structural aspects of the human brain that relate to the regulation of behavioral and peripheral physiologic response systems that are influenced by short-term (acute) and long-term (chronic) stress processes. To acquaint the reader with basic concepts in the field, we provide a general overview of the most common functional and structural neuroimaging modalities. We also consider how these modalities can be used to answer questions about stress-related neural processes, particularly within the context of their relevance to health. We then summarize experimental design and inferential issues relevant to executing and interpreting neuroimaging studies. Afterward, we provide a concluding overview of neuroimaging studies of specific brain systems that play a dual role in processing stress-related information and regulating biobehavioral stress responses.

OVERVIEW OF NEUROIMAGING MODALITIES AND METHODS

Not all neuroimaging modalities and methods are well suited to addressing every question about stress processes. This is particularly true for questions about the relationships between stress-related neuroimaging variables and markers of health status and risk. Furthermore, as readers of this volume are aware, operational definitions of "stress" vary between investigators from different disciplinary backgrounds (Cohen, Kessler, & Underwood-Gordon, 1997; Eichler, Silverman, & Pratt, 1986). Consequently, varied stress definitions will necessarily influence the particular neuroimaging variables that are measured and the stress-related pathways to health that are emphasized in a given study. Importantly, stress-related processes can be conceptualized and measured at multiple levels of analysis, over multiple time scales, and throughout multiple stages of life in different populations (Monroe, 2008). We adopt the conceptual perspective that stress reflects a transactional process arising from real or perceived environmental demands that are appraised in relation to the adaptive coping resources of an individual (Holroyd & Lazarus, 1982; Lazarus & Folkman, 1984; see Smith & Kirby, chapter 15). We also focus on studies of stress processes measured at the level of brain function and structure among otherwise healthy adults. By extension, we assume that the biological, behavioral, and interpersonal responses that ensue from stress perception and appraisal processes may influence risk for and resilience against ill health (Cohen et al., 1997; Lovallo, 2005a). Critically, we emphasize that the brain is a central mediator of these stress regulatory processes, insofar as distributed brain networks encode, filter, and store environmental information according to unique personal histories and life experiences to determine what is "stressful" to the individual (McEwen, 2007; Dallman, chapter 2). Furthermore, we emphasize that the brain is a central target of stress processes, insofar as stressful experiences can affect brain morphology and functional plasticity through interacting feedforward and feedback mechanisms expressed between the central and peripheral nervous systems (McEwen, 2007).

With these points in mind, we suggest that functional neuroimaging methods are well suited in most instances to study shorter-term (acute) stress processes. For example, functional neuroimaging methods can be used to ask questions about the short-term changes in neural activity associated with (i) perceptions of acute stressors encountered inside of an imaging scanner; (ii) subjective appraisals of one's abilities and resources to cope with the demands imposed by such stressors; and (iii) behaviors and peripheral physiologic responses that are modulated by and interact with stress perception, appraisal, and coping processes. By contrast, we suggest that structural neuroimaging methods are well suited in most instances

to study the putative effect of longer-term (chronic) stress processes on brain morphology.

As illustrated below, however, functional and structural neuroimaging can be combined flexibly in a single study to gather multimodal evidence on aspects of the brain associated with acute and chronic stress processes. Indeed, functional neuroimaging methods could be used to study acute stressor appraisal and responding processes among populations characterized by differing histories of chronic life stress. Similarly, structural neuroimaging methods could be used to assess the relationship between brain morphology and short-term changes in functional neural activity and physiologic reactivity elicited by acute stressors.

FUNCTIONAL NEUROIMAGING METHODS

Several functional neuroimaging methods are available for studying stress processes, including positron emission tomography (PET), functional magnetic resonance imaging (fMRI), single photon emission computed tomography, magnetoencephalography, and near-infrared spectroscopy. These methods have been described in detail in several recommended texts (Buxton, 2002; Cabeza & Kingstone, 2006; Frackowiak et al., 2003; Huettel, Song, & McCarthy, 2004; Jezzard, Matthews, & Smith, 2001; Toga & Mazziotta, 2002). For interested students and researchers, there are also a number of introductory workshops and training institutes on these methods that are regularly announced by the Organization for Human Brain Mapping (http://www.humanbrainmapping.org/). Because of their widespread use and availability, we review the most common functional neuroimaging methods, PET and fMRI. These two methods have advantages and disadvantages with respect to one another, and each can provide unique information about stress-related neural processes.

In general, PET and fMRI differ in their invasiveness to the individual, in their ability to localize ongoing changes in neural activity to particular brain areas (referred to as spatial resolution), and in their ability to resolve the timing of changes in neural activity in relation to a given psychological, behavioral, or physiologic process (referred to as temporal resolution). The power of both methods is that they can quantify interactions between neural activity patterns from distributed brain areas in short periods of time. In this way, PET and fMRI can reveal dynamic changes in the activity of brain networks, as opposed to isolated patterns of activity from disparate brain areas. Importantly, these functional changes in brain networks can be related to wide-ranging cognitive, emotional, behavioral, physiologic, and interpersonal processes important for understanding the neurobiological pathways linking stress and health.

We emphasize, however, that PET and fMRI methods evolve rapidly. Consequently, extensive treatments of these methods in a single chapter would be dated by the time the chapter reaches print. Therefore, we consider key issues involved in PET and fMRI research, and we refer readers to in-depth resources where relevant. Throughout, we emphasize the use of PET and fMRI for indirectly measuring regional increases and decreases in brain activity, conventionally referred to as patterns of brain "activation" and "deactivation," which are complexly determined by changes in brain blood flow, oxygen concentration, and metabolism in areas of neural activity.

POSITRON EMISSION TOMOGRAPHY

Both PET and fMRI quantify regional changes in hemodynamic and metabolic activities that are correlated with changes in neural activity (Raichle, 1998, 2006; Savoy, 2001). Neuroimaging methods using PET provide three-dimensional images of the brain that correspond to quantitative levels of glucose metabolism, oxygen consumption, regional cerebral blood flow, and neurotransmitter receptor-binding potentials during passive (e.g., resting) or active (e.g., task-related) behavioral states. This is done by localizing the emission of positrons from radioactive tracers injected into the bloodstream. With PET, these tracers can be distributed and concentrated differentially throughout the blood vessels supplying brain tissue. In general, PET methods capitalize on these distributional and concentration characteristics to assess levels of brain activity because of the close relationships between cellular (neural) activity, blood flow, and metabolism. The most common PET methods rely on 18-fluorodeoxyglucose (^{18}FDG) and hydrogen-2 oxygen-15 (H_2 [^{15}O]) as injected tracers to measure regional cerebral glucose metabolism and cerebral blood flow, respectively. To localize brain activity patterns, PET data are analyzed using kinetic modeling procedures that estimate the spatial concentration of a particular radioactive tracer. The resulting PET images can then be examined within individuals across experimental periods or between individuals at rest or during task performance as a function of another variable of interest (e.g., as a function of stressor-evoked changes in a measure of peripheral physiologic reactivity). For example, changes in heart rate, blood pressure, heart rate variability, and cortisol (peripheral measures often used in stress science) have been linked to regional cerebral blood flow patterns using PET imaging (Critchley, Corfield, Chandler, Mathias, & Dolan, 2000; Gianaros, Van Der Veen, & Jennings, 2004; Lane, Reiman, Ahern, & Thayer, 2001; Pruessner et al., 2007).

FUNCTIONAL MAGNETIC RESONANCE IMAGING

The biophysical basis of fMRI differs from PET in several ways. With fMRI, short-term changes in neural activity (e.g., on the order of seconds) can be localized without

ionizing radiation or radioactive tracers. Specifically, fMRI localizes neural activity by exploiting the blood oxygenation level–dependent (BOLD) effect, a phenomenon discovered in nuclear magnetic resonance physics (Ogawa, Lee, Kay, & Tank, 1990; Ogawa, Lee, Nayak, & Glynn, 1990; for review, see Raichle, 2006). The BOLD effect is based on the concentration of oxygen in the blood that flows to brain areas in which there is a change in neural activity. More precisely, when the activity of neural tissue increases, blood flow to that tissue will increase to provide a metabolic substrate for cellular activity (Buxton, 2002; Huettel et al., 2004; Logothetis, 2002). However, in areas of neural activity, blood flow will change out of proportion to oxygen consumption. As a result, there is a change in the oxygen concentration within blood vessels supplying that tissue. This change in oxygen concentration can be detected with magnetic resonance imaging (MRI) because the oxygen level in hemoglobin (the protein molecule in red blood cells) changes the extent to which hemoglobin disturbs a local magnetic field. Hence, changes in fMRI BOLD signal intensity reflect changes in the ratio of deoxygenated to oxygenated hemoglobin in the blood supplying particular brain areas. Given that the BOLD effect is dependent on measuring relative changes in oxygen concentration, fMRI studies routinely use task paradigms involving a comparison of brain activity during two or more conditions. These comparisons are then used to quantify relative functional neural changes, which have been labeled as patterns of BOLD "activation" and "deactivation."

From a methodological perspective, it is important to emphasize that the fMRI BOLD signal is subject to many confounding factors, including the dramatic effects of even slight (millimeter) head movements, the compromising effect of cerebrovascular insults on the blood vessels supplying brain tissue, the appreciable decrease in the signal-to-noise ratio in particular areas of the brain that abut air–tissue interfaces (i.e., sinus areas near the ventral orbitofrontal cortex), and the physical movement of the brain that occurs with each breath and heartbeat. Furthermore, one disadvantage of fMRI relative to PET is that it poses challenges to recording concurrent changes in peripheral physiology, which is often a major goal in stress research. This disadvantage stems from several sources. One includes the radiofrequency and electrical artifacts introduced into peripheral recordings (e.g., the electrocardiogram) by the changing magnetic gradients imposed by fMRI scanning. Another disadvantage is that the metallic instrumentation often used for peripheral physiologic recording is not safe in the MRI environment (http://www.mrisafety.com/). However, instrumentation for recording peripheral physiology in the MRI environment is becoming increasingly available, and this instrumentation will better allow for the assessment of electroencephalographic, electrocardiographic, blood pressure, respiratory, and skin conductance measures during fMRI protocols. If such instrumentation is not available to the researcher, then an alternative approach to integrating assessments of peripheral physiology into fMRI stress studies is to have participants perform the same stressor task in an fMRI scanner and in a laboratory setting (or even in a plastic replica of the scanner to emulate the same experimental environment [e.g., laying in the same position within a confined space while being exposed to loud, ~90 dB, noise]).

Notwithstanding these issues, fMRI has several advantages over PET, including the ability to scan the same person over multiple sessions within a short period of time (because of the lack of radiation exposure), the higher spatial and temporal resolution of the BOLD signal, and the relatively lower cost and wider availability of fMRI at most institutions. Indeed, the increasing availability of MRI scanners with higher magnetic field strengths (measured in Tesla units, where 1 Tesla = 10,000 Gauss) will provide unprecedented opportunities for localizing functional and structural aspects of the brain with more precise spatial resolution.

ARTERIAL SPIN LABELING

As noted above, the fMRI BOLD signal indirectly reflects relative changes in neural activity because it reflects interacting changes in neurovascular function and oxygen concentration. In this way, measuring the BOLD signal has at least one disadvantage with respect to PET; namely, it provides a surrogate estimate of neurophysiologic activity. However, by using specialized MRI scanning parameters (referred to as pulse sequences), the quantitative parameter, regional cerebral blood flow, can be estimated with MRI methodology by a technique called perfusion imaging (Detre & Wang, 2002). This technique is gaining increasing use in the field, and it has been applied in neuroimaging studies of stress processes by Wang et al. (2005, 2007). Hence, perfusion MRI is an emerging noninvasive technique that may better capture quantitative changes in regional cerebral blood flow that are more closely related to neural activity and metabolism patterns relevant to stress processes.

STRUCTURAL NEUROIMAGING METHODS

In the following, we focus mainly on functional neuroimaging studies of stress processes. However, as part of PET and fMRI scanning protocols, researchers often collect high-resolution structural images of the brain. For functional neuroimaging studies, structural images are often used to localize changes in brain activity to a single person's unique brain morphology. This is done by co-registering functional and structural brain images before statistical analysis (Buxton, 2002; Huettel et al., 2004). An added data preprocessing step discussed below is to co-register both structural and functional brain images from a single individual to a standardized brain

template or coordinate system, which is referred to as spatial normalization.

In addition to these purposes, high-resolution structural images also provide detailed information about gray and white matter brain tissue that can be analyzed to assess quantitative aspects of brain morphology, including the volume of gray and white matter tissue in different brain areas, the thickness of the cortex across the brain, and the integrity and projections of major white matter fiber tracts. In this way, structural neuroimaging methods can be useful for assessing stress-related variables in association with individual differences in brain morphology. Below, we provide examples of structural neuroimaging methods that have been used in studies of chronic life stress and work examining cardiovascular and neuroendocrine reactivity to acute stressors.

BASIC PRINCIPLES OF FUNCTIONAL NEUROIMAGING STUDY DESIGN AND INFERENCE

In most functional neuroimaging studies, one of the goals is to characterize relative changes in neural activity in specific brain areas when a person performs a behavioral task. A longstanding supposition is that achieving this goal will help explicate the specific brain areas involved in mediating cognitive, emotional, and behavioral processes (Raichle, 1998, 2006; Savoy, 2001). For most PET and fMRI studies, this goal is achieved with a canonical "subtraction paradigm," derived from the work of the cognitive scientist, Donders (1969). Using this paradigm in functional neuroimaging studies involves requiring people to engage in a behavioral task with two or more conditions. One (or more) of the conditions will serve as an active condition of interest, whereas another (or more) will serve as a control condition. In a common approach to the analysis of the neuroimaging data, brain "activation" will be determined by subtracting the control condition from the active condition to compute a so-called "contrast" or "difference" image of neural activity.

For example, an active "stressful" task may require a person to read words reminding her or him of a previous traumatic experience. We are not interested in brain areas engaged by reading words per se. Hence, in a hypothetical control condition, we would require the person to read words that are emotionally neutral and not related to the traumatic experience. With this design, we would determine brain "activation" by subtracting BOLD or PET images of the control condition from those of the active condition to reveal brain activity specifically increased by processing trauma-related words. The assumption here is that brain activity common to word reading in both conditions would be cancelled out by the subtraction procedure.

In addition to assessing "activation," patterns of "deactivation" could also be assessed by subtracting BOLD or PET images of the active (presumptively "stressful") condition from those of the control ("neutral") condition to reveal brain areas in which there were relative decreases in neural activity during the trauma word reading condition. Although the logic supporting the subtraction paradigm has been questioned for years, variants of the subtraction paradigm remain dominant in functional neuroimaging studies (Raichle, 1998, 2006; Savoy, 2001).

Importantly, there are a range of experimental designs in which the subtraction paradigm can be implemented. The most common are blocked and event-related designs (Aguirre & D'Esposito, 2000; Culham, 2006; Donaldson & Buckner, 2001; Rosen, Buckner, & Dale, 1998). In a typical blocked design, two or more task conditions are alternated in blocks or epochs for predefined time periods (e.g., ~15 seconds to ~2 minutes, depending on the neuroimaging modality). For each alternating block, only one task condition is administered. According to the subtraction paradigm logic described above, if the task conditions in a blocked design differ only in the process of interest that are engaged (e.g., processing trauma vs. nontrauma words), then the fMRI or PET signal changes in particular brain areas that differentiate the conditions will presumably reveal patterns of neural activity associated with the process of interest.

Although blocked designs are common, one of their disadvantages is that they present challenges to assessing short-term changes in neural activity (e.g., those occurring within a few seconds after a stimulus is presented or after a behavioral response is made). This has led to the development of event-related designs, particularly in fMRI research (at this time, the temporal resolution in PET imaging is insufficient for event-related designs). In event-related fMRI designs, aspects of brief changes in the BOLD signal can be quantified just before or just after a single stimulus (e.g., the presentation of a word or picture) or a behavioral response (e.g., a behavioral error or a correct response during task performance). In this way, short-term changes in the BOLD signal waveform relative to (subtracted) "control" levels can be assessed and associated with individual difference factors or stimulus or response variables (Donaldson & Buckner, 2001; Rosen et al., 1998). Importantly, these short-term changes in the BOLD signal can reveal considerably more information than the aggregate difference in neural activity between two or more conditions, as determined in blocked designs. However, it is also important to note that fMRI BOLD signal changes are small in comparison with the noise inherent to the signal, resulting in reduced statistical power for event-related designs (Donaldson & Buckner, 2001). Hence, an increasing number of fMRI studies use mixed designs that blend both blocked and event-related features (Mechelli, Henson, Price, & Friston, 2003; Visscher et al., 2003).

RESTING STATE ACTIVITY

In addition to assessing task-related changes in neural activity with blocked and event-related designs, there has been a recent increase in research on the so-called "resting state" patterns of neural activity (for review, see Buckner, Andrews-Hanna, & Schacter, 2008). These resting state patterns can refer to the basal metabolic rate, blood flow, and even statistical correlations (connectivity patterns) expressed within and between different brain areas in an unchallenged (resting) period. Importantly, different brain areas may express different levels of metabolic activity and blood flow in the absence of performing any task, and these metabolic differences can vary as a function of individual differences in a given parameter of interest. For example, Wang et al. (2005) used perfusion fMRI to show that resting blood flow to the anterior cingulate cortex and other areas of the prefrontal lobe was associated with heart rate and cortisol reactions to a subsequent mental arithmetic stressor. This particular finding underscores the important role of resting patterns of brain activity in predicting individual differences in stress reactivity. However, the psychological meaning of these resting state patterns of brain activity in relation to patterns of stress reactivity and health status remains to be determined.

In addition to patterns of resting metabolism and blood flow illustrated above, there has been growing interest in characterizing the statistical correlations between spontaneous fluctuations in resting activity in brain areas that are anatomically networked to one another. This approach has yielded important information about the functionally relevant correlations between activity in brain areas comprising broader regulatory neural circuitries, which may be compromised among individuals with and vulnerable to stress-related psychiatric syndromes, including major depressive disorder (Greicius et al., 2007; Greicius, Krasnow, Reiss, & Menon, 2003; Greicius, Supekar, Menon, & Dougherty, in press). Following conventional nomenclature, statistical correlations between concurrent or time-lagged changes in neural activity (e.g., time-varying oscillations in the fMRI BOLD signal) are referred to as patterns of connectivity (Friston, 1994; Horwitz, 2003; Ramnani, Behrens, Penny, & Matthews, 2004).

INFERENTIAL ISSUES

As discussed earlier, neuroimaging methods offer several approaches to studying patterns of brain activity of interest to stress researchers. Unfortunately, however, there are no universally agreed upon ways to design, analyze, and interpret all types of functional and structural neuroimaging studies. Nevertheless, there are some standards of practice that should be considered. First, when possible, neuroimaging studies should be driven by focused hypotheses targeting specific brain areas or networks of interest. This focus could be based on previous animal or human research on the process(es) presumably supported by the brain area(s) of interest. Questions like "Where in the brain does activity change when people are under 'stress'?" are unlikely to move the field forward in a measurable way. Rather, more focused questions like "Does increased or decreased activity in the hippocampus, which regulates the hypothalamic–pituitary–adrenal (HPA) axis, correlate with changes in the release of the stress hormone, cortisol, when people engage in social stressor task?" (cf., Pruessner et al., 2007) are better suited to defining the neurobiological pathways by which stress processes relate to physical and mental health. Second, careful attempts should be made to control for salient confounders in functional and structural neuroimaging studies. For functional neuroimaging studies of task-related changes in brain activity, this often involves matching control and active conditions of interest along as many stimulus and response dimensions as possible. Importantly, this will support stronger inferences using the subtraction procedure described above. Such control could involve matching conditions (e.g., stressor and nonstressor conditions) in terms of the number of motor responses that are made during task performance, the perceptual and cognitive aspects of the stimuli presented, and the peripheral physiologic recording procedures if they are used (e.g., inflating a blood pressure cuff during both control [nonstress] and active [stress] conditions). Again, it is important to remember that any difference between two conditions in a neuroimaging study will likely be reflected in patterns of brain activity revealed by the subtraction paradigm, only some of which are of interest to the researcher. Other inferential issues in functional neuroimaging research have been detailed elsewhere (Logothetis, 2008; Sarter, Berntson, & Cacioppo, 1996).

Furthermore, for both functional and structural neuroimaging studies of individual differences, it is critical to account for factors that could affect between-person variation in brain activity or morphology. These sources of variation may include patient or health status, age, gender, cognitive functioning, and other factors. For example, when comparing two groups (e.g., those who do and do not report previous exposure to major stressful life events) in terms of their functional neural activation to a stressor, a global difference between the groups in intellectual ability may influence task comprehension and performance, resulting in a confounded group difference in stressor-related brain activation. Furthermore, factors such as age and gender are associated not only with aspects of brain morphology (Coffey et al., 1998; Gur, Gunning-Dixon, Turetsky, Bilker, & Gur, 2002; Raz et al., 1997, 2005) but also with aspects of brain activation under certain stressor task conditions (Wang et al., 2007). Thus, accounting for potentially confounding individual difference factors is critical.

Finally, for functional neuroimaging studies, there are a number of statistical procedures available for (i) making simple comparisons between task conditions or event types; (ii) assessing neural activity patterns that vary according to interactions between task conditions and events; and (iii) computing correlations between changes in neural activity to determine connectivity patterns expressed between brain areas. Similarly, for structural neuroimaging studies, there are an equally large number of statistical procedures to assess aspects of brain morphology in association with individual difference factors. For all of these procedures, it is important to account for the inflated likelihood of observing statistically significant effects by chance alone, given that (i) the brain is a three-dimensional structure necessitating multiple (often mass univariate) statistical tests and (ii) multiple (correlated) measures are often derived from repeated observations of the same person over time, as in the case of functional neuroimaging studies and longitudinal structural neuroimaging studies (Genovese, Lazar, & Nichols, 2002; Nichols & Hayasaka, 2003). Hence, it is routine to use random- or mixed-effects statistical analyses to permit appropriate generalizations to the population and to apply corrections for performing multiple statistical tests across the brain (Friston et al., 1995; Worsley, Evans, Marrett, & Neelin, 1992).

APPLICATIONS OF NEUROIMAGING METHODS IN STRESS RESEARCH

We now consider recent functional and structural neuroimaging studies of stress processes. Brain areas in these studies can be referenced both by conventional neuroanatomical labels and by their spatial location in standard three-dimensional coordinate systems. For these coordinate systems, it is assumed that an individual's brain has been co-registered (also called normalized) to a standard anatomical template. The most common of these are the Talairach and Tournoux and Montreal Neurological Institute template coordinate systems (http://imaging.mrc-cbu.cam.ac.uk/imaging/MniTalairach). Within these coordinate systems, anatomical areas or coordinates are defined and reported with respect to their distance in millimeters from two major white matter fiber tracts, the anterior and posterior commissures.

As a general orientation, spatial coordinates for different brain areas are reported along three planes, as illustrated for the amygdala in Figure 39.1. These planes are usually referred to as sagittal, coronal, and horizontal (or axial). In humans, the sagittal plane cuts the brain along its midline, from left to right. The coronal plane cuts the brain from front (anterior, also called rostral) to back (posterior, also called caudal). The horizontal plane runs parallel to the ground and cuts the brain from top (superior, also called dorsal) to bottom (inferior, also called ventral). By using these planes, anatomical coordinates localizing brain areas are reported in *x*, *y*, and *z* values. *X* values locate areas along the sagittal plane, such that positive values are in the right hemisphere and negative values are in the left hemisphere; *y* values locate areas long the coronal plane, such that positive values are anterior (rostral) and negative values are posterior (caudal); and *z* values locate areas along the horizontal (axial) plane, such that positive values are superior (dorsal) and negative values are inferior (ventral). These values can be seen in figures presented later in this chapter that depict areas of brain activation.

FUNCTIONAL NEUROIMAGING STUDIES OF STRESS PROCESSES

To organize the rapidly expanding neuroimaging literature on stress, it may be helpful to categorize studies according to whether they investigate acute, chronic, or some combination of acute and chronic stress processes. This scheme may be particularly helpful in determining which topical questions about stress processes have yet to be addressed with neuroimaging. To this end, neuroimaging studies of stress may be categorized in the following way. Some have used acute stressor tasks administered inside of an imaging scanner (hereafter called a "scanner stressor") to study short-term stress processes, such as acute stressor-evoked neural or peripheral physiologic reactivity. Others have used neuroimaging designs comparing individuals or groups of individuals defined according to a person's characteristic, possibly reflecting an aspect of chronic or ongoing life stress. Furthermore, both acute scanner stressors and chronic stress groups may be categorized as falling into physical, mental, emotional, or social domains. The following list of "scanner stressors" used to evoke short-

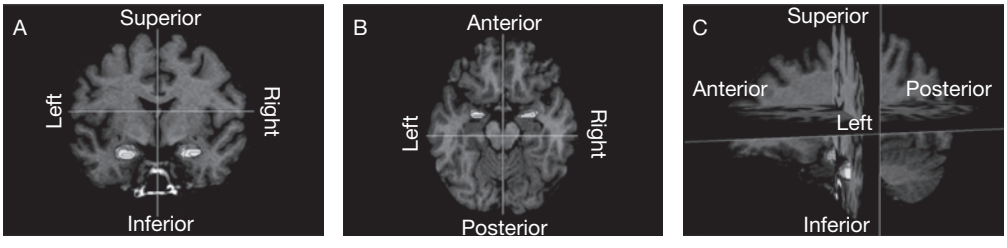

Figure 39.1 ■ The amygdala (highlighted in white) is shown in three spatial planes: **(A)** coronal, **(B)** horizontal (or axial), and **(C)** sagittal. Image provided by Dr. Robert Tamburo. (*See color insert.*)

term changes in stress reactivity in the recent literature is not exhaustive but illustrates this domain-related categorization scheme. Examples of physical stressors include breath holding, yohimbine administration, malodors, and pain (Cameron, Zubieta, Grunhaus, & Minoshima, 2000; Kastrup, Li, Glover, & Moseley, 1999; Schiffman & Williams, 2005; Scott, Heitzeg, Koeppe, Stohler, & Zubieta, 2006). Mental stressors include mental arithmetic with or without social evaluation (Soufer et al., 1998; Wang et al., 2005), unsolvable anagrams (Schneider et al., 1996), and variants of the Stroop color-word interference task (Gianaros, Jennings, Sheu, Derbyshire, & Matthews, 2007; Gianaros, May, Siegle, & Jennings, 2005). Emotional stressors include scripts or pictures of personal stressful life events (Gündel, O'Connor, Littrell, Fort, & Lane, 2003; Sinha, Lacadie, Skudlarski, & Wexler, 2004). Social stressors include social rejection (Eisenberger, Lieberman, & Williams, 2003) or socially evaluative stress (Pruessner et al., 2008). A related set of tasks include tasks designed to measure brain activation during the reduction of stress, such as engaging in biofeedback (Critchley, Melmed, Featherstone, Mathias, & Dolan, 2001), being humored (Watson, Matthews, & Allman, 2007), and performing mindfulness meditation (Creswell, Way, Eisenberger, & Lieberman, 2007) to reduce the experience of stress.

Chronic stress has also been studied in neuroimaging studies and has most often been conceptualized as a characteristic of a person experiencing some form of background or enduring life stress that can range in length and severity along continua. Such sources of life stress could stem from functional medical disorders involving chronic pain or emotional disorders involving persistent psychological distress. Stress-related medical disorders studied with neuroimaging include chronic pain syndromes (Derbyshire, 2003; Williams & Gracely, 2006) and functional gastrointestinal disorders (Drossman, 2005; Hobson & Aziz, 2004; Ringel et al., 2008). Emotional disorders associated with life stress include posttraumatic stress disorder (Bremner, 1999; Nemeroff et al., 2006; Lanius et al., 2004; Tabe, Rauch, Lanius, & Hurley, 2003), major depression (Drevets, 1999, 2000; Phillips, Drevets, Rauch, & Lane, 2003b; Mayberg et al., 2003), clinical anxiety (social anxiety, generalized anxiety, and specific phobias) (Etkin & Wager, 2007), and complicated grief (O'Connor et al., 2008). Other sources of chronic or ongoing social or interpersonal life stress may relate to early life adversity (Bremner et al., 2003; Cohen et al., 2006; Pollak, 2005; Vythilingam et al., 2002) and low socioeconomic status (Gianaros, Horenstein et al., 2007, 2008).

BRAIN SYSTEMS IMPORTANT FOR LINKING STRESS-RELATED PROCESSES TO HEALTH

Much of our understanding of the brain systems that link stress-related social, psychological, behavioral, and physiologic factors to resilience and ill health over the lifespan remains incomplete. Before discussing some of the brain systems that have been most widely studied in human stress neuroimaging research, it is important to emphasize that multiple brain systems act as parallel networks to support a range of "homeostatic" and "nonhomeostatic" functions during stressor processing, which appreciably complicates our understanding of the neurobiological pathways linking stress and health (Soufer, Arrighi, & Burg, 2002). Hence, an exclusive focus on one brain area in isolation of other areas will often lead to oversimplified accounts of the mechanisms linking stress-related factors to particular health outcomes.

The key brain areas anatomically networked to one another that have been studied most often in neuroimaging stress research are referred to as limbic or paralimbic areas, which are also referred to as an integrated system. The development of the concept of a limbic system is widely attributed to Papez (1937, 1995), who described a circuit mediating emotional behaviors, such as emotional expression and feeling (Dalgleish, 2004). Building on the conception of this circuit, MacLean (1949) later modified Papez's definition of the limbic system to include the amygdala. MacLean also suggested a critical role for limbic areas in linking the processing of emotional information to peripheral autonomic and neuroendocrine changes contributing to the pathophysiology of major syndromes of interest to stress researchers (e.g., essential hypertension). Broadly speaking, limbic areas are viewed as networked structures that coordinate behavior with neuroendocrine, autonomic, and immune functions in the service of coping adaptively with emotionally salient environmental stimuli and challenging psychosocial demands that tax an individual's coping resources (Fuchs & Flugge, 2003; Herman, Ostrander, Mueller, & Figueiredo, 2005; Lane, Waldstein, Critchley et al., 2009; Lane, Waldstein, Jennings et al., 2009; LeDoux, 2000; Phillips, Drevets, Rauch, & Lane, 2003; Rolls, 1999).

In the following, we review neuroimaging studies focusing on a set of these anatomically networked limbic areas, including the cingulate cortex, orbital and medial prefrontal cortex, amygdala, hippocampus, nucleus accumbens and related striatal areas, and the hypothalamus. For a more comprehensive treatment and description of these systems within the context of their importance for stress and health, the reader is referred to recent reviews (Lane, Waldstein, Critchley, et al., 2009; Lane, Waldstein, Jennings et al., 2009). In the following sections, we particularly focus, for illustrative purposes, on functional neuroimaging studies of acute stressor-evoked cardiovascular reactivity, because it informs our understanding of the neurobiological pathways that may link stressor processing with cardiovascular reactions implicated in coronary heart disease (CHD) risk. We then review recent functional neuroimaging studies of stress-related neuroendocrine activity also relevant to health outcomes. We conclude with a brief summary of emerging functional and structural neuroimaging studies of chronic stress processes.

FUNCTIONAL NEUROIMAGING STUDIES OF ACUTE STRESSOR-EVOKED CARDIOVASCULAR REACTIVITY

Psychological stress has long been implicated in the development of CHD (Kop, 1999; Rozanski, Blumenthal, & Kaplan, 1999). There are many interacting genetic, environmental, and biobehavioral pathways by which psychological stress may promote CHD risk over the lifespan. One heavily investigated pathway is a person's tendency to show exaggerated cardiovascular reactions to psychological stressors (Krantz & Manuck, 1984). Converging evidence indicates that exaggerated cardiovascular—specifically blood pressure—reactions to acute stressors are associated with CHD risk (Kamarck & Lovallo, 2003; Schwartz et al., 2003; Treiber et al., 2003). However, it is only recently that the neurobiological pathways linking the processing of psychological stressors to blood pressure and other forms of cardiovascular reactivity and CHD risk have begun to be studied and incorporated into integrated theoretical frameworks (Berntson et al., 1998; Lovallo, 2005b; Lovallo & Gerin, 2003). For illustration, we review stress research targeting specific limbic and paralimbic brain systems that may influence cardiovascular, specifically blood pressure, reactivity and risk for CHD.

To begin, stressor-evoked increases in blood pressure result from net changes in cardiac output and peripheral vascular resistance that are mediated by increased sympathetic nervous system activity, suppressed parasympathetic nervous system activity, and increased HPA activity (Obrist, 1981). These cardiovascular, autonomic, and neuroendocrine adjustments are believed to provide metabolic and hemodynamic support for adaptive behavior (e.g., fight-or-flight) (Cannon, 1928; McEwen, 1998; Obrist, 1981; Sapolsky, Romero, & Munck, 2000). Some individuals, however, show exaggerated increases in blood pressure and other types of cardiovascular activity that exceed the metabolic demands of a given psychological stressor (Turner, Carroll, Hanson, & Sims, 1988). These individual differences in stressor-evoked cardiovascular reactions are relatively stable response tendencies (Allen et al., 1987; Gerin, Pieper, & Pickering, 1993; Kamarck & Lovallo, 2003; Llabre, Spitzer, Saab, Ironson, & Schneiderman, 1991; Manuck, Kamarck, Kasprowicz, & Waldstein, 1995) that have been associated with risk for hypertension (Knox, Hausdorff, & Markovitz, 2002; Matthews, Salomon, Brady, & Allen, 2003; Matthews, Woodall, & Allen, 1993; Menkes et al., 1989; Ming et al., 2004), stroke (Everson et al., 2001), and myocardial infarction (Alderman, Ooi, Madhavan, & Cohen, 1990). By extending previous epidemiologic work, recent functional and structural neuroimaging studies have begun to identify some of the brain systems that may centrally link individual differences in cardiovascular reactivity to CHD risk. Specifically, individual differences in blood pressure reactivity have been linked to patterns of activation involving several paralimbic brain areas, including the cingulate cortex, insula, and amygdala. These areas are discussed in the following sections.

CINGULATE CORTEX

The cingulate cortex forms a belt around the corpus callosum. It is broadly viewed to support cognitive, emotional, nociceptive, skeletal-motor, and visceral-motor processes. Regional differences in cellular architecture and projections to and from other brain areas define three putatively distinct functional subdivisions of the cingulate cortex, nominally labeled as (i) a rostral (perigenual) affective division; (ii) a dorsal (supragenual) cognitive motor division; and (iii) a caudal (retrosplenial) evaluative monitoring division (Bush, Luu, & Posner, 2000; Devinsky, Morrell, & Vogt, 1995; Paus, 2001; Vogt, 2005; Vogt, Finch, & Olson, 1992; Vogt, Nimchinsky, Vogt, & Hof, 1995). In addition to supporting cognitive- and emotion-related functions, cumulative evidence implicates each of these cingulate subdivisions in association with stressor-evoked blood pressure reactivity.

The perigenual anterior cingulate cortex (pACC) is believed to support several emotion- and stress-related functions, including the automatic appraisal of salient environmental and personal events, the experience of emotional states, and the regulation of behavioral and autonomic responses to emotional and stressful stimuli (Bush et al., 2000; Critchley, 2005; Paus, 2001; Phillips, Drevets, Rauch, & Lane, 2003a; Vogt, 2005). For example, neuroimaging evidence demonstrates that the pACC is engaged by mood induction procedures (Mayberg et al., 1999), by the presence of distracting emotional information during cognitive task performance (Mohanty et al., 2007), and by committing errors during cognitive tasks (Kiehl, Liddle, & Hopfinger, 2000). Complementing this work, both animal and human findings document an important role for the pACC in supporting stressor-evoked autonomic and cardiovascular reactivity. Such a role for the pACC is instantiated through its reciprocal circuitry with adjacent areas of the orbital and medial prefrontal cortex, anterior insula, amygdala, and areas in the hypothalamus, periaqueductal gray (PAG), pons, medulla, and the presympathetic intermediolateral cell column of the spinal cord (Barbas, 2000; Barbas, Saha, Rempel-Clower, & Ghashghaei, 2003; Buchanan & Powell, 1993; Critchley, 2005; Vogt, 2005). As such, the pACC—along with networked areas of the dorsal and posterior cingulate discussed next—may provide for an interface between automatic stressor appraisal processes and concurrent cardiovascular control. Supporting the view that the pACC is functionality associated with stressor-evoked blood pressure reactivity, greater stressor-evoked pACC activity across individuals has been associated with larger-magnitude blood pressure reactions to a variant of a Stroop color-word interference stressor (Gianaros et al., 2005, Gianaros, Jennings, Sheu et al., 2007, Gianaros, Sheu et al., 2008). Furthermore, there

is parallel structural neuroimaging evidence that individuals with reduced gray matter volume in the pACC also show larger-magnitude blood pressure reactions to the same stressor (Gianaros et al., 2008; Figure 39.2).

Areas in the dorsal anterior cingulate cortex (dACC) are broadly viewed as supporting processes related to attention, effortful executive control, and conflict and error monitoring. These processes are instantiated by reciprocal circuitry with the lateral prefrontal cortex, motor and supplementary motor cortex, and posterior parietal cortex (Vogt & Pandya, 1987). A conventional view is that dACC areas monitor for conflicts between competing streams of incompatible information, which foster the potential for behavioral error (Botvinick, Braver, Barch, Carter, & Cohen, 2001; Holroyd & Coles, 2002; Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004). After conflict detection, dACC areas engage prefrontal, motor, and parietal cortices to resolve conflicts and minimize behavioral error by modulating attention, working memory, and motor control processes (Paus, 2001). Growing evidence also implicates dACC areas in emotion-related processes associated with physiologic reactivity and subjective distress. For example, dACC areas are engaged by states of pain-related anxiety (Ochsner & Gross, 2005; Vogt, Berger, & Derbyshire, 2003), intentional regulation of autonomic activity (Critchley et al., 2002), and awareness of subjective emotional experiences (Lane et al., 1998). Hence, Critchley (2005) posits that the dACC may be particularly important for generating autonomic and cardiovascular responses via projections to subcortical areas to support volitional, cognitive, and emotional behaviors. Consistent with this view, stressor-evoked blood pressure reactivity has been shown to covary with heightened dACC activation (Critchley et al., 2000; Gianaros et al., 2005).

The posterior cingulate cortex (pCC) is believed to support evaluative processes related to cognition and emotion, including (i) maintaining a general representation of the environment; (ii) gauging the emotional salience of environmental events; and (iii) monitoring the environment for threatening stimuli (Gusnard, Raichle,

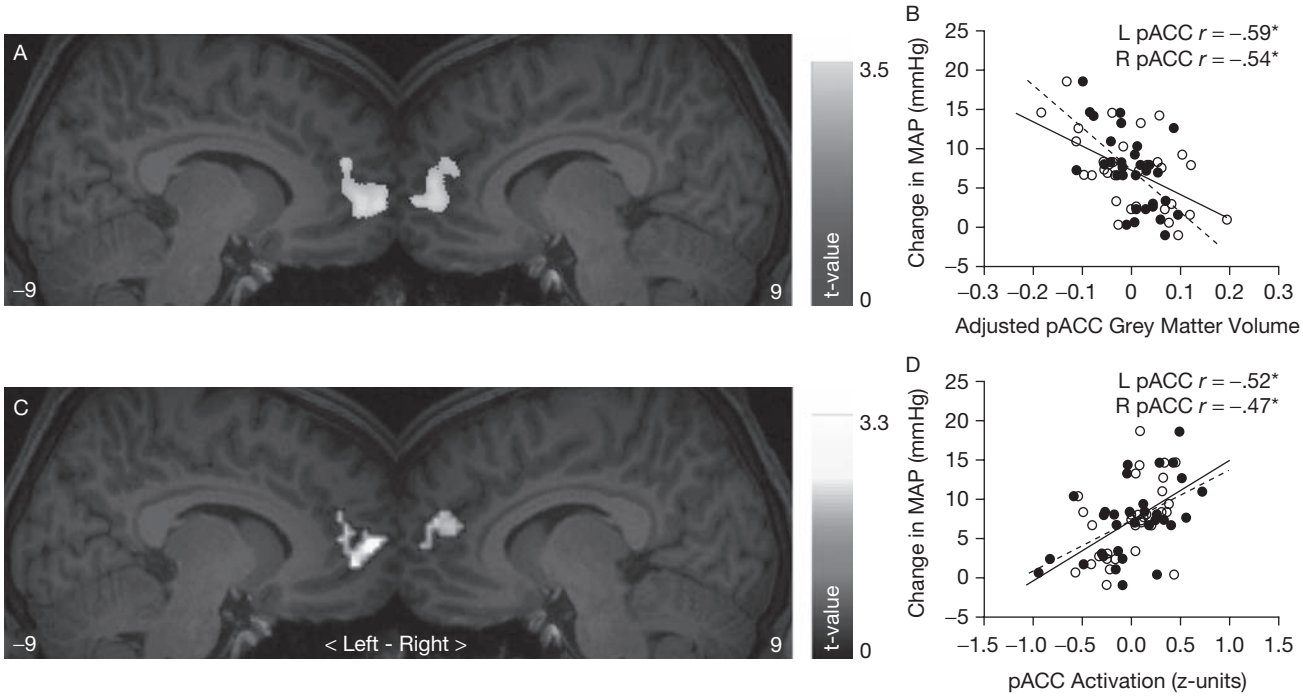

Figure 39.2 ■ Mean arterial pressure (MAP) reactivity to a Stroop color-word interference stressor is shown as a function of gray matter volume and fMRI BOLD activation in the prefrontal cortex, encompassing Brodmann area (BA) 32 of the perigenual anterior cingulate cortex (pACC) and BA 10 of the medial prefrontal cortex. **(A)** Statistical parametric maps derived from a random-effects analysis illustrating left and right pACC areas where MAP reactivity varied with gray matter volume (determined by voxel-based morphometry). **(B)** MAP reactivity is shown as a function of mean-centered and sex- and total-grey matter adjusted volume values extracted from the left (L, open circles, dashed line) and right (R, closed circles, solid line) pACC areas shown in A. **(C)** Statistical parametric maps illustrating left and right pACC areas where greater MAP reactivity varied with greater BOLD activation **(D)**, MAP reactivity is shown as a function of mean-centered and standardized pACC BOLD activation values extracted from the left (open circles, dashed line) and right (closed circles, solid line) pACC areas in (c). *$p < 0.01$. Reprinted with permission from Gianaros, P. J., Sheu, L. K., Matthews, K. A., Jennings, J. R., Manuck, S. B., & Hariri, A. R. (2008). Individual differences in stressor-evoked blood pressure reactivity vary with activation, volume, and functional connectivity of the amygdala. *Journal of Neuroscience, 28*, 990–999. (*See color insert.*)

& Raichle, 2001; Maddock, 1999; Vogt & Laureys, 2005;). These processes are supported primarily by reciprocal circuitry between the pCC, pACC, and parahippocampal cortices (Vogt & Laureys, 2005). In support of its putative role in evaluative processing, a meta-analysis (Maddock, 1999) implicates the pCC in association with the automatic processing of unpleasant, particularly self-relevant, emotional stimuli. Although the pCC broadly lacks direct connections with preautonomic and cardiovascular regulatory brain areas, several neuroimaging studies demonstrate that stressor-evoked autonomic and cardiovascular reactions are associated with pCC activity. For example, individuals classified as stable and high-blood pressure reactors show enhanced pCC activation to a Stroop color-word stressor compared with their less reactive counterparts (Gianaros et al., 2005). Furthermore, resting levels of high-frequency heart rate variability, an indirect indicator of cardiac parasympathetic activity linked to cardiovascular disease risk, has been associated with BOLD activation to grief-related stimuli among bereaved individuals (O'Connor et al., 2007). These findings are noteworthy because the pCC may support the evaluative processing of psychological stressors. In turn, such processing may indirectly influence autonomic and cardiovascular activity via connections with pACC and dACC subdivisions, which do project to areas directly involved in autonomic and cardiovascular control (Gianaros et al., 2005; O'Connor et al., 2007).

INSULA

The insula is located in the Sylvian fissure and is hidden beneath the frontal, parietal, and temporal opercula. Broadly, the insula—particularly the anterior division—expresses efferent and afferent connections that parallel those of the anterior cingulate, including connections with the amygdala, hypothalamus, thalamus, PAG, pons, nucleus tractus solitarius (NTS), and medullary and brainstem areas that control preautonomic nuclei innervating peripheral target organs (Augustine, 1996; Cechetto, 1994; Ongür & Price, 2000; Verberne & Owens, 1998). Furthermore, afferent relays from all peripheral target organs project to the insula along a caudal-to-rostral extent. These afferent projections are routed via the parabrachial nucleus, ventral posterior and mediodorsal thalamic nuclei, and lateral hypothalamic area, and they provide the insula with a "viscerotopic" map of the body (Craig, 2003, 2005). Such a map has been posited to support the integration of interoceptive information with the appraisal of emotion-related stimuli and contextually adaptive behavioral and autonomic responses (Craig, 2005; Critchley, 2005; Paulus & Stein, 2006). Similar to areas of the cingulate, the insula—particularly the anterior division—is engaged by behavioral challenges that elicit errors (Klein et al., 2007) and by unpleasant emotional stimuli (Feldman-Barrett & Wager, 2006; Phan, Wager, Taylor, & Liberzon, 2002). Longstanding animal evidence further implicates the insula in cortical cardiovascular control via efferent and afferent signaling with networked cortical and subcortical areas important for autonomic regulation (Cechetto, 1994; Oppenheimer, 1993; Verberne & Owens, 1998). Consistent with this evidence, insula activation has been reliably associated with stressor-evoked blood pressure reactivity in several studies (Critchley et al., 2000; Gianaros et al., 2005, 2007, 2008).

AMYGDALA

The amygdala is composed of distinct cell groups in the medial anterior temporal lobes. As a cell complex, a critical function of the amygdala in stressor-related processing involves the rapid assignment of emotional salience to environmental events (Davis & Whalen, 2001; LeDoux, 2003; Sah, Faber, Lopez De Armentia, & Power, 2003; Zald, 2003). The amygdala supports such processing by integrating multimodal sensory inputs from distributed cortical, thalamic, and brainstem afferent relays. More precisely, sensory input is relayed through thalamic and cortical-thalamic pathways to the basolateral area via the lateral nucleus, basolateral nucleus, and accessory basal nucleus (LeDoux, 2003; Sah et al., 2003). From the basolateral nucleus, motivationally relevant sensory signals are relayed to the central nucleus. As a primary output nucleus, the central nucleus signals commands for adaptive changes in behavior and supporting physiologic adjustments via the stria terminalis to lateral and paraventricular hypothalamic nuclei and to periaqueductal, medullary, and preautonomic nuclei. Importantly, the central nucleus is also networked with cortical areas involved in stressor-related processing, principally, areas of the pACC, dACC, and anterior insula (Amaral & Price, 1984; McDonald, 1998; Morecraft et al., 2007; Price, 2003). Hence, the amygdala is broadly viewed to interrelate cortical processes supporting the coordination of stressor-evoked changes in behavior and peripheral physiologic (e.g., cardiovascular) reactivity (Berntson et al., 1998; Dampney, 1994; Saper, 2002; Smith & DeVito, 1984; Smith, DeVito, & Astley, 1984). In this context, it is noteworthy that a specific pathway by which the amygdala can regulate blood pressure reactivity is via its influence over the baroreflex (Berntson et al., 1998; Dampney, 1994; Saha, 2005).

The baroreflex is a negative feedback control mechanism that constrains mean arterial pressure around a regulatory set point. Specifically, the baroreflex controls beat-by-beat changes in blood pressure by adjusting heart rate, cardiac output, and vascular resistance. As a negative feedback loop, the baroreflex relies on afferent projections from cardiopulmonary mechanoreceptors and chemoreceptors that signal changes (e.g., increases) in blood pressure to the NTS. Afferent activation of the NTS in turn activates vagal nuclei in the medulla and, via signaling with the caudal ventrolateral medulla, inhibits presympathetic nuclei in the rostroventrolateral medulla

and intermediolateral column. In effect, these dynamic changes in autonomic control adjust heart rate, cardiac output, and vascular resistance to maintain blood pressure within a homeostatic range (Dampney, 1994).

As shown in the conceptual model of blood pressure reactivity depicted in Figure 39.3, the amygdala can gate the baroreflex via projections that inhibit the NTS and that activate the rostroventrolateral medulla (Berntson et al., 1998; Dampney, 1994; Saha, 2005; Saper, 2002). These projections are routed partly through the hypothalamus, PAG, and dorsal pons. Important in the present context, these amygdala projections are paralleled by similar projections from the anterior cingulate and insula, which can also gate the baroreflex on exposure to acute stressors, allowing blood pressure to exceed its regulatory set point (Berntson et al., 1998; Dampney, 1994; Saper, 2002). Furthermore, it has been hypothesized that the amygdala and networked cortical areas may partly underlie individual differences in cardiovascular reactivity by linking stressor-related processing with mechanisms such as baroreflex suppression (Berntson et al., 1998). Consistent with this idea, there is both recent PET (Critchely et al., 2000) and fMRI (Gianaros, Sheu et al., 2008) evidence that stressor-evoked amygdala activity covaries with blood pressure reactivity (Figure 39.4).

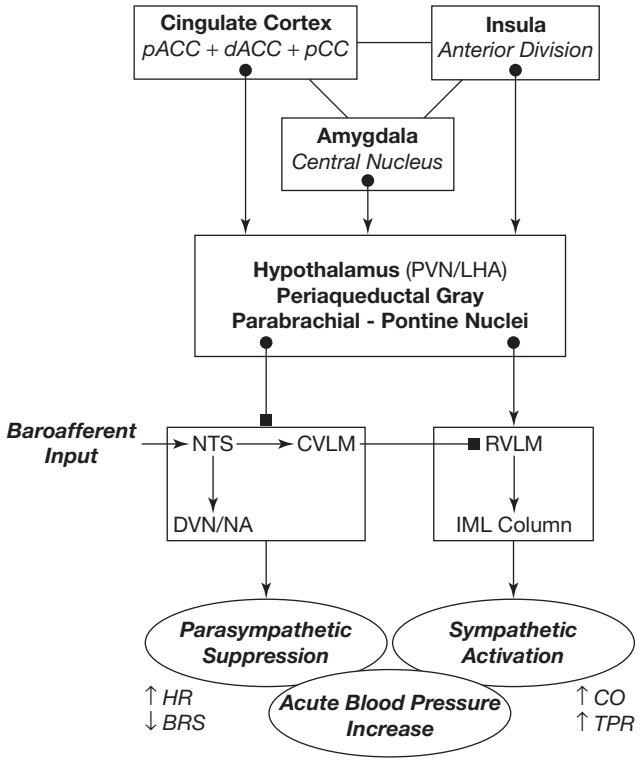

Figure 39.3 ■ Conceptual model of brain systems wherein the differential processing of stressor-related information may relate to the expression of individual differences in stressor-evoked blood pressure reactivity. Although the model is anatomically incomplete, key areas implicated by animal and human evidence are included. PVN, paraventricular nucleus; LHA, lateral hypothalamic area; NTS, nucleus tractus solitarius; DVN, dorsal vagal nucleus; NA, nucleus ambiguous; CVLM, caudal ventrolateral medulla; RVLM, rostral ventrolateral medullary; IML, intermediolateral cell column; HR, heart rate; BRS, baroreflex sensitivity; CO, cardiac output; TPR, total peripheral resistance. Blocked endpoints denote inhibitory influences; arrowed endpoints denote excitatory influences. From Gianaros (2008). (cf., Berntson et al., 1998; Dampney, 1994; Saha, 2005; Saper, 2002).

In addition to these functional associations between individual differences in stressor-evoked cardiovascular reactivity and patterns of brain activation, there is recent structural neuroimaging evidence to suggest that cardiovascular reactivity is associated with clinically relevant patterns of brain morphology. For example, Waldstein et al. (2004) reported that exaggerated stressor-evoked increases in blood pressure are associated with markers of subclinical cerebrovascular disease in white matter brain tissue among older individuals, suggesting a potential role for cardiovascular reactivity in disease vulnerability processes measured at the level of gross brain structure.

In aggregate, these functional and structural neuroimaging studies suggest that limbic brain areas, including the cingulate cortex, insula, and amygdala, may be involved in linking stressor-related processing with forms of cardiovascular reactivity, such as stressor-evoked blood pressure reactivity, that may promote CHD risk among vulnerable individuals. An important direction for future work will be to test whether individual differences in the functionality of these brain systems directly predict CHD endpoints or aid in CHD risk stratification or prevention.

NEUROIMAGING STUDIES OF NEUROENDOCRINE ACTIVITY

CORTISOL

The HPA axis is another major arm of the peripheral stress response system that has been increasingly studied in neuroimaging research, particularly among individuals with stress-related psychiatric disorders such as posttraumatic stress disorder (Liberzon et al., 2007) and among healthy individuals (Eisenberger et al., 2007; Kern et al., 2008; Pruessner et al., 2005, 2007; Urry et al., 2006). As detailed by Lundberg (chapter 38), several endpoints of the HPA axis can be measured reliably. In particular, cortisol can be measured as it changes from pre- to post-stressor periods and as it varies over the course of the day. As illustrated below, individual differences in the functionality of several limbic brain systems discussed above have been linked to both acute (stressor-evoked) and circadian (diurnal) changes in cortisol.

For example, Urry et al. (2006) combined the measurement of diurnal cortisol changes with an experimental paradigm involving emotion regulation. In

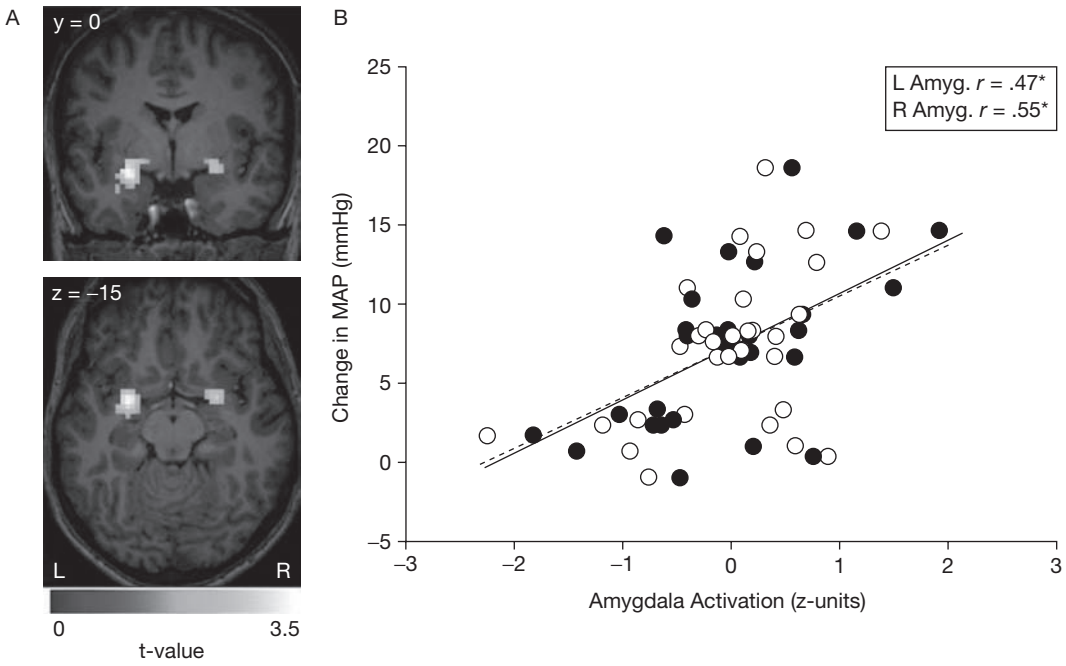

Figure 39.4 ■ Mean arterial pressure (MAP) reactivity to a Stroop color-word interference stressor is shown as a function of stressor-evoked amygdala activation. **(A)** Statistical parametric maps illustrating areas of the left and right amygdala where MAP reactivity varied with fMRI BOLD activation. **(B)** MAP reactivity (change from a resting baseline) is shown as a function of mean-centered and standardized amygdala BOLD activation values extracted from the left (L, open circles, dashed line) and right (R, closed circles, solid line) amygdala areas in (a). *$p < 0.01$. Reprinted with permission from Gianaros, P. J., Sheu, L. K., Matthews, K. A., Jennings, J. R., Manuck, S. B., & Hariri, A. R. (2008). Individual differences in stressor-evoked blood pressure reactivity vary with activation, volume, and functional connectivity of the amygdala. *Journal of Neuroscience, 28*, 990–999. (*See color insert.*)

this paradigm, participants were instructed to increase (upregulate) or decrease (downregulate) their experience of negative affect or to simply attend (control condition) to a set of emotionally evocative pictures during fMRI scanning. Interestingly, when participants were instructed to upregulate their negative affect, greater fMRI BOLD activity was observed in the ventral lateral, dorsolateral, and dorsomedial regions of the prefrontal cortex and amygdala. Furthermore, those individuals who displayed greater levels of prefrontal cortical activity and lower levels of amygdala activity when downregulating their negative affect also showed a steeper decline in cortisol over the day. These findings suggested that individuals who express a greater capacity to engage prefrontal emotion regulatory control mechanisms may also express a potentially less adverse patterning of cortisol change in daily life. Specifically, a more pronounced diurnal cortisol slope has been associated with lower mortality risk among patients with cancer (Abercrombie et al., 2004; Sephton, Sapolsky, Kraemer, & Spiegel, 2000) and with a reduced likelihood of expressing subclinical atherosclerosis in the coronary arteries (Matthews et al., 2006). Thus, functional brain imaging paradigms that include diurnal assessments of cortisol may reveal important information about the neurobiological pathways involved in some forms of health risk.

In another example of how cortisol can be assessed in association with functional neural activity, Eisenberger et al. (2007) demonstrated that cortisol changes elicited by the Trier Social Stress Task (TSST) administered outside of an MRI scanner were correlated with activation during a social rejection task performed inside of the scanner. Specifically, activation of the dACC and dorsal medial prefrontal cortex was correlated with larger cortisol responses to TSST. Moreover, activity in these limbic areas statistically mediated the association between individual differences in perceived social support and cortisol responses. An intriguing conclusion drawn by the authors was that a person's level of social support may modulate how specific brain areas regulate stress-related cortisol reactivity (Eisenberger et al., 2007).

Because of the widespread use of the TSST in laboratory studies of cortisol reactivity (Dickerson & Kemeny, 2004), several attempts have been made to emulate key elements of this stressor paradigm in neuroimaging experimental designs. One important adaptation, the Montreal Imaging Stress Task, was developed by Pruessner et al. (Dedovic et al., 2005). In this task, participants solve challenging mental arithmetic problems as in the laboratory version of the TSST, but the problems are presented and solved while participants are inside of a PET or MRI scanner. Social evaluation is provided by negative feedback

from a computer program and by the investigator after task performance.

Using the Montreal Imaging Stress Task, Pruessner et al. (2007) reported significant correlations between salivary cortisol changes and relative decreases in brain activity during task performance. These "deactivations" were observed across a number of limbic brain areas, including the hippocampus, amygdala, insula, hypothalamus, and pCC. These findings are notable in that these areas may exert a tonic inhibitory control over the HPA axis. Thus, when "deactivated" under stress, such areas may disinhibit the release of cortisol by the HPA axis.

Using a similar mental arithmetic stress task with negative feedback administered during perfusion MRI, Wang et al. (2005) found that activation in the right ventral prefrontal cortex (RVPFC), insula, and putamen—brain areas linked to emotion regulation processes—was associated with task-related subjective stress ratings. Furthermore, sustained activity in RVPFC and dACC after the task covaried with participants' cortisol responses assessed during imaging. However, later analyses of the same data (Wang et al., 2007) suggested that these correlations may have been sex specific. In women, the stress task seemed primarily to elicit activation of the ventral striatum, putamen, and insula, with dACC and pCC activation persisting beyond the task relative to men. Furthermore, in women, significant associations were observed between cortisol reactivity and dACC activity. In men, the stress task primarily elicited activation of the RVPFC and suppression of left orbital frontal cortex, which also persisted beyond the task relative to women. The authors tentatively linked their findings with a sex-specific stress model for "fight or flight" in men and "tend and befriend" in women (see Taylor, chapter 8). Broadly stated, these findings highlighted the importance of assessing sex differences in centrally mediated stress reactivity because men and women may differ in the expression of cognitive, behavioral, social, and physiologic stress processes underlying observed patterns of reactivity.

OXYTOCIN

In addition to cortisol, several recent neuroimaging studies of neuroendocrine functioning have examined functional neural activity in association with oxytocin. Oxytocin is a neuropeptide important for social bonding and attachment. Oxytocin is implicated in the suppression of anxiety to psychosocial stress and in the enhancement of trust (Heinrichs, Baumgartner, Kirschbaum, & Ehlert, 2003; Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). Oxytocin is being studied increasingly in neuroimaging research because of its potential role in centrally mediating social support mechanisms buffering against psychological stress. Because oxytocin can be administered intranasally and because it crosses the blood–brain barrier, the influence of oxytocin on functional brain activity can be measured in neuroimaging paradigms. For example, Kirsch et al. (2005) reported that amygdala activity is reduced in response to fear-inducing visual stimuli in healthy males after intranasal administration of oxytocin. However, Domes et al. (2007) later reported that amygdala activity is reduced by oxytocin in response to angry, fearful, and happy faces, suggesting that oxytocin may affect the processing of emotionally salient social stimuli in general and not just "threat"- or "stress"-specific stimuli in particular. Domes et al. speculated that such a mechanism mediated by oxytocin may facilitate social approach behavior in the context of both positive and negative emotional circumstances. More broadly, these findings highlight the importance of considering both positive and negative emotional stimuli in studies of stress research.

STUDIES OF CHRONIC STRESS PROCESSES

FUNCTIONAL NEUROIMAGING RESEARCH ON BEREAVEMENT

Bereavement, or the period after the death of a close person, provides an opportunity to study a common, ongoing stressful life event that can become chronic. Grief experienced during bereavement comprises the emotional, physiologic, and behavioral response to the death of a close person, which can be intense for many. However, most will adapt to their loss, with the intensity of grief waning with time (Bonnano et al., 2002). Stress- and grief-related factors occurring during bereavement have long been associated with negative physical health outcomes (Kraus & Lilienfeld, 1959), with several studies showing moderate, but reliable, associations between bereavement and morbidity and mortality rates (Stroebe, Schut, & Stroebe, 2007). Bereavement and grief are experienced by nearly everyone and thus can be studied in among those who are mentally and physically healthy.

Evoking grief in bereaved individuals during neuroimaging is one way to evaluate the potential neurobiological pathways linking bereavement and health. This has been done using personalized stimuli to evoke grief in blocked neuroimaging paradigms (Gündel et al., 2003). Stimuli that are personally relevant (such as pictures of a deceased family member) are likely to elicit strong negative emotions comprising the experience of grief. To facilitate the study of grief, O'Connor and colleagues created grief stimuli using photos of the deceased provided by study participants (Gündel et al., 2003; O'Connor et al., in press). These photos were then matched with photos of a stranger to serve as stimuli for a neutral comparison condition in a blocked fMRI design. In addition, grief-related words from participants' narratives were matched with neutral words on several potentially confounding factors, including number of letters, number of syllables, parts of speech, and usage frequency in the language. These words

and pictures were then shown simultaneously to participants during testing. By creating composites of pictures and words, a 2 × 2 design can be used in studies examining the differential activity between four conditions (1, deceased-grief word; 2, stranger-grief word; 3, deceased-neutral word; 4, stranger-neutral word) (Figure 39.5).

In one study using this grief-eliciting paradigm, responses to the grief versus neutral stimuli were first assessed both by self-report and by changes in skin conductance, which reflects sympathetic nervous system outflow to the eccrine sweat glands (Gündel et al., 2003). Graded responses across the four conditions were detected for both self-reports and skin conductance, such that neutral words paired with photos of strangers produced the weakest responses, and grief words paired with photos of the deceased produced the strongest responses

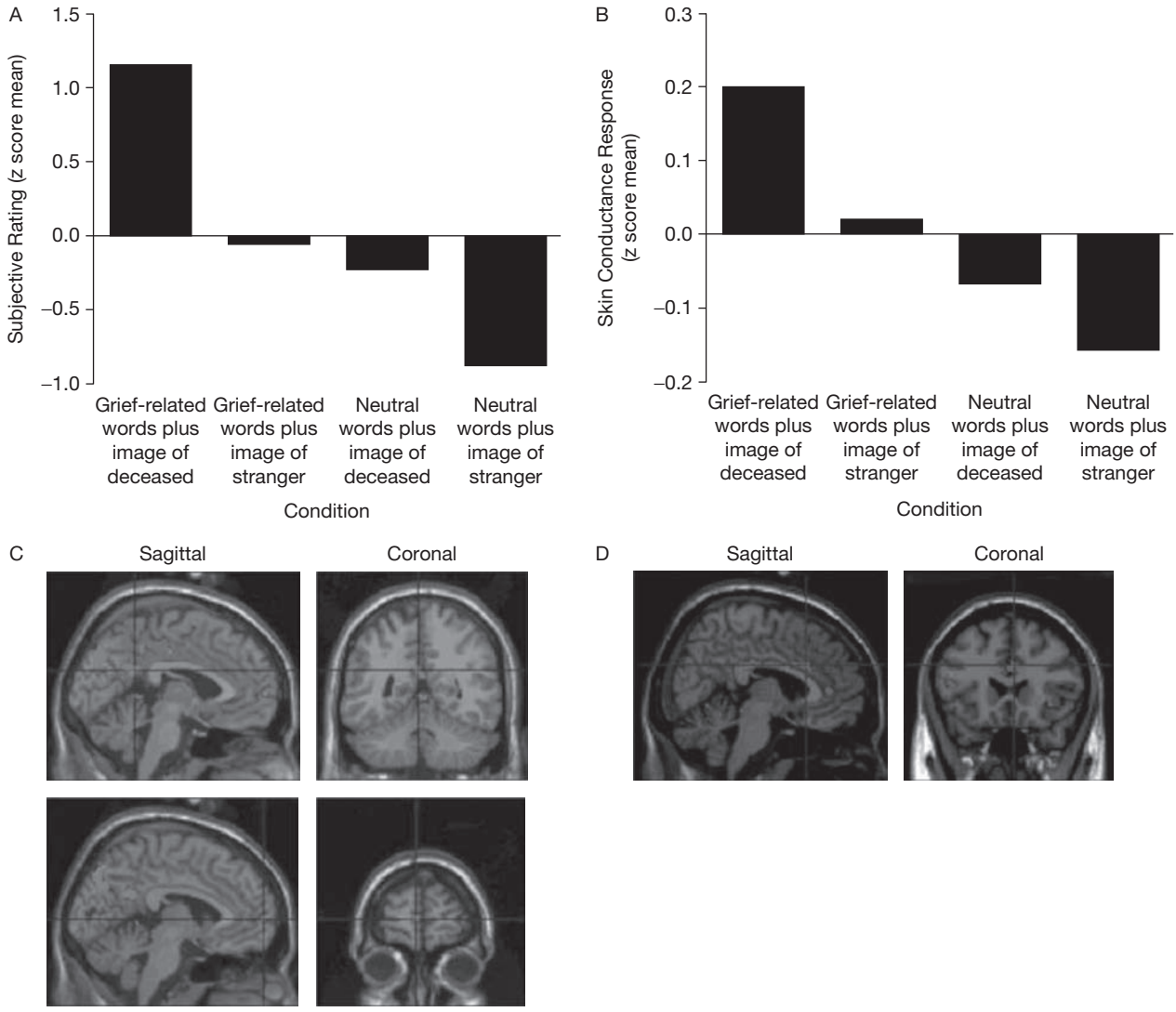

Figure 39.5 ■ *Results from a functional neuroimaging study of grief in bereaved individuals*: **(A)** Subjective grief ratings of eight bereaved women viewing words and pictures related or unrelated to a deceased relative. Grief-related stimuli elicited stronger subjective responses than the non-grief-related stimuli. **(B)** Skin conductance (electrodermal) responses of the women viewing the same composites of words and pictures. As for subjective ratings, grief-related stimuli elicited stronger electrodermal responses than the non-grief-related stimuli. **(C)** Brain images showing activated areas in the women when they viewed grief-related words (Word Factor) in the picture-word composites. Areas demarcated by cross-hairs are the posterior cingulate cortex (retrosplenial cortex) and medial prefrontal cortex. **(D)** Brain images showing areas activated in response to a photograph of their deceased relative (Person Factor) in picture-word composites. Brain area demarcated by the cross-hairs is the dorsal anterior cingulate cortex. Reprinted with permission from Gündel, H., O'Connor, M.-F., Littrell, L., Fort, C., & Lane, R. D. (2003). Functional neuroanatomy of grief: An fMRI study. *American Journal of Psychiatry, 160*, 1946–1953. (*See color insert.*)

across measures. These observations provided the basis for subsequent neuroimaging results to be interpreted as correlates of these bereavement-related subjective and physiologic changes.

Hence, in an fMRI subtraction paradigm used within an event-related experimental design, patterns of brain activation that were associated with the picture and word factor contrast localized brain activation in several limbic brain regions discussed above, including the dACC, pCC, and insula. Together, these findings suggested that acute experiences of grief may be characterized by activity changes in a distributed network supporting emotional information processing, episodic memory retrieval, processing familiar faces, visual imagery, and the modulation/coordination of these functions.

In a recent extension of this work (O'Connor et al., 2008), bereaved individuals with complicated (prolonged and unresolved) grief were compared with those with noncomplicated grief in an event-related fMRI paradigm. As predicted based on previous work, both groups showed BOLD activation in areas sensitive to social pain (e.g., the dACC) in response to reminders (pictures and words) of their relatives who had died of breast cancer. Notably, women experiencing complicated grief showed increased activation of the nucleus accumbens, a central component of a distributed reward-related striatal circuit. Moreover, greater nucleus accumbens activity covaried with greater levels of self-reported yearning, and not time since death, age, and positive/negative affect. These results were interpreted within a conceptual framework, suggesting that persistent attachment during bereavement is associated with greater activity in reward systems, such as the nucleus accumbens, which could reflect dysregulated adaptation to losing a loved one. Together, these studies of bereavement offer examples of the application of neuroimaging methods to understand chronic or ongoing stress processes in a population at risk for adverse health outcomes.

STRUCTURAL NEUROIMAGING STUDIES OF CHRONIC LIFE STRESS

Complementing functional neuroimaging studies of the stress-related processes reviewed above, a growing number of structural neuroimaging studies have begun to examine longer-term or chronic stress-related and psychosocial factors in association with aspects of brain morphology, particularly brain tissue volume. Much of this work is based on an extensive animal literature documenting the effects of chronic and early life stress on markers of brain and neural morphology. In particular, a number of animal models demonstrate that chronic stressful experiences (e.g., prolonged immobilization, housing in dominance hierarchies, and early maternal separation) can remodel neurons and result in changes in the gross morphology of several limbic areas, most reliably areas of the prefrontal cortex and hippocampus. For example, prolonged immobilization simplifies the branching complexity and shortens the length of dendrites of pyramidal neurons in the rat prefrontal cortex (McEwen, 2007). In both rodent and non-human primate models, chronic stressors also remodel neurons in the hippocampus and arrest the proliferation of new neurons, two types of cellular changes that may partly contribute to a decrease in hippocampal volume (Fuchs & Flugge, 2003; McEwen, 2007). Such stress-related changes in the morphology of areas in the cortex and hippocampus can result from alterations in central glucocorticoid levels and receptor densities, acting in conjunction with alterations in the transmission and expression of excitatory amino acids and neurotrophic factors that regulate cellular plasticity and neurogenesis (Fuchs & Flugge, 2003; McEwen, 2000a, 2000b; Sapolsky, 2005b).

In parallel to animal evidence, there is indirect human structural neuroimaging evidence that stressful experiences may be associated with morphologic changes in several brain areas. For example, individuals with stress-related psychiatric disorders, such as major depressive disorder and posttraumatic stress disorder, consistently show volumetric changes of the prefrontal cortex and other limbic brain areas, including the hippocampus (Fuchs & Flugge, 2003; McEwen, 2007). In addition to patient studies, there is emerging evidence for a relationship between stressful experiences and limbic morphologic changes. For example, among otherwise healthy postmenopausal women, higher levels of chronic perceived stress, as measured over an approximate 20-year period of life, have been associated with reduced gray matter volume in the hippocampus and orbital prefrontal cortex (Gianaros et al., 2007). Furthermore, more than three 3 years after the terrorist attacks on the World Trade Center buildings on September 11, 2001, otherwise healthy adults living in close proximity to the buildings showed reduced gray matter volume in the amygdala, hippocampus, insula, anterior cingulate, and medial prefrontal cortex (Ganzel, Kim, Glover, & Temple, 2008). Finally, there is evidence from healthy adults that the perception of holding a lower social standing than others, a putative source of life stress, is associated with reduced gray matter volume in the anterior cingulate cortex (Gianaros, Horenstein, et al., 2007).

Without longitudinal evidence, however, it has not yet been established that stress-related variation in brain morphology in patient or healthy adult populations is invariably the consequence of so-called "neurotoxic" chronic stress-related mechanisms (Sapolsky, 1996, 2002). It is possible, for example, that preexisting individual differences in limbic brain morphology partly increase vulnerability and sensitivity to life stress and traumatic events (Lupien et al., 2007). These individual differences might emerge early in life and result from a combination of genetic and developmental influences. In line with this notion, there is recent evidence that individual differences in self-esteem and locus of control, which emerge early in life and modify the appraisal of environmental demands,

are associated with hippocampal volume and cortisol changes in both young and elderly people (Pruessner et al., 2005). Furthermore, there is evidence that birth weight predicts hippocampal volume in adulthood, particularly among women reporting low maternal care, suggesting that the postnatal environment may affect neurodevelopmental consequences of prenatal risk (Buss et al., 2007). Finally, otherwise healthy adults reporting that they were exposed to more frequent early traumatic and adverse childhood events show smaller volumes of the anterior cingulate cortex and caudate volumes than those not reporting exposure to such events, further suggesting the important influence of early developmental processes affecting brain morphology and possibly later vulnerability to life stress (Cohen et al., 2006). In aggregate, these structural neuroimaging studies complement functional neuroimaging studies of stress processes in that they may reveal both vulnerability and experience-dependent patterns of brain morphology relevant to risk for and resilience against ill health.

CONCLUSION

We close with a quote from Herbert Weiner, a leading researcher on stress and health whose death came just before the widespread availability of functional neuroimaging. In *Perturbing the Organism: Biology of the Stressful Experience*, Weiner wrote "The neuronal links between stressful environments and changes in behavior and bodily function are being forged: The 'black box'—the brain—is not as impenetrable as it once was! (Weiner, 1992, p. xii)." We hope that we have illustrated that this enthusiastic statement is even truer today than it was in 1992. With neuroimaging methods, stress researchers are poised to define the "neuronal links" between stressful experiences and neurobiological processes impacting health and well-being throughout life. In this chapter, we attempted to provide an overview of how functional and structural neuroimaging methods can be specifically incorporated into human stress science. With continued development and integration with other multilevel social, cognitive, behavioral, and physiologic assessment methods, neuroimaging methods will offer opportunities to better explicate the neurobehavioral pathways linking stress-related processes instantiated in the brain to health. In this regard, there are a number of open questions for future research that can be addressed by incorporating neuroimaging methods in human stress science. For example, we know little about how stressor appraisal and coping processes are instantiated in the developing and aging human brain; how stress appraisal, coping, and response processes interact with genetic and environmental factors to influence aspects of brain functionality and morphology influencing mental and physical disease risk; how stress appraisal, coping, and response processes interact with specific forms of emotional experience and emotion regulation; and how markers of brain functionality and morphology may contribute to our understanding of disease etiology and risk stratification. To address these questions, it will be important for stress scientists interested in neuroimaging methods to collaborate as members of multidisciplinary teams operating within multilevel frameworks.

ACKNOWLEDGMENTS

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40 Interview Assessment of Stressor Exposure

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INTRODUCTION

The notion that life stress can influence both our physical and mental well-being has been the focus of several decades of research across multiple disciplines. One of the most voluminous areas of life stress research has focused on the relationship between the exposure to environmental stressors, life events that occur in the social and physical environment, and health outcomes. Associations between environmental stressors and disease have been well documented; the strongest evidence for these associations is available for depression, cardiovascular disease, and HIV/AIDS (Cohen, Janicki-Deverts, & Miller, 2007). In addition, emerging evidence indicates that environmental stressors may moderate the effects of genetic factors on health and behavioral outcomes (e.g., Moffitt, Caspi, & Rutter, 2005). Yet, controversy remains about the etiological importance of environmental stressors to mental and physical health outcomes. Part of this controversy is due to the lack of consistency in the both the description and measurement of environmental stressors across studies, rendering comparisons and research synthesis problematic (Dohrenwend, 2006; Monroe, 2008; McQuaid et al., 1992). Other concern is focused on the lack of specificity about the dimensions of stressor exposure, specifically, the nature and types of stressors that may have the most deleterious effects on physical and mental health (Monroe, 2008). In other words, it has been difficult to establish with precision to what degree objective features in the social and external environment contribute to poor health.

The aim of this chapter is to review research approaches to the study of exposure to environmental stressors in adults. First, we present a brief history of the "environmental stressor" perspective. Second, we discuss the two original research traditions in this area, *respondent-based assessment*, which is based on the use of self-report checklists, and *investigator-based assessment*, which typically involves the use of a semistructured personal interview to elicit features of the stressor. Third, we provide a brief review of contemporary instruments, referred to as second-generation tools (Dohrenwend, 2006; Zimmerman, Pfohl, & Stangl, 1986), that have attempted to address some of the conceptual and methodological problems associated with each of these two approaches. Finally, we conclude with some of our preliminary work on the development of a new instrument that we hope may represent a third generation of stressor exposure assessment tools. As will become evident in this chapter, the development of comprehensive and objective tools to assess exposure to social and environmental stressors is a rather complex endeavor. Nonetheless, further advances in understanding the contribution of environmental stressors to disease development, progression, and outcome depend on methodological advancements in quantifying stressor exposure.

THE MEASUREMENT OF STRESSOR EXPOSURE: A SHORT HISTORY OF THE ENVIRONMENTAL PERSPECTIVE

The concept of stress as a scientific research endeavor is credited to Hans Selye and his seminal work on the identification and study of physical and physiological stressors in animal models (Selye, 1936, 1956). For Selye, stress was conceptualized as a nonspecific change in the organism evoked in response to discrete and observable environmental stimuli (Selye, 1936). The study of exposure to external life stress and health outcome in humans is also indebted to the work of Adolf Meyer. Meyer developed a life chart methodology, embedded in the medical examination, to elicit and record important aspects of a patient's life history (e.g., marriage, job changes, psychiatric and physical illnesses, and concurrent stressful life circumstances). Meyer noted that important life occurrences frequently appeared to precede illness onset and therefore advocated the idea that such life circumstances may be important in understanding the etiology of disease (Meyer, 1951). Based on this premise, a substantial body of research conducted during the 1940s and 1950s documented that stressful life circumstances, that is, stressors that occur within the common experience of the average person, appear to be related to a variety of physical illnesses (Wolff, Wolf, & Hare, 1950). In these studies, however, recent life circumstances were not measured

systematically, with researchers often relying on anecdotal assessment of life circumstances, rendering comparisons across studies problematic.

RESPONDENT-BASED METHODS FOR THE ASSESSMENT OF STRESSOR EXPOSURE: THE CHECKLIST APPROACH

Further impetus for the study of environmental stressors and illness came about with the development of the Schedule of Recent Experience (SRE) (Hawkins, Davies, & Holmes, 1957). A major assumption of this approach is that an individual's level of stress can be defined by the cumulative amount of change or adaptation brought about by events, either positive or negative, which have occurred in the recent past. The SRE represented one of the first systematic attempts to document recent life event experiences in a comprehensive manner, either by self-report checklist or through interview using a checklist format. In administering the SRE, the respondent is presented with a checklist of 43 items, derived from clinical studies, and including life occurrences such as marriage, death of a spouse, and vacation; the amount of stress experienced by an individual was measured as a simple count of the number of items endorsed. Initially, this method of measuring stress assumed that all life occurrences evoked the same magnitude of adjustment to change. In other words, the SRE did not differentiate between severe life occurrences, like death of a spouse, and minor changes, such as a vacation. A major modification of the SRE, the Social Readjustment Rating Scale (SRRS) (Holmes & Rahe, 1967), applied a scaling procedure based on the estimated magnitude of adjustment to life change required by each event. Marriage was used as the pivotal event to which each of other 42 events was compared. The scores for each event, endorsed as occurring in some specified time frame, were added together to represent the total amount of life stress experienced by an individual. Even though checklist instruments, such as the SRE and SRRS, have been criticized for methodological flaws (Dohrenwend, 2006; Katschnig, 1986a; Monroe, 2008), at the time of their development, they represented important advancements in the field by providing a standard list of "reportable" life events and a replicable method of stress quantification. (It should be noted that the SRE was expanded and rescaled in 1975 to create the Recent Life Change Questionnaire, RLCQ [Rahe, 1975]; the RLCQ was rescaled again in 1995 [Miller & Rahe, 1997].) In this way, Holmes and Rahe formulated the idea that distinctive changes in an individual's life circumstances, specific and documentable life occurrences, could be assessed in an objective manner.

The SRE and its revisions have been readily embraced by researchers and have served as the foundation of most current checklist life events scales, thus launching a methodological paradigm that continues to be the dominant research procedure for estimating variations in stressor exposure in the social and physical environment (Dohrenwend, 2006; Rahe, 1978). Indeed, there have been thousands of empirical studies that have examined the association between stressful life circumstances and health outcomes by utilizing some variation of the checklist method. A substantial number of checklists have been generated and used in this research since the publication of the SRE, but none of these checklists have been endorsed as a standard in life stress research. There is some consensus in the literature, however, that it is negative, threatening, or undesirable events, rather than positive events, that are associated with adverse mental and physical health outcomes (Thoits, 1983; Zautra & Reich, 1983; see also Turner & Wheaton, 1995, for a review), so that it is usually negative events that are counted in the total of life events experienced by a respondent. The overall acceptance of the checklist paradigm appears to lie in the intuitive appeal of the stress concept, the assumption that "more events are worse" and the efficiency and economy of the method.

A typical checklist measure consists of a series of yes/no questions, asking respondents to report if any of the items listed has occurred over a past period of time (e.g., typically 1 month or 1 year). Checklist measures are typically used to produce a summary score of the estimated stressfulness of changes experienced in the external environment within a defined time interval (Wethington, Almeida, Brown, Frank, & Kessler, 2001). Further elaborations of checklist measures have included attempts to get more detailed (and theoretically important) information about the inventoried items, such as a more detailed description of the circumstances surrounding the occurrence, the date of occurrence, and self-reported stressfulness or unpleasantness associated with the occurrence. Even with these methodological advances, it is typically the number of occurrences endorsed that is used as the primary measure of experienced stressor exposure (Turner & Wheaton, 1995).

Checklist methods have been associated with only modest test–retest reliability; a number of methodological issues with these tools may contribute to problems with their reliability and content validity as measures of stressor exposure (see Dohrenwend, 2006). These problems include the following: (1) vagueness of the stimulus (broad or nonspecific questions open to multiple interpretations), (2) lack of comprehensiveness (too few, too general, or population-biased items), (3) inclusion of inappropriate events (e.g., too minor), (4) poor recall of stressors (indicated by the falloff of reporting of stressors over time), (5) imprecise dating of the stressor in relationship to the outcome, (6) problems determining the duration of exposure to a stressor, (7) changes in intensity or severity over time, and (8) lack of distinction between episodic stressors (events) and ongoing chronic stressors (chronic difficulties). Checklists have also been criticized for including items that can be viewed as symptoms of physical or mental health problems, or the consequences

of such problems, suggesting that observed associations may be an artifact of operational confounding (Monroe, 2008; Shrout et al., 1989).

Perhaps the most fundamental limitation of the checklist method comes from the lack of consistency or standardization in the operational definition of an environmental stressor. Although checklists include a standard set of items, the interpretation of an individual item resides with the respondent (McQuaid et al., 1992; Monroe, 2008). For example, a common item on a checklist, "a serious argument with a close family member," may appear at first glance to be relatively unambiguous. On further examination, however, it becomes apparent that the meaning of this item is not nearly so clear. What is seen as "serious" by one person may not be the same for another, what constitutes an "argument" for one may not be for another, and how one defines a "close family member" will also differ across persons. In other words, without precise definition of each item in an inventory category, the same response to a simple question may denote a wide range of experiences. This problem associated with checklist methods, imprecision in definitional constructs and operational products, has been referred to as *intracategory variability* (Dohrenwend, 2006).

This type of ambiguity in potential meaning raises a host of issues that need to be addressed when creating an event inventory for a life stress assessment tool (McLean & Link, 1994; Turner & Wheaton, 1995):

(1) What kinds of experiences should be included within a particular category of stressor (e.g., minor or major, positive or negative, episodic or chronic);
(2) Whose exposures other than the respondent's should be included in a comprehensive inventory and for which stressor category should these individuals be included (e.g., a child's school experience, a spouse's difficulty at work);
(3) How should the other life circumstances (context) in which a particular stressor occurs or is embedded be assessed (e.g., an unplanned pregnancy in the context of a stable versus unstable partner relationship);
(4) How should other measurement issues be addressed such as redundancy (a respondent may report the same stressor under a different stressor category, thus reporting it twice) or recall problems (a respondent may report the same stressor under a different stressor category at a later date, thus appearing to be unreliable in the recall of that stressor);
(5) Is it possible to ascertain the origin or source of the stressor as external (not dependent on the person's behavior) or dependent on a person's own behavior (i.e., does a job loss occur because a manufacturing plant closes or as a consequence of repeated tardiness?).

A second major limitation of the checklist approach concerns the problem of establishing the temporal precedence between stressor exposure and health outcome as well as elucidating the temporal relations between concurrent and consequent stressors, or between episodic and chronic circumstances. Establishing temporal precedence between stressor exposure and outcome is crucial given the possibility that an initially acute stressor or the outcome may generate or prolong exposure to a variety of life stressors (Hammen, 2005; Monroe & Harkness, 2005; Thoits, 1995). Furthermore, when the onset and the offset of a particular stressor are not ascertained, it is difficult to quantify not only the duration of exposure to that stressor but also exposure to any consequent stressors or preexisting stressors that may exacerbate impact. For example, an episodic or acute stressor, such as a biopsy for breast cancer, may trigger the emergence of a new chronic health problem, breast cancer (that in turn may involve surgery, chemotherapy, or other treatments over the course of the time). The breast cancer diagnosis and treatment may occur within the context of prolonged unemployment (without the benefit of health care insurance), or treatment for breast cancer may result in a medical leave of absence with benefit of health care insurance. For the most part, checklist methods tend to use a more general strategy of assessing dates such as endorsement of an occurrence for the past 1 month or past 1 year without specifying at what point during the period the occurrence actually took place. Very little attention, if any, focuses on the temporal relations between stressors, including onset and offset, making the quantification of the duration and severity (or changes in severity over time) of stressor exposure difficult. The duration and severity of the effects of the breast cancer biopsy in this example would be difficult to quantify with precision using simple checklist methods.

Monroe and colleagues (McQuaid et al., 1992; Monroe, 2008) along with others (Dohrenwend, 2006; Gorman, 1993; Grant, Compas, Thurm, McMahon, & Gipson, 2004) have argued that further elaborations on the checklist measurement method are unlikely to reduce or control the problems of intracategory variability and temporal precedence well enough to provide reliable and valid measurement.

INVESTIGATOR-BASED METHODS FOR THE ASSESSMENT OF STRESSOR EXPOSURE: THE INTERVIEW APPROACH

The second traditional approach in life stress assessment, the investigator-based interview method, was derived from a different theoretical perspective than the readjustment/adaptation perspective associated with the checklist paradigm (Holmes & Rahe, 1967). Thus, the two measurement paradigms differ not only in their measurement strategies but also in their theoretical approach to defining the meaning of stressors. The investigator-based approach is driven by a perspective that assumes that social and environmental changes that threaten the *goals, plans, commitments, and social roles* of an

individual are the basis for experienced stress and that those changes experienced as severe, within the individual's context, threaten physical and mental health (Brown & Harris, 1978, 1989). In other words, the crucial aspect of an environmental stressor is thought to be its disruptive impact in the context of specific life circumstances of the individual ("contextual threat") rather than the amount of change it required per se (as emphasized by the checklist approach). The investigator-based method uses a personal interview to collect detailed information about the occurrence of life stressors through qualitative probes. These probes are designed to specify more precisely the characteristics of life stressors, including the personal and social context in which the stressor occurs. The interviewer collects and records the detailed narrative information about an occurrence of each stressor and compares this information to a set of established rating rules and codes, which allows investigators, rather than relying on respondent interpretation, to rate which experiences meet set thresholds for qualifying as an "event" as well as specifying the magnitude or degree of severity associated with the occurrence of each. A key component of most investigator-based methods is the use of response enhancement techniques, such as respondent-specific calendars, to ascertain the exact date of the occurrence as well as its temporal relations to the other occurrences and to the outcome of interest. With its emphasis on narrative descriptions of stressors as an alternative approach to the assessment of environmental stressors (including strategies for ascertaining temporal relationships), the investigator-based interview approach appears to be less affected by the problem of intracategory variability and temporal precedence (Dohrenwend, 2006; Grant et al, 2004; McQuaid et al., 1992; Monroe, 2008).

AN EXAMPLE OF THE INVESTIGATOR-BASED METHOD: THE LIFE EVENTS AND DIFFICULTIES SCHEDULE

The most well-documented example of an investigator-based interview assessment of life stress is the Bedford College Life Events and Difficulties Schedule (LEDS) (Brown & Harris, 1978, 1989). This life stress assessment involves a three-part process (see Table 40.1). First, the evaluation begins with a semistructured interview that is used to ascertain the presence of events and difficulties (difficulties are typically termed "chronic stressors" in the American research literature; the distinction between acute and chronic stressors is an important one that has emerged in the literature on life stress [George, 2004, 2007; Wheaton, 1999]). Difficulties are stressors whose objective disruptions or impact may persist for a month or more and are assessed across the same 10 life domains used to describe events (e.g., work, marital and/or romantic partner relationships, health). A set of previously developed and clearly specified rules is used to determine whether a particular incident meets the threshold for inclusion as an "event" and whether a chronic problem meets the threshold for the inclusion as a "difficulty." These rules are documented in a set of comprehensive manuals or "dictionaries" containing precedents of more than 2,000 life events and difficulties (derived and developed from a program of research conducted by Brown and Harris over the course of 30 years [see Brown & Harris, 1978, 1989]). Relevant context for a particular stressor can involve any combination of the following sources of context: biographical context (including gender, education, occupation, marital status, and history of exposure to certain types of acute or chronic stressors), social context (including current social roles and other life circumstances such as chronic stressors), and environmental or societal context (including characteristics of the neighborhood, school, or broader social or cultural environment). These contextual factors are important in specifying the magnitude of the stressor exposure assigned to each event and/or difficulty. The key rating dimension then for each identified stressor is referred to as the *contextual threat rating*, which is based on the likely response of an average person to a stressor occurring in the context of a particular set of biographical and social circumstances, taking no account of the respondent's emotional or subjective reaction to the stressor. All interviews are recorded on audiotape to facilitate subsequent ratings of the contextual severity of the events and difficulties.

The manner in which the LEDS interview is conducted, a conversational style of discourse in which both the respondent and the interviewer can search for clarification from each other, converges with evidence from the fields of autobiographical memory (Belli, 1998) and cognitive aspects of survey methodology (Schwarz, 2007) as to some of the more important aspects of facilitating recall of life occurrences. For example, Schwarz (2007) indicates that performance is improved when the respondent has the opportunity to clarify the question, or obtain a better understanding of the nature of the question, through an exchange with a knowledgeable individual. One of the most important processes that occur during the LEDS interview is this type of exchange, which results in a better match between what the investigator intends to measure and how the respondent interprets the question, that is, the meaning or definition of the life occurrence that is being discussed. The LEDS interviewers guide this process through their knowledge of the rules, the aim of which is to standardize measurement. Another key aspect of the interview process that relies on this conversational style is the dating of events and difficulties in relation to each other as well as to health outcomes. Response enhancement techniques, such as respondent-specific calendars, are similar to techniques demonstrated to be effective for the sequential assessment of contiguous experiences over a full day (such as Day Reconstruction Method [Kahneman, Krueger, Schkade, Schwarz, & Stone, 2004]) or life events over a retrospective time frame using event history calendars (Martyn & Belli, 2002). Establishing temporal precedence is crucial for assessing duration of stressor exposure, and

Table 40.1 ■ Semistructured Retrospective Life Events and Chronic Stressors Assessment: Interviewing, Rating, and Consensus Assessment

Interview	Rating	Consensus Assessment
1. Biographical assessment a. demographics b. social relationships c. work, education, occupational history 2. Life events and chronic stressors, assessed by 10 life roles/domains, aided by: a. calendars specific to respondents b. context-specific recall techniques 3. Contextual probing of events/stressors a. application of pre-established, documented thresholds b. context-based probes relevant to different domains and stressors c. event dating in relationship to other events, chronic situations and outcome	1. Interviewer review of audiotape and rating of: a. severity/magnitude of situation, based on application of established, documented thresholds b. reported severity (separate rating) c. type, duration, change-points in magnitude of stressor[a] d. dependence of occurrence on subject's behavior 2. The product of the rating process, the life stress profile, consists of a biographical synopsis, events in temporal order, followed by chronic stressors.	1. Interviewer: consultation of standardized manuals of documented thresholds and contextual ratings (previously established by consensus meetings of investigators) 2. Consensus panel or Expert rater[b] a. presentation of case; panel members blind to subject's symptom profile, timing of onset of dependent disorder, subject's subjective reaction, and interviewer's initial ratings b. final rating assigned by panel discussion or by expert rater

[a] Chronic stressors differ from acute stressors in that a particular chronic stressor may have more than one change point over the course of the interview period. Any time the contextual circumstances surrounding a particular chronic stressor change and that change in contextual circumstances is sustained for at least one month (i.e., 28 days), the contextual threat rating may be changed; this is referred to as a *change point*. For example, a marital situation characterized by weekly arguments over money, for a period of 28 days or longer, will be considered a chronic stressor and will be assigned a threat rating. If at some later date during the time period of interest, the spouse asks for a divorce (an event) and moves out (an event), and this "change" is sustained for 28 days or longer, it may be assigned a different threat rating (in this case, it would most likely be an increase in severity).

[b] In many cases, the panel or expert rater can rely on the event or difficulty already having a specific rating assigned in the LEDS manuals so that a significant proportion of the panel rating is routinized.

these interactive techniques used in the LEDS allow for greater precision in estimating duration for both events and difficulties.

Once the interview is completed, the second part of the process involves the interviewer reviewing the audiorecording and rating the events and difficulties described with respect to their contextual threat rating and a variety of other rating dimensions. Interviewers are guided through the process of separating the respondent's subjective response (i.e., the respondent's emotional reaction to the occurrence), reporting style, or current symptomatology (such as depressive or anxious symptoms) from contextual rating through the use of the manuals.

In the third and final step in the assessment process, interviewer raters bring identified events and difficulties to consensus rating meetings involving other trained members of the research team, who are blind to the subject's symptom profile, timing of the onset of the health outcome, and the respondent's subjective reactions to the event or difficulty. Once an event and/or the difficulty are described, the interviewer points the other group members to the precedent example in the manual that informed his or her rating; however, the actual rating given is not revealed. If necessary, group members then discuss similarities and differences between the precedent and the occurrence being rated. The final rating of an event or difficulty is subject to a vote, providing a further check on interviewer bias. In many instances, raters can rely on the event or difficulty already having a specific rating assigned in the LEDS dictionaries so that a significant proportion of the panel rating is routinized. In addition, with experienced research teams, group meetings may be held only to deal with problematic ratings and/or to prevent rater drift. In these cases, a review process by an expert rater is utilized.

In the LEDS system, acute (event) and chronic (difficulty) stressors can be linked to each other in several important ways. For example, an acute stressor may trigger the emergence of a new difficulty or influence contextual changes that result in a change in intensity (more severe to less severe in contextual threat ratings or vice versa) for an existing chronic stressor. Knowledge about acute stressors allows for greater specification of the nature of chronic stressors such as dating, intensity of the threat rating, and dependence (the extent to which the exposure to the stressor was brought about by the respondent's actions or agency). In turn, knowledge of chronic stressors allows for more precise specification of an acute stressor that may be related to one or more ongoing difficulties. This type of rating in the LEDS process allows for a *dynamic* assessment of changes in exposure to stressors over time, including duration and intensity, resulting in a *life stress profile*; a temporal array of acute and chronic stressors arranged and linked in chronological order.

It has been suggested that the LEDS may provide more reliable retrospective reports of stressor exposure than comparable respondent-based methods (Brown & Harris, 1989; Dohrenwend, 2006; Katschnig, 1986b; McQuaid et al.,

1992; McQuaid, Monroe, Roberts, Kupfer, & Frank, 2000; Zimmerman, 1989). For example, the concordance between respondents and informants in the identification of events is higher with the LEDS than with checklist methods. Neugebauer (1983) reported that only 22% of events from the Psychiatric Epidemiology Research Interview (PERI) Life Events Scale were endorsed as having occurred by both outpatient schizophrenic patients and their relatives. In a sample of 102 nonpatient men, Yager, Grant, Sweetwood, and Gerst (1981) reported agreement for only one third of events reported by the participant or significant other on the SRE. In contrast, event concordance using the LEDS was 81% between schizophrenic patients and relatives (Brown & Harris, 1978) and 79% between depressed patients and relatives in two independent samples (Brown & Harris, 1978, p.71; Brown & Harris, 1982)

The LEDS has shown a high degree of inter-rater agreement in the occurrence, severity, and dating of events and difficulties (Brown & Harris, 1978, Parry, Shapiro, & Davies, 1981; Tennant, Smith, Bebbington, & Hurry, 1979). For example, in the study of depressed patients and relatives noted earlier, there was a high level of agreement between ratings of contextual threat based on the reports of depressed patients and close relatives when interviewed by different interviewers; when ratings for the *same* events were compared, there was a 91% agreement about *severe* events occurring in the year before interview (Brown, Sklair, Harris, & Birley, 1973). More recently, in a sample of depressed men and women and nondepressed contrast subjects, inter-rater reliability of threat ratings for events was quite good ($\kappa = 0.86$) (Sherrill et al., 1997).

The LEDS appears to be associated with superior reliability over time as well as across informants when compared with checklist methods, at least with respect to one measure of event recall. Specifically, there is some evidence that the LEDS is associated with a more favorable pattern of "falloff" in event reporting (change in number of events reported within the same period as the recall interval is lengthened) compared with checklist measures. Monthly falloff in reporting is estimated to be about 1% per month with the LEDS (Brown & Harris, 1989) as compared with rates reported for checklist methods, which are estimated to be about 5% per month, in general (Dohrenwend, 2006; Funch & Marshall, 1984; Paykel, 1983). Other work has demonstrated that it is possible to collect information about severe life events (SLEs) and difficulties for a 5-year period without a serious falloff in reporting of such occurrences (Neilson, Brown, & Marmot, 1989). Interestingly, the retest reliability of the major LEDS ratings by respondents, to our knowledge, has never been reported.

There is, of course, ample evidence for the predictive (criterion) validity of the LEDS (Brown & Harris, 1989; Dohrenwend, 2006). Researchers have demonstrated that life events and chronic difficulties, assessed with the LEDS, are associated with elevated risk for a number of mental and physical health conditions, including depression, anxiety, myocardial infarction, abdominal pain, and menstrual disorders (see Brown & Harris, 1989). With respect to depression in particular, the LEDS (i.e., severe events) has been found to be related to depression onset in a number of community studies (e.g., the estimated odds ratio ranges from 7 to 13; see Paykel, 1978; Surtees & Duffy, 1989). In a recent study of young adults using a checklist measure, the odds ratio for the onset of depression was estimated to be 1.53, substantially lower than that observed with the LEDS (Turner & Lloyd, 2004). More recently, LEDS measures of major life stressors have been linked to susceptibility to viral infection (Cohen, Frank, Doyle, Skoner, & Gwaltney, 1998) and to exacerbation in multiple sclerosis (Ackerman et al., 2002a, 2002b). Despite evidence for the greater reliability of the LEDS, there have been few efforts to compare the predictive validity of the LEDS and checklist methods within the same study.

To the extent that LEDS measures appear to be more psychometrically solid than those associated with life events checklists, there are several features of this instrument that may account for these results (Brown & Harris, 1989; Wethington, Brown, & Kessler, 1995). Most importantly, the criteria for defining whether or not a life occurrence meets threshold for classification as a stressor is relatively objective in the LEDS, as it is derived from the standard coding manuals ("dictionaries") that are the backbone of this system. The use of the LEDS coding system is associated with enhanced reliability with respect to the scoring of event dating, severity, and other event characteristics as well. In the LEDS, the "onset" and "offset" of every stressful occurrence is dated as precisely as possible, using standard criteria and an effective memory aid (a personalized calendar). The dating makes it possible to assess whether an event in fact occurred during the period of observation (a critical feature that may enhance concordance between observers and informants), what the duration of the event may have been (a dimension of increasing interest in the assessment of risk factor exposure (Hammen, 2005; Tennant, 2002; Thoits, 1995), and the temporal relations between stressors and health outcomes (a key issue in assuring the criterion validity of measurement). With respect to event severity, rather than ascertaining responses to a list of broadly defined categories of life stressors (e.g., job change, marital problems), the LEDS assesses each event for contextual features that will be associated with the severity or meaning of its impact. For example, the loss of employment after 30 years due to a plant closing has a very different meaning than leaving a summer job before returning to college. The assessment of context allows for an objective determination of stressor magnitude (contextual threat), another key feature of the LEDS scoring system. In contrast, endorsement of a "job loss" item on a conventional respondent-based self-report method may reflect very different experiences in terms of magnitude (severity or stressfulness of the stressor), duration (short-term versus chronic), and timing before the onset of health problems

(temporal precision). In summary, for the investigator-based interview method, both the information derived from the interview as well as the rating of such information are guided by standardized rules and criteria that appear to enhance reliability and validity.

COMPARISON OF METHODS: INVESTIGATOR-BASED AND RESPONDENT-BASED METHODS

There are very few studies that have attempted to compare the LEDS with checklist measures in the same sample of adults. In one such study, Katschnig (1986b) compared life events reported by depressed patients (n = 147) using both the checklist method (Schedule of Recent Experience [SRE] [Holmes & Rahe, 1967]) and the investigator-based method LEDS for a 2-year period preceding hospital admission. Both of these assessments were conducted only after the depressive episode had remitted, thereby minimizing the possible influence of depressed mood on the recall of events (Schless, Schwartz, Goetz, & Mendels, 1974). For both assessment methods, the results indicated that there was a clear-cut increase in the mean number of stressors experienced prior to hospitalization, especially in the proximal 6-month period, suggesting that the two methods yield similar results.

More detailed examination of the data, however, results in a different conclusion. For the example, in the 6-month period immediately preceding hospitalization, the total number of SRE life changes recorded was 538 (for an average of 3.66 life changes per respondent), whereas the LEDS yielded only 220 life events (for an average of 1.50 events per respondent). The correlation between the number of LEDS events and SRE life changes was relatively modest (r = 0.31), suggesting a lack of congruence between the measures. Katschnig (1986b) offered two plausible explanations for the lack of congruence: (1) the two methods measure different types of stressor exposures or (2) the SRE, which has demonstrated low reliability in previous studies (Katschnig, 1980), produces less accurate results.

McQuaid et al. (1992) used a test–retest design to examine factors accounting for differences in assessment of stressor exposure yielded by checklist and investigator-based assessments. In a sample of depressed patients (n = 92), life events were assessed using a modified self-report PERI Life Events Scale (Dohrenwend, Krasnoff, Askenasy, & Dohrenwend, 1978), a widely used checklist measure. Participants were asked to indicate whether any of the 110 listed items had occurred in the 12 weeks prior to the assessment date. Following completion of the PERI, using specific probes that were tailored to each PERI item, and based on the LEDS criteria, each respondent was queried about each item endorsed on the PERI in a semistructured personal interview. For each item endorsed on the PERI, a panel of raters who were trained to apply a contextual rating system based on the LEDS used the contextual information gained through the semistructured interview first to determine whether the endorsed PERI item corresponded to or met the criteria for a LEDS defined event or difficulty and, second, to assign a contextual threat rating.

Similar to the results reported by Katschnig (1986b), the correlation between the number of PERI items and number of LEDS rated events was modest (r = 0.41), again suggesting a lack of congruence between the measures. In this study, however, the researchers attempted to detail the sources of discrepancies between the two methods. Approximately 62% of all the items endorsed on the PERI did not match a LEDS-identified stressor. These discrepancies were accounted for by the following factors: (1) the PERI failed to distinguish between acute occurrences and ongoing difficulties (36% of the all discrepancies); (2) on the PERI, participants reported items that did not meet LEDS criteria for an event (25% of the all discrepancies); (3) participants reported PERI items that were outside of the time period (12% of the all discrepancies); (4) participants endorsed PERI items that were redundant with another PERI item, that is, the same item was endorsed twice under two different categories (e.g., "trouble with the boss" and "trouble at work" referred to the same set of circumstances) (7% of the all discrepancies); and (5) inconsistencies in the categories to which participants assigned their experience (5% of the all discrepancies). The investigators also noted that discrepancies resulted from items being written into the checklist (7%) and unreported on the checklist but elicited during the interview (2%) and PERI items that were both mislabeled and redundant with another PERI item (6%).

Six weeks after the first assessment, participants completed the PERI for the second time followed by a semistructured interview (identical to the procedures used for the first assessment). When inconsistencies were noted between the first and second assessment for items endorsed on the PERI, the respondent was asked directly about the discrepancy. About 60% of the occurrences endorsed on the PERI at the first assessment were inconsistent with those reported on the PERI 6 weeks later. Approximately 40% of all the occurrences reported at the first assessment were not reported at the second assessment, 10% were reported at the second assessment but not the first, 6% were reported at both assessments but classified differently at each time point, and 4% were reported at both assessments but actually represented two or more different events. Some gender differences were noted in that males had more discrepancies (5.3 on average) than females (2.8 on average) in their checklist responses. For example, men were more likely to report the same occurrence in two different categories, report an occurrence at the first administration but not the second, and to use different categories for the same occurrence at the two administrations. Note that because the PERI was used as the basis for deriving LEDS ratings, the

study was not designed to independently examine retest consistency in the LEDS.

In sum, the findings from the study of McQuaid and colleagues (1992) support other research that has indicated that the major methodological flaw in the checklist approach lies in the core problem of intracategory variability, leading to serious concerns about reliability and validity (Dohrenwend, Raphael, Schwartz, Stueve, & Skodol, 1993; Dohrenwend, 2000; Katschnig, 1986b; see also Dohrenwend, 2006; Gorman, 1993; Monroe, 2008, Zimmerman, 1989 for review). This research raises doubts about whether a checklist can be constructed with adequate psychometric properties. Dohrenwend (2006) acknowledges that the economic feasibility and ease of administration of the checklist method has resulted in a proliferation of research using this approach. Monroe (2008) concurs by suggesting that "self-report event checklists are too easily overvalued and misleading, providing an illusion of accurate stress measurement despite extensively documented unreliability" (p. 47).

Limitations of the LEDS

The LEDS is considered to be the "gold standard" for life stress assessment (McQuaid et al., 1992; Monroe & Roberts, 1990) but has not come into general use. There have been two major criticisms of the LEDS. First, it is costly to implement with respect to training and rating. Training usually consists of 1 week of instruction in interviewing techniques and rating procedures followed by several weeks of supervision by a trained LEDS rater. Periodic retraining is necessary to maintain consistent quality in the interviews as well as in the complex rating system. Rating time for each interview can be considerable even for an experienced rater, as every hour spent interviewing can translate into an hour of rating time. The additional cost incurred from the panel rating method is also seen as a significant deterrent. The total time to complete the LEDS process in our research has ranged from 6 to 9 hours per interview.

The second criticism focuses on a different area of concern. As noted earlier, the primary rating assigned to an identified acute or chronic stressor is referred to as the contextual threat rating. For the most part, this rating takes into account both the biographical circumstances of the individual (e.g., age, gender) and the situational circumstances (e.g., quality of the marital relationship, poor work performance) in which the stressor is embedded. The most often cited criticism, which has never been resolved, is that measures of contextual threat are based on two theoretically distinct criteria: (1) magnitude of event severity and (2) social vulnerability to a stressor (Dohrenwend et al., 1993; Tennant, Bebbington, & Hurry, 1981). Confounding of these two theoretically distinct factors would lead to inflated estimates of the impact of specific events and difficulties. The combination of event severity and vulnerability in rating varies across types of LEDS events (e.g., LEDS ratings of death events are more affected by social vulnerability than are ratings of health situations and job losses). In addition, the LEDS ratings of context may conflate socioeconomic status with severity ratings. Socioeconomic status of the respondent is embedded more widely across LEDS ratings than other indices of social vulnerability. American researchers have preferred to measure severity, vulnerability, and socioeconomic status factors separately, as exemplified by a number of longitudinal studies of specific events such as widowhood (Umberson, Wortman, & Kessler, 1992) and job loss (Kessler, Turner, & House, 1987). However, it should be noted that the majority of LEDS event and difficulty ratings are not influenced by factors related to social vulnerability; for instance, ratings of health events are based on objective factors such as the life threat or disability posed by the illness and its impact on work and other life routines (Brown & Harris, 1989). Similarly, ratings of job losses are based not on social vulnerability but rather on objective factors such as the unemployment rate, supply of jobs comparable with the one lost, and the proportion of family income lost. As noted earlier, these ratings are guided by rules and precedent examples that provide the rater with guidelines as to what "social vulnerability" features, if any, should be considered in the rating. As will be described later, one of our goals in developing a new assessment tool is to make these rules, as well as relevant context (including indices of "social vulnerability"), more transparent in the rating of an environmental stressor.

SECOND-GENERATION LIFE STRESS ASSESSMENT TOOLS

In an attempt to address the major limitations associated with the checklist and investigator-based approaches, a number of investigators have constructed alternative life stress tools, often referred to as "second-generation" life stress assessment tools (Dohrenwend, 2006; Zimmerman et al., 1986). Many of these second-generation assessment tools attempt to include some of the conceptual features of objective assessment embodied in the LEDS to ensure comprehensiveness, reliability, and conceptual validity of the new instrument. For proponents of the checklist methods, the goal is to develop strategies for reducing intracategory variation in a cost-effective manner; for the proponents of the investigator-based methods, the goal is to develop strategies for reducing the amount of time required to train, interview, and rate the interviews. These procedures have involved the following strategies: (1) specification of inclusion and exclusion criteria for items inventoried by a checklist, (2) development of qualitative probes to be administered by interview for any items endorsed on a checklist, and (3) construction of modified or shortened versions of the LEDS interview through structured probing. Several procedures have attempted to exclude vulnerability and socioeconomic

factors from affecting ratings of severity to make contextual stressor assessment more consistent with American research practices. Brief descriptions of some of these more developed instruments are provided.

THE STANDARDIZED EVENT RATING SYSTEM

Source Document: Dohrenwend, B. P., Raphael, K. G., Schwartz, S., Stueve, A., & Skodol, A. (1993). The structured event probe and narrative rating method for measuring stressful life events. In L. Goldberger & S. Breznitz (Eds.), *Handbook of stress: Theoretical and clinical aspects* (pp. 174–199). New York: Free Press.

The Structured Event Probe and Narrative Rating (SEPRATE) system was developed to reduce the problem of intracategory variability through the use of structured probes, while maintaining the distinction between objective features of event and the respondent's social situational and personal characteristics. The SEPRATE is derived from the PERI (Dohrenwend et al., 1978) life events checklist and consists of 84 individual items that a respondent endorses as occurring or not occurring. For those items that are endorsed as occurring, an interviewer uses a number of structured probes to provide a narrative description of each occurrence and to produce a standardized assessment of several rating dimensions, including the following: (1) magnitude of change in daily routines brought about by the occurrence for an average person experiencing the event, (2) desirability of the occurrence, (3) fatefulness or independence from the respondent's behavior, (4) the extent to which the event is life-threatening, and (5) whether the change is assessed as physically exhausting. The distinction between acute occurrences (events) and chronic circumstances (difficulties) appears not to be as well developed as in the LEDS. Unlike the LEDS, SEPRATE ratings are specifically developed to exclude individual vulnerability factors from contextual rating of the stressors. The investigators note that the event descriptions extracted from the narrative material do not include information about the respondent's social and personal characteristics (e.g., occupational circumstances, marital status), outcome status, or emotional response to the event. Each event description is rated by two or more judges (other than the interviewer); some of the ratings are considered "normative" in that judges are instructed to rate how "most people" would experience the event described, whereas other ratings are particular to the respondent and involve an assessment of what triggered the occurrence (e.g., independence of the occurrence).

Limited data are available with respect to reliability and validity. In one study, Shrout et al. (1989) compared the SEPRATE (for 12 selected events) with the PERI as a means of distinguishing 96 depressed patients from 404 community residents. The resulting odds ratio associated with the SEPRATE events, rated as both fateful and disruptive to life routines, was approximately double that obtained by the checklist method (PERI). The authors concluded that the use of detailed information obtained about the checklist item refined the event-exposure experience. Other studies indicate that moderate to excellent inter-rater reliability has been obtained across interviewers and raters (Mazure, Bruce, Maciejewski, & Jacobs, 2000; Shrout et al., 1989).

Similar to the LEDS, the SEPRATE has manualized interview and rating procedures such that extensive training is required for the investigator and/or research staff. Very little information is available in published studies that have used the preliminary version of the SEPRATE (Lennon, Dohrenwend, Zautra, & Marbach, 1990; Mazure et al., 2000; Shrout et al., 1989; Stueve, Dohrenwend, & Skodol, 1998) with respect to cost of implementation (i.e., time estimates for narrative production, coding, and rating, as well as training costs). Primarily, the SEPRATE has been used with adult community and patient samples; it does not appear to have been widely used in the life events literature to date.

MUNICH EVENTS LIST

Source Document: Wittchen, H., Essau, C. A., Hecht, H., Teder, W., & Pfister, H. (1989). Reliability of life event assessments: Test–retest reliability and fall-off effects of the Munich Interview for the Assessment of Life Events and Conditions. *Journal of Affective Disorders, 16*, 77–91.

This interview measure (Munich Events List [MEL]) consists of 85 concretely specified event descriptions that are endorsed in the timeframe of interest. For those event descriptions endorsed as occurring, the respondent is queried for relevant context. Subjective (respondent-based) and objective (interviewer based) ratings of severity are made on several dimensions (gain or loss, positive or negative impact, independence from respondent's behavior) for each event endorsed.

Limited data on the psychometric properties of the MEL are provided by the authors, but they appear to be adequate. Test–retest reliability for the MEL, based on a sample of 42 subjects, was quite high over a 6-week recall period; nearly perfect concordance was reported for severe events such as deaths (κ not reported), with lower agreement reported for less severe events ($\kappa = 0.74$). The average monthly falloff rate was estimated be 0.36%; the falloff rate was reported to be higher for nonsevere and positive events than for severe events. This rate is lower than for the LEDS, which is about 1% per month (Brown & Harris, 1989).

No information is provided with respect to the time (and costs) involved in training, interviewing, and rating the interviews. It does not appear that this measure has been used in many other studies appearing in the literature.

PAYKEL BRIEF LIFE EVENT LIST

Source Document: Paykel, E. S. (1997). The interview for recent life events. *Psychological Medicine, 27*, 301–310.

The Interview for Recent Life Events consists of 63 specific events and one nonspecific item (any other event) and is administered as a semistructure personal interview. Each event is defined with instructions contained within the interview; the 63 events are classified into 10 categories: work, education, finance, health, bereavement, migration, courtship and cohabitation, legal, family and social relationships, and marital relationships. Each endorsement of a specific event by the respondent is followed by a series of semistructured probes used to ascertain objective features of its occurrence. Each event is rated along several dimensions including month of the occurrence, independence, and objective negative impact based on context. Context in this measure, similar to the LEDS, excludes the respondent's emotional response or reaction to the event, but it does include, when relevant, the respondent's previous experience of the event, the desirability of the event, expectedness, social support received after or during the event, and personal circumstances of the respondent's life. A supplementary interview is available to assess chronic situations, similar to "difficulties" in the LEDS, but the methodology for rating is not as well developed as it is for events (Paykel, Cooper, Ramana, & Hayhurst, 1996; Paykel, Rao, & Taylor, 1984). It should be noted that the early work on the interview commenced separately from the LEDS, but subsequent refinements (independence and objective negative impact) were influenced by the LEDS.

Some reliability data are available. For example, inter-rater reliability of the main rating dimensions, assessed in a small sample of 21 respondents, appears to be adequate: 0.95 for specific event occurrence, 0.85 for month of occurrence, 0.87 for independence, and 0.76 for objective negative impact (Paykel, 1983). In a replication study by Cooke (1985), using a larger sample of 122 community residents, inter-rater agreement was comparable, except for objective negative impact ($\kappa = 0.64$), which is just within adequate range. Monthly falloff in reporting events was estimated to be about 1% (Paykel, 1983), which is comparable with the LEDS (Brown & Harris, 1989).

Training (3 weeks) is required for conducting and rating the interview. The interview takes 30–75 minutes to administer, depending on the length of the recall period, respondent's ease with the interview process, and the amount of additional probing required. It appears that coding and rating the events (approximately 10–15 minutes of additional interviewer time), including a brief written summary of the each occurrence, can be accomplished during the course of the interview or immediately following the interview.

The interview has been used in a number of studies examining both physical and mental disorders and symptoms with adult community and patient samples. In addition, the measure has been translated into several languages, including Italian and French.

LIST OF RECENT EXPERIENCES

Source document: Henderson, S., Byrne, D. G., & Duncan-Jones, P. (1981). *Neurosis and the social environment*. New York: Academic Press.

This interview measure is based on a life events scale developed by Tennant and Andrews (1976). Again, once one of the enumerated life events is endorsed by the respondent, probes are used to ascertain dating, to obtain a brief description of event occurrence, and to obtain a respondent's rating regarding the severity of impact. The method distinguishes between discrete life events and ongoing chronic difficulties. Independent raters are used to acquire objective ratings of severity.

The authors report on test–retest reliability, which appears to be more than adequate (Steele, Henderson, & Duncan-Jones, 1980). In a study of 52 clinic patients, the List of Recent Experiences was administered on two occasions, 7–14 days apart. High levels of test–retest reliability were found for the scale score (mean score for distress or change over all events), estimated at 0.89–0.94. However, the reporting of specific events was less reliable: Only 70% of events endorsed at either time period were reported under the same category at both administrations of the interview. The authors also report that the relative risk of experiencing a high level of neurotic symptoms among patients reporting a high level of life stress, compared with those patients reporting a low level of life stress, was 2.88.

No information is provided with respect to the time (and costs) involved in training, interviewing, and rating the interviews. The method has been used with adult community and patient samples examining psychological or emotional health outcomes.

UNIVERSITY OF CALIFORNIA, LOS ANGELES, LIFE STRESS INTERVIEW

Source Documents: Hammen, C., Mayo, A., Demy, R., & Marks, T. (1986). Initial symptom levels and the life event-depression relationship. *Journal of Abnormal Psychology, 95,* 114–112.
Hammen et al. (1987) Children of depressed mothers: maternal strain and symptom predictors of dysfunction. *Journal of Abnormal Psychology, 96,* 190–198.

This interview schedule is based on an events list developed by Paykel and Mangen (1980) and modeled after the contextual threat approach used in the LEDS. In a later study, an interview assessing chronic strains is described (Hammen et al., 1987); it is based on the work of Pearlin, Menaghan, Lieberman, and Mullan (1981) and Brown and Harris (1978) and includes an assessment of role content areas, employment, finances, and relationships with children and other family members. Similar to the LEDS method, once an enumerated event or chronic strain has occurred, the respondent is queried regarding the date and details surrounding the occurrence, including duration, expectedness, previous exposure to similar occurrences, available resources

and support, consequences of the occurrence, and any other relevant background. An independent team then rates each of the narratives prepared by the interviewer for each occurrence. As with LEDS event and difficulty descriptions, any specific information about how the respondent felt or reacted to the event is omitted from the narrative. Objective ratings for threat and independence are made by the rating team and not the respondent or interviewer.

Inter-rater reliability appears to be adequate for both measures. For example, for events, using two separate teams of raters, κ coefficients were estimated to be 0.84 for objective threat and 0.75 for independence ratings (Hammen et al., 1986). For chronic strains, assessed in a separate study (Hammen et al., 1987), overall inter-rater agreement for two-person teams making ratings for 34 depressed patients was 0.97. For specific areas of strain, inter-rater reliabilities range from 0.93 for finances to 0.99 for respondent's health. The authors also reported that for a separate sample of 44 patients, test–retest reliability over a period of 6–20 months was estimated to range from 0.58 to 0.74 for the various subscales (Hammen et al., 1987).

Training in the instrument is available at the Hammen Lab at the University of California, Los Angeles (1–1.5 days). According to the authors, an average interview takes about 45 minutes and rating takes another 20–30 minutes. A team rating system is used to produce the final ratings (Hammen, personal communication, July 2008). This method has been used extensively by Hammen and her colleagues in a variety of community and outpatient adult and adolescent samples for both physical and mental health outcomes. It has also been adopted by several other investigators, including a version that has been adapted and modified for children and young adolescents (Rudolph & Hammen, 1999).

KENDLER LIFE STRESS INTERVIEW

Source Document: Kendler, K. S., Karkowski, L., & Prescott, C. A. (1998). Stressful life events and major depression: Risk period, long-term contextual threat, and diagnostic specificity. *The Journal of Nervous and Mental Disorders, 186*, 661–669.

This interview schedule consists of probes designed to collect information on the occurrence of 11 personal event types occurring primarily to the respondent as well as four classes of events occurring primarily to, or in interaction with, an individual in the respondent's social network. The 11 personal event types include the following: assault, divorce/separation/breakup, major financial problem, serious housing problems, serious illness or injury, job loss, legal problems, loss of a confidant/loved one/close friend, serious marital problems, being robbed, and serious difficulties at work. The four classes of network events include the following: serious problems in a relationship with a network member, serious personal crisis of a network member, death of a network member, and serious illness of a network member. Similar to the LEDS, once an event has occurred, the respondent is queried regarding the date and details surrounding the occurrence. Interviewers make objective ratings of long-term contextual threat (LTCT) (defined as lasting at least 10–14 days after the event) and dependence; rules and rating procedures are manualized. Similar to the LEDS, LTCT is a rating to reflect how most people would be expected to react to an occurrence in a particular set of biographical and life circumstances, with such a rating produced independently of the respondent's judgment of threat or unpleasantness, or emotional reaction to the occurrence. Dependence of an event reflects the probability that the respondent's own behavior contributed to the occurrence of the event (rated on a four-point scale: clearly independent, probably independent, probably dependent, and clearly dependent) (Kendler, Thornton, & Gardner, 2000).

Inter-rater reliability for the occurrence and dating of SLE categories was assessed to be in the good to excellent range; for the occurrence of SLEs, $\kappa = 0.93$, and for the dating of the SLEs, $\kappa = 0.82$ (Kendler et al., 1995). Reliability of the LTCT was assessed on both an inter-rater and test–retest basis (Kendler, Karkowski, & Prescott, 1998). Inter-rater reliability, whereby experienced interviewers rated 92 randomly selected SLEs, was assessed to be [κ] 0.67 for LTCT and [κ] 0.79 for dependence. The interview was readministered to 191 female respondents approximately 4 weeks later; test–retest reliability was assessed to be [κ] 0.69.

Training takes approximately one day. Dependence and LTCT ratings are made during or immediately after completion of the interview without a consensus meeting to review the ratings. Ratings are reviewed by two independent editors who can query any SLE rating that seems inappropriate (Kendler et al., 1998). No information is available regarding the length of the interview.

This method has been used extensively by Kendler and his colleagues in numerous studies of the relationship between depression and life stress using a cohort of twin pairs (Kendler et al., 2001a, 2001b, 2002; Kendler, Kuhn, & Prescott, 2004). For example, in a study of female twins, the risk for a depressive onset given the number of SLEs within 1 month was found to be as follows: no event, 0.9%; one SLE, 3.4%, two SLEs, 6.8%; and three SLEs, 23.8% (Kendler et al., 1998).

STRESSFUL LIFE EVENTS AND DIFFICULTIES INTERVIEW

Source Document: Leserman, J. (2003b). *Stressful life events and difficulties (SLED) interview: Training and rating manual for the PREDICT Study.* Chapel Hill, NC: Department of Psychiatry, University of North Carolina at Chapel Hill.

This semistructured interview method is based on a modification of the PERI and includes 111 items. Once an enumerated event or difficulty has been reported, trained

interviewers use semistructured probes designed for each life domain to ascertain the dating and contextual circumstances surrounding the occurrence. Most noteworthy is that the author has developed a stress rating manual containing a detailed set of rating rules, norms, and vignettes for rating each of the 111 stresses. The ratings are based on the LEDS ratings of contextual severity. The norms for each of the 111 stressors are based on the degrees of threat that most people would likely experience given a particular set of circumstances that may include a consideration of the following objective factors: financial impact, degree of control, life threat, personal involvements, or nature of relationships to others involved. Although subjective ratings of stress are obtained from respondents for each event and difficulty endorsed, the contextual ratings of stress are made by raters independent of the respondent's rating of threat as well as the respondent's manner of coping with the occurrence.

Inter-rater reliability for two raters was demonstrated by having each rater independently score 53 interviews, including 494 stressful events or difficulties. With respect to the 53 interviews, the two raters agreed on the exact severity rating in 81% of the cases ($\kappa = 0.70$); raters disagreed on whether a stressor was severe only 2% ($n = 11$) of the time (Evans et al., 1995, 1997).

The method is manualized and requires a series of training sessions (six to eight 2-hour session or approximately 16 hours). An average interview takes about 45 minutes, and rating takes an additional 5–10 minutes (Leserman, personal communication, September 2008).

Leserman and her colleagues have used the method in several studies examining the relationship between stressors and disease progression in HIV infection (Evans et al., 1995, 1997; Leserman, 2003a, 2008; Leserman et al., 1999, 2000, 2002). For example, in a study of 93 HIV-positive homosexual men without clinical symptoms at the time of study enrollment, the more severe the life stress experienced (the stress score was based on the total number of severe stressors), the greater the risk of early HIV disease progression (Evans et al., 1997). Specifically, the risk of early disease progression was doubled for every one severe stressor experienced per 6 months of the observation period. For those individuals who had been in the study for at least 24 months ($n = 66$), higher severe life stress increased the odds of developing HIV disease progression about fourfold (odds ratio = 3.7). In an earlier study of 99 asymptomatic HIV-positive and 65 HIV-negative homosexual men (Evans et al., 1995), data demonstrated that for HIV-positive men only, severe stress was significantly associated with reductions in killer lymphocytes (natural killer cell populations and cytotoxic/suppressor T lymphocyte subsets). These studies are the first prospective reports that demonstrate that severe life stressors, assessed contextually, are associated with an increased rate of early HIV disease progression as well as other indicators of immune changes.

THE DETROIT COUPLES STUDY LIFE EVENTS METHODS

Source Document: Kessler, R. C., & Wethington, E. (1991). The reliability of life event reports in a community survey. *Psychological Medicine, 21*, 723–738.

Similar to the SEPRATE, this interview uses a checklist embedded in a personal interview to ascertain the occurrence of a particular life event. Then, a series of standard domain-specific queries along with semistructured probes (to assess meaning) are used to derive estimates of objective stress severity. Similar to the LEDS, acute life events are differentiated from chronic stressors (difficulties) and temporal priority of events, difficulties, and health outcomes are established using standardized probes. The authors note that even with the probes used to assess meaning, not enough contextual information is collected to approximate the contextual severity ratings made in the LEDS (Wethington et al., 1995). An important feature of this measure is the development of techniques to improve recall and accurate dating of life events, including a calendar filled out jointly by the interviewer and respondent. The ratings assigned to events and difficulties are not based on detailed contextual ratings. Rather, events and chronic stressors are rated on the basis of a more limited number of probes (e.g., death of a spouse or child is rated as more severe than the death of an acquaintance; the severity of an unemployment period is rated based on the length of time out of work).

Results from the Detroit Couples study demonstrated that the interview has acceptable psychometric properties overall, in that respondents were able to recall severe negative events over a 12-month recall period with adequate reliability and that respondents could date event occurrence with good consistency. The monthly falloff rate for severe event reports was estimated to be from 2% to 3%. The relative risk of onset of depression associated with severe events in the previous 12 months was estimated to be 2.43 (odds ratio), which is lower than the estimates associated with the LEDS (ranges from 7 to 13, Brown & Harris, 1989) and the SEPRATE (Shrout et al., 1989). The investigators also presented some interesting observations (Kessler & Wethington, 1991). For example, with respect to severe events, the average reliability of reports was 0.64 for husbands and 0.68 for wives (husbands and wives interviewed from the same couple). Sensitive events, such as criminal activities or marital difficulties, were less reliably reported. In addition, personal events (reported by the respondent) were reported more accurately than events occurring to the respondent's spouse.

Use of this instrument requires training, but the authors indicate there is significantly less training time (1 day), interviewing time (average length of the interview was 78 minutes), and coding time (2 hours or less) when compared with the LEDS. This measure was designed to be used in large-scale community surveys. An offshoot

of this measure was used in the National Survey of Health and Stress (Kessler, 1990), which sampled 8,000 Americans, aged 15–54.

THE STRUCTURED LIFE EVENTS INVENTORY

Source Document: Wethington, E., Kessler, R. C., & Brown, G. W. (1993). *Training manual and technical report for the structured life events inventory.* Ithaca, NY: Life Course Institute, Cornell University.

The Structured Life Events Inventory (SLI) was designed to be a more structured version of the LEDS (more consistent with standard survey techniques) with the purpose of reducing the amount of time required for training as well as for producing contextual ratings similar to those available from the LEDS. The method consists of two sets of probes for each life domain: (1) probe sequences are designed to filter out events that are determined not to reach threshold for severity and (2) for those events deemed to be above threshold, additional probe sequences are administered that attempt to clarify the circumstances surrounding the event. In addition, the interviewer has the option of probing further in a less structured fashion to ascertain any other information thought to be needed to make the contextual ratings. In this way, similar to the LEDS, this method requires interviewers to make decisions about the probes they use during the interviewing process to gather enough information about the circumstances to estimate the ratings associated for each identified event and difficulty. For each event, ratings are made by interviewers for contextual severity, event type, and focus, which are similar in concept to the LEDS ratings.

The method is manualized and requires a 3-day training sequence. As with the LEDS, training exercises based on examples in the LEDS dictionaries are used to teach interviewers the rules for deciding on the thresholds for inclusion of events and difficulties as well as to demonstrate the importance of probe sequences to ascertain the relevant contextual and biographical information needed to make the ratings. The goal of this type of didactic training, along with the provision of key instructions in the interview schedule, is to reduce reliance on interviewer memory.

Importantly, the authors provide some preliminary data from a study designed to examine the reliability and validity of the SLI in comparison with the LEDS. A sample of 243 community-dwelling residents was interviewed, half with the LEDS and half with the SLI. Most noteworthy is the considerable reduction in time for training, interviewing, and rating of the SLI in comparison with the LEDS in this study. The average LEDS interview production time, which includes the time required for interviewing, coding, and rating, was 16 hours, compared with the 9 hours required by the SLI. The SLI interviewers were able to distinguish severe events from nonsevere events reliably; however, the LEDS seemed to be superior in eliciting and rating chronic difficulties. The LEDS and SLI appeared comparable in estimating the risk of depression onset. This method has only been used with adults. Contextual ratings do not distinguish objective severity from vulnerability.

NEXT STEPS IN METHODS FOR ASSESSING EXPOSURE TO ENVIRONMENTAL STRESSORS

As we have noted throughout the chapter, the task of defining, conceptualizing, and measuring exposure to environmental stressors is complex; the empirical evidence suggests that reliable and valid assessment needs to go beyond the simple enumeration of items endorsed on a checklist as the metric of exposure. Moreover, the need for reliable and valid assessment is greater than ever if the assessment of stressor exposure is to keep pace with the advances in biomedical and genetics research (Paykel, 2001; Monroe, 2008). The second-generation tools described earlier represent important progress in the advancement of the assessment of exposure to environmental stressors. Many of these second-generation tools are used in programs of research that continue to advance our understanding of the role of stressors in a variety of health outcomes such as depression (Hammen, 2005; Kendler et al., 2001a) and HIV/AIDS progression (Leserman et al., 2002). One of the most salient aspects of research using these tools is the growing consensus that the objective and/or contextual features of stressors, adapted in some form from the LEDS ratings, may be among the most important characteristics of stressor exposure (see Table 40.2). Although these tools differ in the exact methods by which this assessment is made, they all involve criteria for determining inclusion of an acute or chronic set of circumstances as a stressor and for determining the severity of that stressor based on its meaning (i.e., objective and/or contextual threat). These aspects have become key considerations in the assessment of stressor exposure (Dohrenwend, 2006; Monroe, 2008; Thoits, 1995; Turner & Turner, 2005; Turner & Wheaton, 1995).

However, even with these advances, there remain some important limitations in the second-generation tools. For example, although the distinction between acute and chronic stressors is generally recognized in second-generation measures, the tools differ in their ability to assess duration of a particular stressor as well as changes in magnitude or severity in the same stressor (especially for chronic stressors) over the time period of interest. This limits the ability to assess the duration of "total" stressor exposure as well as the duration of exposure to stressor sequences and changes in severity or magnitude that may occur over the course of exposure during the time period of interest. On a pragmatic level, similar to the LEDS, many of these second-generation instruments have not found their way into more general use in the literature; this is likely because their use requires training as well as more extensive interviewing and coding

Table 40.2 ■ Second-Generation Measures of Environmental Stressors

Instrument	Reliability/Validity	Rating System	Coverage of Life Domains	Manual/Training	Chronic Stressor Assessment	Administration Time
SEPRATE	Very good inter-rating reliability; superior predictive validity compared with checklist	Panel contextual rating of severity, independence; social vulnerability excluded from ratings	Comprehensive coverage	Training required; ratings manual developed	Included	Not reported
MEL	Very good test–retest reliability for high magnitude events; low falloff for severe events	Investigator ratings of severity, independence	85 concretely specified events	Unknown (??)	Included	Not reported
IRLE	Very good inter-rater reliability; low falloff for severe events	Panel ratings of severity, independence	63 specific events	Training required; ratings manual available (??)	Supplemental interview available, not as well developed as the events	30–75 minutes for interview; 10–15 minutes for rating
LRE	Adequate test–retest reliability	Investigator ratings of severity	Comprehensive coverage	Unknown	Included	Unknown
UCLA	Very good inter-rater reliability; test–retest average to good	Panel ratings of severity, independence	Comprehensive coverage	Training required	Included	45 minutes for interview; 20–30 minutes for rating
Kendler	Very good inter-rater reliability; very good predictive validity	Investigator ratings of severity, independence; consensus panel	Comprehensive coverage	Training required	Included	Unknown
SLEDS	Very good inter-rater reliability	Investigator rating of severity	111 specific items	Training required; ratings manualized	Included	45 minutes for interview; 5–10 minutes for rating
DAS-C	Very good inter-rater reliability for severe events; low falloff for severe events	Severity rating applied by expert rater; not full contextual ratings	Comprehensive coverage	Training required; ratings applied during coding	Included	45–70 minutes for interview; rating applied during coding
SLI	Predictive validity comparable with LEDS	Severity rating by interviewer; checked by expert rater	Comprehensive coverage	Training required; ratings checked by expert coder	Included	55 minutes (average) for interview; expert rating approximately 1 hour per interview

time than traditional checklist approaches (although several appear to have achieved some improvements in training and rating time economies as compared with the LEDS). Also, there have not been, to our knowledge, any direct comparisons of these second-generation tools with the LEDS or with self-report checklists within the same study, leaving untested the issue of their relative merit in defining, conceptualizing, and measuring exposure to environmental stressors.

We are attempting to address some of the limitations that are evident in both the LEDS and the second-generation tools through the development of a new field-deployable instrument, the Life Events Assessment Profile (LEAP). The LEAP is designed to reduce investigator burden and some of the expense associated with fielding second-generation tools, while also preserving the key advantages (i.e., objective and/or contextual rating, the distinction between acute and chronic circumstances). In addition, the LEAP will incorporate strategies that enhance the assessment of temporal relationships between stressors to allow for more precision in duration of exposure and changes in magnitude over the course of exposure.

Since the LEDS is perhaps the most well-defined and manualized stressor exposure system, as well as the one with which we have the most experience (Ackerman et al., 2002a, 2002b; Cohen et al., 1998; Duggal et al., 2000; Frank, Anderson, Reynolds, Ritenour, & Kupfer, 1994; Frank et al., 1996; Karp et al., 1993; Kessler & Wethington, 1991; Malkoff-Schwartz et al., 1998, 2000; Sherrill et al., 1997; Wethington, 2000, 2002; Wethington, Kessler, & Brown, 1993; Wethington & Serido, 2005; Williamson et al., 1998), the design of the LEAP began with a review of all existing LEDS documentation, including manuals and dictionaries (Brown & Harris, 1978, 1989). For each domain (e.g., relationships, work, health) of life events and chronic life stressors ("difficulties"), key objective or behavior-specific contextual features were extracted, with particular emphasis on identifying the LEDS criteria for distinguishing negative or "stressful" occurrences. A standard set of behavior-specific probes was developed

for each identified event or difficulty. In contrast to the open-ended questions used in LEDS, use of behavior-specific probes is intended to reduce interviewer training demands and to increase efficiency of administration. Following each standard probe, we included lists of key specific contextual features that serve to (1) determine whether the occurrence meets criteria for an event or difficulty and (2) distinguish between a severe and non-severe life stressor. The goal is to characterize the contextual and objective features of each life stressor in a more efficient, direct, and transparent manner than is evident in the semistructured format of the LEDS.

The LEAP comprises a web-based computer administration and data management system. This system is a custom-written database program using Oracle and PHP code, securely accessible worldwide using a standard web browser. Following user authentication, a concise set of menus and functions directs the flow of the interview. Our web-based system is being designed to facilitate movement across interrelated life domains (e.g., work, marriage, health) by handling and navigating through complex skip patterns often required during the course of the interview. At the same time, the recursive nature of the interview, which requires the interviewer to interact with a calendar or timeline system and to update the calendar throughout the interview, is handled with the use of relational database features of the program. This is critical to characterize the onset and offset of events and difficulties across domains as well as the temporal relations between events and difficulties, allowing for an objective estimate of duration and magnitude (severity) of exposure (Cohen et al., 1998; Cohen, Kessler, & Gordon, 1995; Thoits, 1995; Herbert & Cohen, 1996; Turner & Turner, 2005; Turner & Wheaton, 1995). This feature is available in the LEDS but has not been well developed in the second-generation tools. This system will provide a platform to permit real-time algorithm-based scoring, whenever possible, such that upon the completion of the interview, the interviewer will have complete access to a series of ratings without the need for transcription or the use of consensus meetings.

Recently, we have undertaken a preliminary study examining the psychometric utility of the LEAP. In particular, we are investigating the concurrent validity of the LEAP by comparing it with the LEDS, as well as to a standard checklist measure, in a community-based sample of adults. We plan to compare the discriminant and convergent validity of the LEAP with the LEDS and the checklist method by examining their associations with measures of physical and psychological symptomatology. We will also examine the test–retest reliability of the LEAP and compare this with the test–retest reliability of the life events checklist. Given the use of structured behavior-specific probes and computer-based algorithms, it will also be possible using this instrument to efficiently explore alternative methods of rating that will exclude (as much as possible) social vulnerability and socioeconomic factors from the ratings of severity. The results from these efforts should inform further refinements in the interview content, algorithm-based scoring procedures, and training procedures. Although we cannot yet document the reliability and validity of our new research tool, we hope that this type of effort involving empirical comparisons between standard and newly developed measures can revitalize life stress research in important and productive ways.

CONCLUSION

Environmental stressors in the form of acute events and chronic difficulties are important representations of social and environmental demands. Although the checklist method of environmental stressor assessment offers ease of administration in its economic feasibility and apparent standardization, it has been demonstrated to be unreliable. The interview method, on the other hand, although more reliable, has not been widely used because its complexity, embedded in the requirement of extensive training for administration and rating, has rendered it impractical in many research applications. Although second-generation tools have provided important progress in life stress assessment, a next generation of instruments is necessary to enhance disseminability of these methods and to assist in the quantification of risk exposure. The use of a structured interview format in conjunction with calendar-based dating procedures, a computer-administered format, and an automated scoring platform represents significant advances in the design of research approaches for the assessment of major environmental stressors. Once such instruments become available, considerable work will be needed to move beyond generic associations with "life stress" to understand the dimensions and qualities of environmental stressors that may or may not contribute to disease outcomes and to characterize the mechanisms that underlie those relationships.

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41 Combining Checklist and Interview Approaches for Assessing Daily Stressors: The Daily Inventory of Stressful Events

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There are features and events in the daily environment that pose risks to well-being, such as demanding work conditions, financial pressures, and work–family conflicts. Often referred to as daily stressors or hassles, these events represent tangible, albeit minor interruptions that may have a more proximal effect on well-being than major life events such as job loss and divorce (Lazarus, 1999). In terms of their physiological and psychological effects, reports of major life events may be associated with prolonged arousal whereas reports of daily stressors may be associated with spikes in arousal or psychological distress that day. In addition, minor daily stressors exert their influence not only by having separate and immediate direct effects on emotional and physical functioning, but also by piling up over a series of days to create persistent irritations, frustrations, and overloads that may result in more serious stress reactions such as anxiety and depression (Lazarus, 1999; Zautra, 2003).

Although the research community has accepted for some time the notion that daily stressor exposure is associated with poorer physical and mental health, it has been harder to establish with precision how specific features and events in the daily environment contribute to poorer health. It may not be enough simply to know if a stressor occurred, but rather to consider multiple facets of the stressful experience, including the objective characteristics of the event, such as content, as well as aspects of an individual's subjective appraisal of the stressor, such as perceived severity (Almeida, 2005). Arguably, some daily stressors (e.g., family member diagnosed with cancer) will be worse than other stressors (e.g., mechanical breakdown at work). Research addressing these issues requires comprehensive, reliable, and valid measures of stressor exposure that are relevant to the experiences of diverse groups.

In this chapter, we review various daily stressor measures including checklist and open-ended narrative approaches. We also describe a new and innovative daily event assessment method, the Daily Inventory of Stressful Events (DISE; Almeida, Wethington, & Kessler, 2002), which is designed to examine multiple components of daily stressor exposure. A primary aim of this method is to capture variability across stressful situations, between persons of different groups, or within persons over a period of time. Capturing situational variability is vital to elucidating how stressors influence adaptation. Dohrenwend (2006) has detailed how situational variability is poorly captured by the traditional events checklist approach (e.g., McQuaid et al., 1992). A case in point is that not all arguments are the same. They vary in content, objective threat (shouting versus physical violence), and appraised meaning. The DISE is designed to capture intracategory variability across situations for stressful events such as arguments. This chapter will present findings documenting a great deal of variability in stressor severity across different types of stressors, as well as variability in severity within a specific type of stressor across days. The final portion of the chapter highlights the research potential of the DISE by comparing its validity to that of checklist approaches and by providing several examples of research using the DISE to assess daily stressors and well-being.

CHECKLIST APPROACHES IN DAILY STRESSOR RESEARCH

A typical study of daily stressors (or hassles) uses a self-administered checklist consisting of a number of common occurrences that are believed to be associated with variations in mood or physical health symptoms. Early daily stressor checklists, such as the Hassles Scale (Kanner, Coyne, Schaefer, & Lazarus, 1981) and the Inventory of Small Life Events (Zautra, Guarnaccia, & Dohrenwend, 1986), relied on retrospective reports of experiences over a fairly long time frame (e.g., the past month) and contained many items. For example, the Hassles Scale consists of 117 items assessing experiences in areas of health, interactions, and events with friends and family, and work, among others, and asks respondents to endorse those events that were experienced over the past month, and to rate the severity of each. These early measures captured a breadth of experiences, but were somewhat hampered by their length and reliance on retrospective recall of events *over the course of a 1-month period*. Although early

instruments were quite effective at providing a great deal of information regarding the types of events that people experience in their daily lives, they did not capture individual's experiences in time and place, for example, as they unfold during the course of a single day. Therefore, this early approach is probably better suited for characterizing individual differences in the experience of daily stressors than for temporally linking the experiences of a given day to relevant daily health indices.

Completing event checklists on a daily basis provides better temporal resolution of daily stressors by focusing on sampling events that happen on specific days. For instance, Stone and Neale (1982) developed the Assessment of Daily Events (ADE) checklist, and its current revised form, the Daily Life Experiences (DLE) checklist. The ADE/DLE checklist comprises a list of 78 events that represent various domains in daily life, and scales for obtaining subjective ratings of the desirability and meaningfulness of each experienced event. Brantley and Jones (1989) developed a similar measure, the Daily Stress Inventory, which assesses 58 minor events as well as a subjective rating of how stressful each event was. Similarly, DeLongis and colleagues (DeLongis et al., 1998) revised the Hassles Scale to include only 53 items, assessing domains similar to those captured in the original version, but conducive to use in a daily diary research design. Zautra and colleagues (Zautra et al., 2005) have also shown that, with minor revisions (e.g., reduction to an 18-item list), the Inventory of Small Life Events can be effectively adapted for use in a daily diary design.

The approach of administering event checklists on a daily basis has important implications for the assessment of daily stressors. The repeated daily assessment of individuals using checklists allows for improved precision in characterizing the typical days of individuals as the day is the unit of analysis. Checklists such as the ADE/DLE that also include subjective ratings about each event provide more information than whether an event simply occurred, adding multidimensional data about events, days, and individuals. A limitation of the daily checklist approach that it shares with the monthly sampling approach discussed previously is that the experience of a broad range of events is obtained at the expense of obtaining intimate, and potentially useful, in-depth knowledge about any of the events.

Bolger and colleagues have attempted to overcome some of the shortcomings of traditional checklist measures by using checklists that assess only events that occur with regular frequency. This reduces the number of items to which participants need to respond, which frees up space and time in a study to collect more in-depth information about each event that is reported. Using daily diary data from couples, Bolger and Schilling (1991) compiled a checklist of 22 events that assessed categories such as demands at home and work, arguments, and interpersonal tensions, and also included a number of follow-up questions whereby respondents rated the events on psychological dimensions (e.g., perceived control, how much responsibility the participant felt). Such an approach represents an innovative way to better characterize the stressors that people *most commonly* experience. One must consider the extent to which particular events are important for a broader-based assessment of daily stressors if the frequency with which they occur is quite low. Events with a low frequency of occurrence may be informative if those events are of particular theoretical interest, but may not provide a substantial contribution to the assessment of daily stressors for individuals on average. Furthermore, the inclusion of these low-frequency events may take up space and time in the study protocol that could potentially be used to include other measures that may be of greater theoretical interest given the foci of the particular study.

Several methodological concerns have been raised about daily checklist measures. First, there is evidence that memory for daily events may be imperfect. Recall of minor events decays after only a few hours (Stone, Kessler, & Haythornthwaite, 1991). Second, individual differences in what constitutes evaluation of something as a stressor—stressor *appraisal*—may affect the tendency to report the occurrence of an incident. The consequence of such individual differences is that subjective appraisal and the putatively "objective" report of a stressor are confounded (McQuaid et al., 1992). Third, to assure adequate responses, the daily diary questionnaire must be relatively brief. Brevity increases compliance, but may reduce comprehensiveness (Herbert & Cohen, 1996).

NARRATIVE APPROACHES TO DAILY STRESSOR ASSESSMENT

An alternative to the checklist approach is using an open-ended assessment of stressors whereby participants provide a description of the daily events that they have experienced. Such an approach, born out of major life events research, utilizes semi-structured interview methodology (see Wethington, Brown, & Kessler, 1995). An example of an open-ended interview-based assessment tool, coming from Roghmann and Haggerty (1972), has people describe events in which things went wrong at home, at work, and with family members. A similar approach was used by Eckenrode and colleagues to assess daily stressors in a study of low-income women and children (Caspi, Bolger, & Eckenrode, 1987; Eckenrode 1984; Gortmaker, Eckenrode, & Gore, 1982). Participants were asked whether "Anything went wrong today in the house, with the children or others in the household, at work, or elsewhere", and provided an in-depth narrative if something indeed happened. The narratives provided by participants in both studies subsequently were independently classified into specific categories. In contrast to checklist instruments, open-ended assessments capture fewer events per day per individual, but potentially yield a greater amount of information about each event that

is captured. It can be time and labor intensive to collect such detailed data, and the more limited range of events that can be captured may at times be a significant drawback. The use of independent raters to classify the events does, however, provide an innovative take on the assessment of daily stressors in that events can be standardized in ways that circumvent potential confounds that occur with subjective reports such as individual differences in response tendencies.

The foregoing discussion provides only a quick, illustrative overview of the types of approaches used to assess daily stressors (for more comprehensive reviews, see Eckenrode & Bolger, 1997; Bolger, DeLongis, Kessler, & Schilling, 1989). Nonetheless, certain patterns can be observed. There is a clear tradeoff between the range of events that can be assessed and the depth of information that can be obtained about any given event. Checklist approaches allow for sampling a wider variety of events, whereas open-ended interview-type approaches offer the most information per event. Even when it comes to supplementing checklist events with subjective ratings (e.g., severity, impact, desirability), the researcher must balance the protocol between the breadth of events sampled, and the subsequent ratings tied to each event. Obviously, assessment methods can be altered to fit the purposes of the study. If a particular type of event is of interest, few events and many questions about the specific event(s) may be in order. If characterizing the types of stressors individuals typically experience is an important focus, assessing more events may be warranted. An attractive compromise would be to be able to make use of the main advantage of checklist-based approaches, thereby sampling a range of events that occur somewhat regularly, and combine it with in-depth information about each event obtained via interview methods, to provide a wealth of information both quantitatively and qualitatively about daily stressors and experiences. Indeed, Eckenroade and Bolger (1998) called for such an integration of methods for daily stress research. To this end, the DISE (Almeida et al., 2002) was designed.

THE DISE

The development of the DISE was guided by concerns about self-report bias in the measurement of daily stressors. An assumption underlying daily stressor measures is that they objectively capture the stressors themselves. Yet the typical measure of daily stressors asks for self-report of an event and of the event's severity to assess objective exposure and objective differences between stressors. The reliance on self-reports means that stressor measures may be biased. Self-report of stressor severity may be confounded with the correlates of stressor appraisal—personality, mood at the time of recall, and history of exposure to stressors. Thus, self-reports of stressor exposure may reflect stable individual differences as well as reactivity to stressors, thereby undermining their discriminant validity.

To address demands for comprehensiveness, reliability, and validity, the DISE adopted several innovations in daily event measurement. To assure comprehensiveness, the DISE was developed using samples representative of the U.S. population. To enhance validity by reducing one type of self-report bias, the DISE includes a system of *investigator ratings* to assess the severity of stressor exposure on a daily basis, as well as respondent ratings of severity. To permit access to representative samples and implement investigator ratings of stressor exposure, the DISE is designed to be administered over the telephone.

DEVELOPMENT OF THE DISE

The DISE method was originally developed for the National Study of Daily Experiences (NSDE) to assess exposure to daily stressors. The NSDE is one of the in-depth satellite studies of the Midlife in the United States Survey (MIDUS), and includes a nationally representative sample of 1,031 adults (562 men, 469 women), aged 25–74, randomly selected from the larger MIDUS in 1995–1996. A second wave of data was recently completed and the sample expanded to include a nationally representative sample of 2,022 adults aged 35–84 from the larger MIDUS Wave 2 sample (see Almeida, McGonagle, & King, 2009 for a description of the sample and design).

During both waves of the NSDE, respondents participated in 8 consecutive days of daily telephone interviews, in which they answered questions about their daily experiences. On the eighth day of interviewing, respondents answered several questions about their previous week. The initial and final interviews lasted approximately 15–20 minutes. The other six interviews lasted approximately 10–15 minutes. Data collection consisted of separate "flights" of interviews with each flight representing the 8-day sequence of interviews from approximately 25 respondents. The initiation of flights was staggered across the week to control for day-of-week bias. On average, respondents completed over seven of the eight daily interviews.

The DISE Method. The DISE is a semistructured telephone interview instrument, assessing a wide variety of stressors and stressor characteristics (Almeida et al., 2002). The interview consists of a series of "stem" questions asking whether certain types of events (e.g., arguments, work-related stressors) have occurred over the past 24 hours, along with a set of guidelines for probing affirmative responses. Pilot testing resulted in seven stem questions that asked about arguments and disagreements, instances of avoided arguments, events at work or school, events at home, experiences with discrimination, events that occurred to a close friend or relative, and an open-ended question asking about "anything else." The number of stem questions was comprehensive enough to include most daily stressors (Herbert & Cohen, 1996), but small enough to limit respondent burden.

After obtaining an affirmative response to a stem question, the interviewers were instructed to probe to elicit a short narrative description of the stressor. These open-ended responses were audio recorded and later transcribed. Once an event was endorsed, the interviewer asked questions about the objective circumstances surrounding the event. The purpose of these probes is to gather enough information to rate various components of the discrete events. After the narrative was obtained, the interviewer asked the respondent to rate the severity of the stressor by appraising the event as not at all, not very, somewhat, or very stressful. For each event rated as "somewhat" or "very stressful," the respondents also were asked a series of structured questions that assessed primary appraisal of the stressors. These questions were based on the work of Lazarus and Folkman (1984) and measured what was perceived to have been at risk in the situation, such as disruption to daily routine, financial situation, physical health or safety, plans for the future, others' health or well-being, and views about oneself.

The investigator rating method. A unique aspect of the DISE is the implementation of investigator ratings. To our knowledge, we were the first group of researchers to apply investigator rating methods to the study of daily stressors. After transcribing respondents' open-ended descriptions of their daily stressful events, a team of independent raters then coded the short narratives for various dimensions of each stressor, including the topic or content of the situation, who was involved in the event, dimensions of threat, and investigator ratings of stressor severity.

We believed that adapting investigator ratings could lead to major innovations in the study of daily stressors. First, investigator ratings make it possible to distinguish the objective characteristics of an event from respondents' subjective evaluations of the stressor, which may be confounded with individual differences in appraisal and its correlates (Wethington, Brown, & Kessler, 1995). Second, early checklist measures of stressors included affective responses to stressors (e.g., Dohrenwend, Dohrenwend, Dodson, & Shrout, 1984), whereas investigator ratings provide a means of separating the respondent's description of the occurrence of an event (e.g., argument with spouse) from the respondent's affective response to the event (e.g., crying). Third, this approach addresses the issue of stressor variability (Dohrenwend, 2006) by classifying events by content, severity, and dimensions of threat based on standardized criteria. Finally, this approach makes it possible to obtain an in-depth assessment of stressor exposure, without burdening the respondent with an exhaustive list of all possible stressors. For example, although only one stem question directly inquires about arguments, the narrative format gives respondents the opportunity to identify other arguments by endorsing another stem question, such as the question about events at work, and the investigator ratings provide a means of classifying the work-related event as an argument. Together, these innovations provide a comprehensive picture of people's daily stressful experiences.

Developing DISE investigator ratings. Still, several challenges arose in adapting investigator ratings to a study of daily events. First, severity ratings could not be based on existing dictionaries focused on events that meet high thresholds of severity (e.g., death of a spouse), because these events are far more severe than those typically considered as daily stressors. This is important because minor events that occur on a daily basis are likely to have a fleeting effect on mood and severity ratings. Being forced to leave work to pick up a sick child from school is a stressful situation for a short time, but its effect on the future differs greatly from that resulting from having a spouse suffer a heart attack. Second, adapting the DISE to large scale studies such as the NSDE required logistical and training innovations. Investigator rating methods are typically used only in smaller samples (i.e., $n < 200$) because of the expense of training and retraining to achieve and maintain consistency and reliability (Wethington et al., 1995).

In the first wave of the NSDE, a team of graduate students received 10 hours of training to learn the coding system. During the training period, the coding team met to review the coding of events and resolve discrepancies in ratings. Once the coders attained adequate reliabilities, they began coding events independently. Even after inter-rater reliability was established, the coding team continued to meet weekly to check accuracy, review training, and resolve discrepancies in ratings. New coders who joined the project had to demonstrate inter-rater reliability equal to that of experienced coders before they began coding events. This same procedure is being used to classify events from the second wave of the NSDE. A team of undergraduate research assistants participated in 15 hours of coder training, and to date, this research team has coded nearly 5,000 stressful events. As the second wave of measurement for the NSDE is currently underway, DISE coding of the data for that wave is still in progress.

Specific DISE ratings and their reliability. The training manual for the DISE was developed based on the Structured Life Event Interview (SLI: Wethington et al., 1995), interviewing and coding manual. The strategy was to develop ratings over time in response to accumulated knowledge of what constituted the universe of stressful experiences reported in interviews. Key elements of investigator rating were selected from stressor dimensions used in the Life Events and Difficulties Schedule (LEDS; Brown & Harris, 1978). Consistent with the methods used by Brown and colleagues, the DISE manual was continuously updated with event and rating examples as it was developed (Almeida, 1998; Almeida & Cichy, 2007). Table 41.1 presents a description of the DISE measures of stressor content, focus, threat, severity, and primary appraisal. The first two measures in Table 41.1 assess the objective nature

Table 41.1 ■ Description and Interrater Coding Reliability of DISE Measures

Coding Category	Description	Interrater Reliability
Content Classification	Stressful events are categorized into one of three broad classifications and 63 specific subclassifications. These are: interpersonal tensions (21 subclasses), overloads (35), and network events (7).	0.82
Focus of Involvement	Focus of involvement refers to who was involved in the event: *respondent*, *other*, and *joint*.	0.70
Threat Dimensions	Threat dimensions describe the implications of the event for the respondent. *Loss* is the occurrence of a deficit. *Danger* is the risk of a future negative occurrence. *Disappointment* occurs when something does not turn out as the respondent had expected. *Frustration* occurs when the respondent has little or no control over the events. *Opportunity* is a chance for positive outcome.	0.88
Investigator-rated Severity	Investigator-rated severity refers to the degree and duration of disruption and/or unpleasantness created for the respondent *(1=low severity, a minor or trivial annoyance, 2=medium severity, 3=high severity, 4=extreme severity, a severely disruptive event).*	0.72
Subjective Severity	The subjective assessment of severity is the respondent's assessment of the degree of stressfulness involved in the event *(1= not at all stressful; 2=a little, 3=somewhat, 4=very stressful).*	Not coded by raters
Primary Appraisal Domains	Primary appraisal domains refer to the respondent's report of how much the following areas were at risk or at stake in the situation: (1) disruption of routine; (2) finances; (3) how respondent feels about self; (4) how others feel about respondent; (5) health or safety; (6) well-being of one close to respondent; (7) future plans *(1=not at all, 2=a little, 3=some, 4=a lot).*	Not coded by raters

of the stressor. Stressor content combines the broad classification of the event (e.g., interpersonal tension) with the content or topic of the event (e.g., household tasks). These broad classifications differentiate three types of events: *interpersonal tensions*, representing arguments or avoided arguments (e.g., disagreement with a coworker over an issue at work); *overloads*, representing having too much to do and not enough time to do it (e.g., unexpectedly having to babysit for a grandchild); and *network events*, representing events where something happens to a close friend or relative that turns out to be stressful for the respondent (e.g., a family member is hospitalized).

These independent assessments provide information that might be masked if we were only to consider the stem questions endorsed by the respondent. For example, a respondent may provide an affirmative response to the question asking about stressors at work, whereas the coding of the respondents' description of the stressor might reveal that the respondent actually had an argument with a coworker. Based on our coding protocol, nearly 14% of coded stressful events would be misclassified if we relied solely on the respondents' endorsement of the stem questions. Further, these investigator ratings make it possible to obtain detailed assessments of stressors experienced during the day without having to ask an exhaustive list of questions during the daily interviews. In addition, the independent raters determined the focus, or who was involved in the event, by considering whether the event was relevant only to the respondent (respondent-focused), only to another person (other-focused), or to both the respondent and another person (joint-focused).

The remaining investigator ratings in Table 41.1 assess the stressful implications of the event for the respondent. Threat can take many forms and refers to the extent to which the event may be expected to diminish the respondent's well-being. Independent raters evaluated each event for five dimensions of threat. The DISE includes three dimensions of threat assessed in the LEDS: *loss* of a possession, time, self-image, or a valued relationship; *danger* that involves the risk of a future negative occurrence; and *disappointment*, defined as something not turning out as the respondent hoped or expected (Brown & Harris, 1978). Raters also evaluated two additional dimensions of threat, namely, frustration, defined as the amount of control the respondent had over the situation, and *opportunity,* or the potential for a positive outcome. In the first wave, threat was evaluated as present or not present. For the second wave, we revised the coding system for the dimensions of threat to assess the degree of each type of threat on a scale ranging from 0 (*not present*) to 3 (*clearly evident*). Investigator-rated severity represents the degree and duration of the disruption and unpleasantness of the event. Coders evaluated the severity of the event on a scale ranging from 1 (*not at all stressful*) to 4 (*extremely stressful*).

Table 41.1 also presents the inter-rater reliabilities for the DISE investigator ratings. The relevant coefficients range from good to excellent, with reliabilities from 0.70 to 0.88. The reliability estimates for stressor content and focus reflect the average kappa across all possible coder pairs, whereas reliabilities for dimensions of threat and investigator-rated severity represent intraclass correlations. In both waves, approximately 20% of events were independently rated by at least two coders.

In addition to the expert coding manual (Almeida, 1998; Almeida & Cichy, 2007), coders constructed a rating dictionary, classifying events by content, focus, threat, and severity. The final dictionary consisted of nearly 4,000 entries stored in a searchable, cross-referenced database. Coding for the second wave of the NSDE is currently in progress, and a second dictionary is being constructed with additional events. Table 41.2 presents sample dictionary entries for three stressful events. The first column includes the respondent's verbatim description of the

Table 41.2 ■ Examples of Daily Stressors and Coding Using the DISE Instrument

Stressor Description	DISE Ratings and Codes
"I was helping open and close the store so I had to get up this morning, get my son ready, drag him to work, pick up somebody who didn't have a car, pick them up, take them to work, open the store, make sure they were okay, take him back for kindergarten, drop him off at the bus, go back to work, pick him up from the bus, run to swimming lessons for 45 minutes and then go back to work to close the store. I think that's a little bit stressful." (R had to open and close the store because the manager that usually does it was on jury duty.) "I feel good about myself for being able to get it all done today."	*Broad Classification*: Overload *Specific Classification*: Time Pressure *Focus*: Self *Objective Severity*: 2 *Subjective Severity*: 2 *Self-rated Primary Appraisal Domains* Disrupting Daily Routine: 3 Finances: 3 Way Feel About Self: 1 Way Others Feel About You: 1 Physical Health/Safety: 1 Health/Well-Being of Close Other: 3 Plans for Future: 1
"I had a problem with an employee. And also today she called and had cancelled something I had ordered three months ago and now I have to start running and searching and waiting for something. It was a big disappointment. It wasn't an argument, it was her fear that she had ordered the wrong thing and she didn't want to go through the stress and stuff. Nor did I obviously. Both of us. Since she had doubts that she had done the right thing, she cancelled the order. So, it was very stressful for me."	*Broad Classification*: Interpersonal Tension *Specific Classification*: Job Procedures *Focus*: Joint/Coworker *Objective Severity*: 3 *Subjective Severity*: 2 *Self-rated Primary Appraisal Domains* Disrupting Daily Routine: 4 Finances: 4 Way Feel About Self: 4 Way Others Feel About You: 3 Physical Health/Safety: 4 Health/Well-Being of Close Other: 1 Plans for Future: 4
"It was regarding my mom. It's just that she was supposed to be picked up by a family member, and they didn't pick her up and didn't bother to call me. My mother is 86, so that's why it was stressful for me."	*Broad Classification*: Network *Specific Classification*: Family Responsibility *Focus*: Other/ Parent *Objective Severity*: 2 *Subjective Severity*: 4 *Self-rated Primary Appraisal Domains* Disrupting Daily Routine: 3 Finances: 1 Way Feel About Self: 3 Way Others Feel About You: 3 Physical Health/Safety: 1 Health/Well-Being of Close Other: 4 Plans for Future: 3

stressor. The second column lists the type of stressor, ratings for focus of involvement, investigator-rated severity, subjective severity (which may differ), and the respondent's primary appraisal ratings. Higher numbers represent higher severity and greater perceived disruption. The overall pattern of correlations between ratings indicates a modest degree of independence between severity ratings, threat dimensions, and appraisal domains. Further, investigator-rated severity ratings were only moderately associated with respondents' subjective ratings of severity (r=0.36, p<0.05), indicating that these measures are not redundant.

PREVALENCE OF DAILY STRESSORS

A major goal of the NSDE was to provide estimates of the prevalence of daily stressors among different groups. During the first wave of data collection, respondents reported experiencing at least one stressful event on 39.4% of study days and multiple stressful events on 10.4% of study days. Table 41.3 provides a breakdown by various stressor categories. Although the most common stressors for both men and women were interpersonal arguments and tensions, accounting for half of all reported stressors, gender differences were evident. Women were more likely to report stressors that occurred within a network of relatives or close friends, and men were more likely to report paid work stressors, such as technical breakdowns, that were not interpersonal in nature (Almeida et al., 2002). Within the primary appraisal domains, stressors that risked the way respondents felt about themselves tended also to be perceived as a risk for the way others felt about them. Stressors that posed a risk to respondents' financial plans were related to respondents' plans for the future. Of the stressors, roughly 30% involved some sort of loss, nearly 37% posed danger, and 27% frustration. On

Table 41.3 ■ Description of Project 2 Measures of Stressor Content, Focus, Threat, Severity, and Primary Appraisal

Variables	Total (*N* = 1,031)	Men (*N* = 469)	Women (*N* = 562)
Content classification (% events)[a]			
Arguments/tensions	50.0%	49.1%	50.3%
Work/school	13.2	15.7	11.2*
Home	8.2	8.0	8.3
Health care	2.2	1.6	2.7
Network[b]	15.4	12.5	17.8*
Miscellaneous	3.5	4.4	2.7
Threat dimensions (% events)			
Loss	29.7%	29.9%	29.5%
Danger	36.2	35.7	36.6
Disappointment	4.2	4.0	4.4
Frustration	27.4	28.3	26.6
Opportunity	2.3	2.1	2.4
Stressor severity (mean)[c]			
Expert-rated assessment	1.8	1.7	1.9
Subjective assessment	2.7	2.5	2.9*
Primary appraisal domains (mean)[d]			
Disrupting daily routine	2.3	2.3	2.3
Financial situation	1.3	1.4	1.2*
Way feel about self	1.5	1.4	1.5
Way others feel about you	1.4	1.3	1.4*
Physical health or safety	1.3	1.3	1.3
Health/well-being of someone	1.5	1.5	1.5
You care about plans for the future	1.4	1.4	1.3

[a] Seven percent of events could not be placed into these content classifications.
[b] Events that happen to others.
[c] Range: 1–4 (not at all stressful to very stressful).
[d] Range: 1–4 (no risk to a lot of risk).
* Significant gender difference, $p < 0.01$.

average, the respondents subjectively rated stressors as having medium severity, whereas objective coders rated the stressors as low in severity. Daily stressors most often were perceived to threaten disruption of the respondent's daily routine as compared to threats in other life domains (e.g., finances, health, and safety).

The DISE categories significantly predicted physical symptoms and psychological distress (Almeida, et al., 2002). Multilevel models revealed that the entire set of DISE stressor variables accounted for 17% of the within-person variance in physical symptoms and 31% of the within-person variance in psychological distress. Specific types of daily stressors such as interpersonal and network stressors (i.e., events that occur to close others) were unique predictors of both physical symptoms and psychological distress. In addition, both objective severity and subjective severity measures predicted physical symptoms and distress. Individuals who reported a greater proportion of stressors that posed high severity, loss, or danger experienced more symptoms and greater psychological distress. Furthermore, stressors appraised as disrupting daily routines or threatening physical health and safety were also shown to be unique predictors of symptoms and mood.

INTER- AND INTRAEVENT VARIABILITY

The DISE approach is well suited to provide insight regarding variation both across different types of stressor events, or interevent variability, and variation across different stressors of the same type, or intraevent variability. The former reflects differences in appraisals and outcomes that are due to fundamental differences in the types of stressors that are experienced (e.g., an argument with one's spouse versus having a deadline to meet for work), whereas the latter reflects such differences in events that are, at least at a nominal/superficial level, similar (e.g., an argument with one's spouse versus an argument with one's neighbor). Given that people's experiences are sampled repeatedly, daily diary designs can be used to examine mean differences in daily stressor appraisals, such as their subjective severity. This sort of examination can provide information indicating whether different types of daily stressors are appraised, on average, to have different levels of severity. The repeated sampling of experiences, on a daily basis, also allows for examining variability in subjective severity ratings within stressor events that are nominally similar (e.g., interpersonal tensions).

Figure 41.1 depicts the various levels of analysis from which stressor severity can be examined. Typically, subjective severity is treated as a characteristic of the individual (i.e., interindividual level in Figure 41.1), and to this end, severity ratings are averaged across all possible stressor events. While collapsing across all stressors provides a concise estimate of severity, it glosses over potentially important sources of variation by assuming that severity across types of events and the stressors themselves are equivalent. Given that different types of stressors are assessed, it is possible to identify systematic differences in severity as a function of event type, shown at the interevent level in Figure 41.1. At this level, severity is still the relevant construct. However, it is expressly acknowledged that severity may differ across stressor types, and also may be differentially predictive of outcomes depending on the type of stressor. Furthermore, if stressors are repeatedly assessed across days, it is possible to examine how different stressors of the same type vary in terms of their severity, which is shown at the intraevent level in Figure 41.1. At this level, it is possible to consider why some interpersonal tensions, for example, are rated as more severe than others. The conceptual model of different levels of variation in subjective severity is rooted in the notion that while subjective severity (or any other characteristic of stressors) is an important theoretical construct, variability at different levels of analysis reflects different theoretical constructs, and may very well be explained by completely different factors. Specifically, the reason some people may rate their stressors to be more severe than others (i.e., interindividual

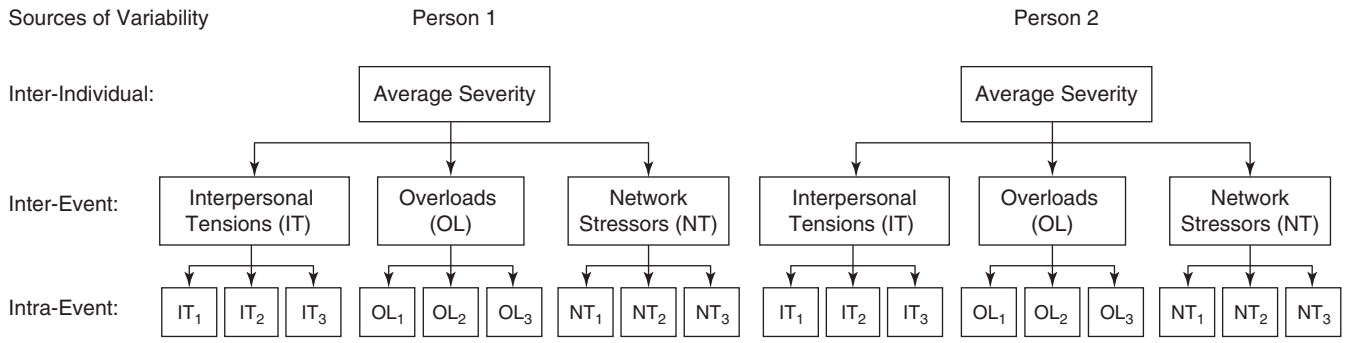

Figure 41.1 ■ Various levels of analysis from which stressor severity can be examined.

variation) may be completely different from why interpersonal tensions are reported to be less severe than network stressors (i.e., interevent variation), which, in turn, is different from why some interpersonal tensions are reported to be more severe than others (i.e., intraevent variation).

To elucidate the importance of considering interevent and intraevent variability in daily stressor, we turn to an examination of the subjective severity of daily stressors reported during the second wave of the NSDE. We examined interevent variability in stressors by considering mean differences in subjective severity appraisals of reported daily stressors. To examine mean differences in subjective severity ratings, we used multilevel modeling (Snijders & Bosker, 1999), as events are nested within days, which are nested within individuals, requiring a 3-level model. Preliminary analyses indicated that there was no systematic day-to-day variation in severity ratings, and as such, we ignored the level of the day in our analyses, effectively treating the data as events nested within individuals, resulting in a simpler 2-level model. To allow for mean differences in subjective severity ratings by event type, a categorical variable was added as a predictor to represent the four primary types of stressors: interpersonal tensions, overloads at work, overloads at home, and network stressors. This effect of stressor type was highly significant, $F(3, 1131) = 41.27$, $p<0.0001$,indicating that subjective severity ratings varied as a function of the type of stressor reported. As can be seen in Table 41.4, on average, network events were rated to be the most severe, followed by overloads at home, overloads at work, and finally, interpersonal tensions. Pairwise comparisons between the stressor event types revealed that all severity ratings were significantly different from one another ($p < 0.0001$) with the exception of network events and overloads at home ($p = 0.53$). The significant difference in subjective severity across different types of daily stressors suggests that there is indeed evidence of interevent variability.

Next, we examined intraevent variability in subjective severity ratings for each type of event using multilevel models. Such models allow us to decompose variability in subjective severity ratings into variability due to between-person differences in how individuals rate the severity of their interpersonal tensions (or any other type of stressor event) and within-person variability reflecting how different an individual's subjective severity ratings are across the interpersonal tensions (or other types of event) they reported experiencing. Variance decomposition can also be used to calculate the intraclass correlation coefficient (ICC), which reflects the proportion of the total variability that is attributable to stable individual differences in subjective severity ratings. The ICC can range from 0 to 1, with higher values indicating a greater proportion of variability reflective of stable individual differences. Thus, in the context of the current study where stressor events are repeatedly assessed (nested) within individuals, large values for the ICC would indicate that variability in subjective severity reflects differences across individuals. By contrast, small values for the ICC would indicate that the variability reflects within-person differences in subjective severity across events, constituting evidence of intraevent variability. The right-hand portion of Table 41.4 provides estimates of between-person and within-person (event-to-event) variability and the ICCs for subjective severity ratings by event type. For each type of event, the within-person, or event-level variance was almost twice as large as the corresponding between-person, or person-level variance. These values translate into ICCs ranging from 0.26 to 0.35, indicating that between 26% and 35% of the variability in subjective severity ratings reflects between-person differences in how individuals rate their stressors.

Table 41.4 ■ Means and Variances for Subjective Severity Ratings by Event Type

Event Type	Mean (SE)	BP Variance	WP Variance	ICC
Interpersonal tensions	1.65 (.02)	0.20	0.53	0.28
Overloads—Home	1.98 (.03)	0.19	0.44	0.31
Overloads—Work	1.82 (.03)	0.24	0.45	0.35
Network events	2.01 (.03)	0.12	0.34	0.26

BP, between-person; WP, within-person

This means that between 65% and 74% of the variability in subjective severity ratings of stressors is due to within-person differences across events (as well as some measurement error), and provides evidence consistent with the notion that variability in subjective severity ratings of daily stressors, regardless of the type of event, largely reflects characteristics specific to the events reported, with stable individual differences in how individuals subjectively rate their stressors playing a comparatively smaller role. Together, these results support the premise that all stressors are not created equal by providing evidence for both inter- and intraevent variability. The comprehensive assessment of stressor exposure obtained from the DISE approach offers the opportunity to begin to explain this variability by identifying the specific characteristics (e.g., threat posed by the event) that contribute to situational variability across different types of events as well as variations across different events of the same type.

THE RESEARCH POTENTIAL OF THE DISE

Use of the DISE in research on daily stress processes has the potential to contribute to multiple disciplines, including (but not limited to) the sociology of the life course and life span psychology, health and developmental psychology, and the study of the contribution of genes and the environment to health and well-being. We briefly illustrate this potential with findings from published studies using data from the NSDE.

Findings documenting age differences in objective and subjective characteristics of daily stressors, for example, are relevant to life course sociology and life span psychology (Almeida & Horn, 2004; Birdett, Fingerman, & Almeida, 2005). Young (25–39 years) and middle-aged individuals (40–59 years) reported a greater daily frequency of experiencing at least one stressor and multiple stressors than did older individuals (60–74 years), consistent with previous research documenting that older adults tend to experience fewer life events and daily stressors. Compared with older adults, young and midlife adults also perceived their stressors as more severe and as more likely to affect how others felt about them, and experienced a greater proportion of overloads and stressors that cause disruption to their daily routines. The age-related patterns reflect the varying demands of social roles across the life course. Subsequent analyses used multilevel modeling to assess age differences in reactivity to daily stressors. Overall, younger adults were more emotionally reactive to interpersonal tensions and older adults were more reactive to network stressors, again reflective of varying life course demands.

Another series of analyses assessed the interconnections between socioeconomic status, stress, and physical and mental health by specifying differential exposure and reactivity models (Almeida, Neupert, Banks, & Serido, 2005; Almeida, Serido, & McDonald, 2006; Grzywacz, Almeida, Neupert, & Ettner, 2004). Consistent with the broad literature describing socioeconomic inequalities in physical and mental health, the results of these analyses indicated that on any given day, better-educated adults report fewer physical symptoms and less psychological distress. In contrast to previous studies, however, stressor exposure increased with greater levels of education. Analyses using multilevel models indicated that differences in severity and stressor appraisal accounted for education differences in physical health symptoms.

In a different set of analyses, we found a stronger association between daily stress and negative affect for persons high in neuroticism compared to those low on this trait, a relationship that was stronger for older individuals (Mroczek & Almeida, 2004). This finding suggests that older people high in neuroticism may be particularly sensitive to daily stressors. Some have hypothesized that neuroticism, and the frequently elevated levels of negative affect that accompany this trait, may, over a lifetime, lead to dysregulated emotion in older adulthood (Kendler, Thornton, & Gardner, 2001). Our results are consistent with this hypothesis, as we found that older adults who were high in neuroticism were more emotionally reactive to daily stressors than younger adults.

In another paper we examined age and control belief differences in reactivity to four stressor domains (interpersonal, work, home, and social network) (Neupert, Almeida, & Charles, 2007). Stressor domains may vary in their salience across adulthood; for example, work appears to be especially important at midlife (e.g., Clark-Plaskie & Lachman, 1999). Thus, reactivity to stressors of varying domains could be associated with life stage, as well as with feelings of control over one's life. Findings indicated that age and control beliefs played an important role in a person's reactivity to interpersonal, network, and work stressors. Specifically, older age and lower perceived constraints were each related to lower emotional and self-reported physical symptom reactivity to interpersonal stressors. High mastery buffered the physical effects of work stressors for younger and older adults, but adults in midlife were physically reactive even when they reported high levels of mastery.

Another line of work has examined the accumulation across and linkages between different types of stressors over time (Serido, Almeida, & Wethington, 2004). Although they may share a common etiology, we found that reports of persistent, chronic stressors at work or at home, and daily stressors related to those domains, are distinct types of stressors with unique effects on psychological distress. Also of note was the finding that on days when stressors occurred, those who also previously reported chronic stressors were more likely to experience psychological distress.

A data collection supplemental to the NSDE, in a MIDUS subsample of 240 twin pairs, has made it possible to examine the behavioral genetics of daily stress processes. One set of papers has focused on daily and weekly levels of negative affect, as well as intraindividual

variability in daily affect (Neiss & Almeida, 2004). Genetic and environmental influences on exposure to daily stressors have also been investigated (Charles & Almeida, 2007). Both genetic and environmental effects account for portions of the variance in stressor occurrence, whereas shared family and environmental effects, but not genetics, account for the variance in perceived severity of these stressors.

PERFORMANCE OF THE DISE IN COMPARISON TO SELF-ADMINISTERED DAILY DIARY METHODS

The previous sections describe the flexible ways in which the DISE can be used to address a number of questions related to the relationship of daily stressors to well-being. However, we have not yet addressed an important methodological question: Is the DISE a significant improvement over self-administered checklist daily diary methods? To explore this question, Wethington and Almeida (2009) presented a series of analyses comparing the performance of the DISE with that of diary measures used in the Detroit Area Study Life Experiences Study (DAS, Bolger et al., 1989). The DAS was a 6-week self-administered diary study of married couples in the Detroit area in 1986. Respondents responded daily to a checklist of 22 stressor items, primarily representing work and family.

In general, DISE respondents reported significantly fewer stressors than comparable respondents in the DAS, except for arguments and tensions. One interpretation of this difference is that asking fewer questions results in reporting fewer events. Consistent with this interpretation, the DISE estimates also include arguments that were avoided, presumably increasing the total reported. A second possible interpretation is that a combination of fewer questions and investigator rating reduces the likelihood of counting the same event twice and excludes events that are affective reactions rather than objective occurrences. Consistent with this interpretation, respondents to the DISE reported a lower percentage of days with any stressors (42.4% vs. 68.2%, $t = -13.5$, $p < 0.01$), and fewer days with multiple stressors (11.1% vs. 31.7%, $t = -12.6$, $p < 0.01$). Both explanations for the differences between the two modes probably have some validity.

A question that follows is whether the DISE sacrifices predictive power by evoking fewer event reports. The answer to this question is: probably not. The evidence for our conclusion is that relatively few respondents volunteered reports of other types of stressors not covered by the seven daily event questions. Stressors were reported in response to the "other stressor" question on only 1.7% of study days. There is additional evidence that the DISE did not sacrifice predictive power in relationship to daily symptoms. Table 41.5 presents a second comparison between the DISE and the DAS, correlations between daily stressors and physical health symptoms. The correlations between "any stressors" and symptoms and "multiple stressors" and symptoms do not differ significantly between the two samples. With regard to specific types of stressors, the correlation between arguments and symptoms is significantly lower in the DAS, whereas the correlation between network stressors and symptoms is lower in the DISE. Otherwise, differences were not statistically significant.

This comparison is not definitive, however, because there is no way to estimate which of the methods produces a truer picture of the prevalence and effect of daily stressors on well-being. Nonetheless, the DISE telephone-based approach did provide several advantages. The first is that telephone interviewing with a limited number of questions appears to have produced a reasonably comprehensive estimate of the prevalence of daily stressors with a minimal number of questions. Second, the limited time frame of the DISE and telephone administration may have reduced respondent burden. Respondents were called at times convenient to their schedules and the average interview length was only about 15 minutes. A third advantage is that the use of telephone interviewing reduces instances of missing data because there is more control over reporting.

Table 41.5 ■ Correlations between Daily Stressors and Physical Health Symptoms: DISE vs. DAS

	Physical Health Symptoms (%Days)			
	DISE Total Sample	DISE Restricted[1]	DAS	DISE-DAS z
Interpersonal tensions	0.23*	0.27*	0.13*	1.97*
Home	0.16*	0.17*	0.30*	−1.86
Work/school	0.08	0.08	−0.03	1.48
Network stressors	0.17*	0.15*	0.31*	−2.04*
Other stressors	0.15*	0.16*	0.07	1.22
Any stressors	0.28*	0.31*	0.29*	0.29
Multiple stressors	0.21*	0.23*	0.28*	−0.73

[1]Restricted sample that matches demographic characteristics of the DAS sample.
*$p < 0.05$
**$p < 0.01$

We hoped that telephone interviewing, the smaller number of questions, and the shorter time frame would also reduce fall-off in reports of daily stressors over the contact period. We found that fall-off was less than that reported in the self-administered DAS study, but remained significant over the 8-day period. In other words, the method reduces fall-off, but does not eliminate it completely (Almeida et al., 2002).

SUMMARY AND NEXT STEPS

MEASUREMENT INNOVATIONS

The DISE approach addresses two important methodological issues in the measurement of daily stressors. First, this method provides a means of addressing intracategory variability (Dohrenwend, 2006), by obtaining in-depth information about the nature of events, including respondents' subjective appraisals and investigator ratings for each event. For example, by assessing content, severity, and appraisal, this approach makes it possible to distinguish minor disagreements (e.g., argument with a child over homework) from major conflicts (e.g., argument with a spouse over alcohol abuse). Further, although the DISE estimates a lower prevalence of daily stressors than checklist measures (see Bolger et al., 1989), this discrepancy can be explained by features of the interview. This approach reduces the instances of reporting the same stressor multiple times by applying objective criteria to counting a report as an event. Using these criteria, 5% of events in the NSDE failed to be recognized as events. Finally, the telephone method presents its own distinct advantages by making it possible to obtain in-depth information on daily stressors from a national sample, at the same time significantly improving compliance while reducing the burden on respondents.

The most significant advantage of the DISE method is the ability to obtain a comprehensive assessment of both investigator-rated characteristics of daily stressors as well as respondents' subjective appraisals. It is important to acknowledge, however, that this in-depth assessment, although less burdensome for the respondent, is quite labor and time intensive for the investigator. Therefore, this approach may be less desirable for smaller scale studies, where it may be more useful to rely on self-administered checklist measures. The telephone interview may also be limited in assessing daily stressor exposure in groups with restricted access to the phone, such as low-income Americans.

Finally, although the DISE makes it possible to separate respondents' affective responses from the objective circumstances of the event, it is not without its limitations. The DISE still relies on the respondent's self-report that something stressful has happened. Therefore, although this method reduces confounds between stressor occurrence and appraisal, it cannot entirely eliminate this problem. In addition, some of stem questions contain the word "stressful," which contributes to this concern.

The DISE method does not alleviate all concerns about event reporting. Similar to all self-report methods for assessing stressors, there is no way to determine whether respondents are fabricating or exaggerating their reports of daily stressors. At the other end of the spectrum, the DISE does not completely eliminate the fall-off in reports of stressors over the course of a study. Although this method seems to reduce fall-off, there is still evidence that people learn that if they say "no" to the stem questions, then the interview will be shorter.

THEORETICAL INNOVATIONS

Perhaps the most valuable feature of diary methods and specifically the DISE approach is the ability to assess *within-person* processes. This represents a shift from assessing mean levels of stressor and well-being between individuals to charting the day-to-day fluctuations in stress and well-being within an individual. Stress is a process that occurs within the individual, something that research designs need to reflect. For example, instead of asking whether individuals with high levels of work stress experience more distress than individuals with less stressful jobs, a researcher can ask whether a worker experiences more distress on days when he or she has too many deadlines (or is reprimanded) compared to days when work has been stressor-free. This within-person analytic approach allows the researcher to rule out temporally stable personality and environmental variables as third variable explanations for the relationship between stressors and well-being. In addition, the intensive longitudinal aspect of the daily diary design permits a prospective examination of how stressors are associated with changes in well-being from one day to the next. By establishing within-person associations between varying daily stressors and well-being as they unfold over time, researchers can more precisely establish the short-term effects of concrete daily experiences (Bolger, Davis, & Rafaeli,, 2003; Larson & Almeida, 1999).

Research with the DISE also pioneered several innovations that provide new ways to look at the relationship between daily stressors and health outcomes. The DISE addresses head-on the problem of intracategory variability, that is, the fact that individual experiences reported in response to closed-ended event checklist questions are in fact highly variable in terms of severity and type of threat (Dohrenwend, 2006). One exciting prospect for research is application of the DISE method to allow for more concrete specification of the physiological and physical and mental health consequences of different types of daily stressors depending on the type of threat they pose (see Miller, Chen, & Zhou, 2007). Daily stressors posing the threats of loss or danger may be more likely to result in sad or depressed mood. Daily stressors that involve frustration may be more likely to produce physical or

psychological fatigue. As well, daily stressors that present "opportunity" may be more likely to produce more positive mood, or may buffer the effect of negative daily stressors. We also believe that the DISE method can contribute to the study of stressor proliferation across roles and domains of life, such as work and family, and over time, in a person's life.

The DISE approach has recently been applied to multiple areas of research, including assessments of daily stressors in diverse samples and among multiple members of the same family. Currently, this approach is being used to characterize the daily stressful experiences of parents of children with disabilities (Seltzer et al., 2009). Other research applies the DISE paradigm to evaluate the stressful experiences of individuals with chronic health conditions, such as diabetes (Skaff et al., 2009) and those with spinal cord injuries (Charles, Piazza, & Almeida, 2008). Further, this daily approach has been used to understand family life, including how the stressful experiences of one family member may influence other members within the same family. For example, the DISE approach has been adapted to study the health implications of daily work–family stressors for hotel employees and their families (Almeida et al., 2007) as well as to evaluate the benefits of a workplace intervention for employees and their children (Almeida, McHale, Klein, & Crouter, 2008). Finally, this daily stress paradigm is being used to assess stressor exposure among older adult married couples (Mroczek, 2008; Yorgason, Almeida, Neupert, Spiro, & Hoffman, 2006). Together, these various studies illustrate the potential value of this approach for advancing the study of stressor exposure in diverse contexts and populations.

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42 Measuring Psychosocial Stress Using Ecological Momentary Assessment Methods

Thomas W. Kamarck, Saul Shiffman, and Elaine Wethington

Research reviewed throughout this Handbook has included a number of different self-report instruments used to measure psychosocial stress. Most of these instruments have involved retrospective methods. In this chapter, we argue that an alternative self-report methodology, capturing the manifestations of psychosocial stress *as it unfolds over the course of daily life*, may have some distinct advantages when the study design permits. This approach is sometimes referred to as ecological momentary assessment (EMA), and it involves the real-time capture of real-world behavior and experience. Although encompassing a number of different research aims and methods (Shiffman, Stone, & Hufford, 2008; Stone & Shiffman, 1994), EMA has several core features. First, it involves the sampling of experience or behavior in the context in which it naturally occurs, rather than in the clinic or the laboratory. Frequently, self-report strategies are used for this purpose. Ambulatory assessment of physiological states also fit into the rubric of EMA, but because these are covered more extensively elsewhere in this volume, they will not be the focus of this chapter. Second, EMA involves the assessment of subjects' current states, such as current activities or mood, rather than involving the use of recall over long periods of time or summaries of typical behavior. Third, EMA uses repeated assessments over time, allowing the investigator to characterize how experiences and behavior vary over time and across situations. Fourth, a related and important feature of EMA involves the strategic selection of sampling patterns for these repeated assessments in a manner designed to target phenomena of interest. For example, the use of random or frequent fixed-interval assessments may be suitable when a representative sample of experience is the goal (e.g., research designed to characterize individual differences in daily mood) (Moskowitz & Cote, 1995). Alternatively, the use of self-initiated event-related assessments may be preferred when the characterization of specific episodes is of interest (e.g., research examining the antecedents and consequences of smoking behavior) (Shiffman, 2005). These methods have gained prominence in recent years in studies of phenomena as diverse as chronic pain, work activity and satisfaction, medication compliance, psychopathology, illicit drug use, self-esteem, and social interactions (Bolger, Davis, & Rafaeli, 2003; Shiffman et al., 2008; Stone & Shiffman, 1994; Stone, Shiffman, Atienza, & Nebeling, 2007).

WHY USE EMA FOR ASSESSING PSYCHOSOCIAL STRESS?

Epidemiologists who study the effects of environmental risk factors for disease (e.g., passive smoking, air pollution, or asbestos exposure) (Al-Delaimy, Crane, & Woodward, 2000; Maskarinec, Jenkins, Counts, & Dindal, 2000; Timonen et al., 2006) have long believed that the effect of such characteristics on health should be expected to vary as a function of the frequency and duration of daily exposure. Documenting the extent of daily environmental risk exposure is a challenge for those who study such phenomena, and all the more so when such exposures involve psychosocial processes. Indeed, this challenge is the subject of a major new "exposure biology" initiative at the National Institutes of Health (Schwartz, 2006), an initiative that has recognized the importance of measuring exposure to behavioral factors such as diet, physical activity, and psychosocial stress, as well as to biological and chemical agents.

Evidence suggests that retrospective estimates of the frequency or duration of daily events invoke heuristics that are fraught with systematic bias, which can distort recall even after relatively short intervals (Robinson & Clore, 2002; Schwarz & Oyerman, 2001; Schwarz & Sudman, 1997; Stone et al., 1999). A person asked about the extent of daily exposure to stress at work, for example, is faced with the task of recalling, averaging, and summarizing his or her daily experiences at the workplace. Retrieval and summary processes of this sort are both subject to error, in part because undue weight is typically given to recent and salient instances at the expense of more typical and distal events (Stone et al., 1999). Collecting data in the natural environment and in real time aims to avoid the pitfalls of retrospective report, reducing measurement errors in estimates of daily stress exposure attributable to memory accessibility and distortion. One of the unique

characteristics of EMA methods is their ability to capture representative time samples during daily life, permitting us to derive cumulative estimates of ongoing stress exposure.

In addition to their utility in the quantification of average stress exposure, a critical feature of EMA methods is the extent to which they permit us to examine the *topography* of the stress process, allowing us to examine the behavioral and biological consequences of ongoing daily stress more directly than can be done with traditional measurement methods. The premise of much of the work linking psychosocial stressors with health risks is that the chronic daily life exposures to "toxic" social environments trigger continuous or episodic biological or behavioral adjustments that are associated with cumulative pathophysiological effects. Unfortunately, social environments and their behavioral and biological concomitants are usually assessed using instruments (e.g., retrospective questionnaires) and methods (e.g., laboratory stressors) that are abstracted from the context in which these effects may occur. This makes it difficult to identify with confidence the mechanisms that account for the associations between psychosocial stress and adaptive outcomes. In contrast, EMA data allow examination of the dynamics of stress, for example, by revealing how time-bound variation in stress exposures may be associated with variations over time in physiological reactions or in symptoms. This feature makes EMA methods uniquely suited for the development and testing of mechanistic hypotheses linking stress with health in human samples.

An example of the advantages of EMA for helping us understand causes of disease or disorder can be gleaned from the literature on high blood pressure and diseases of the cardiovascular system. Blood pressure measures collected in the physician's office (so-called "clinic blood pressure") are generally the gold standard in the literature linking high blood pressure with enhanced cardiovascular risk. When blood pressure is sampled in the natural environment, however, using ambulatory blood pressure (ABP) monitoring, observed relationships with disease risk are typically strengthened (Janicki & Kamarck, 2008; Kamarck, Polk, Sutton-Tyrrell, & Muldoon, 2002; Verdecchia, 2000). Blood pressure is altered acutely in response to psychosocial events in the natural environment; mean ABP, therefore, reflects the average effects of these exposures in a manner that may be difficult to discern in the setting of the doctor's office. Deleterious effects of blood pressure on health outcomes, in turn, may reflect, in part, the cumulative effects of such alterations as they emerge in the process of daily living, potentially explaining the superior prognostic utility of ABP. We have shown that some EMA-based measures of psychosocial demands appear to be associated with blood pressure during daily life but not with blood pressure in the clinic (Kamarck, Janicki, et al., 2002), consistent with the possibility that exposure to daily stressors may account, in part, for the unique prognostic value of ABP.

Another example involving EMA assessment for the purpose of examining mechanisms linking stress and disorder involves work exploring the relapse process among ex-smokers. In this work, we have taken advantage of the longitudinal, sequential nature of EMA data to test the hypothesis that stress can heighten the risk of relapse. In an analysis of the days and hours preceding a return to smoking among people who were struggling to quit smoking, we found that negative affect during the preceding few days had no apparent effect on the risk of smoking, but that it appeared to have an acute effect over a period of hours preceding the smoking episode (Shiffman & Waters, 2004). This illustrates the importance of assessing stress dynamically over time.

In addition to using EMA methods to achieve greater fidelity in the measurement of stress exposure and to examine mechanisms linking stress and health outcomes, a third rationale for an EMA approach to psychosocial stress assessment is to help shed light on the *moderators* of stress effects, across different types of people or across life domains. This use of EMA, once again, relies on the ability of this approach to capture the topography or patterning of stress processes in daily life using repeated daily life sampling, and it capitalizes, as well, on the ecological validity of real-time assessment in the natural environment when compared to laboratory or traditional self-report methods. Testing moderator effects across life domains, we can, for example, use EMA methods to examine whether interpersonal conflict arising in marriage may have a different effect than conflicts arising in other interactions, or whether demanding and uncontrollable jobs result in a differential effect when compared to demanding and uncontrollable households or neighborhoods.

Testing moderator effects across persons, we recently (with Elizabeth Vella) used EMA to study the effects of social interactions on ABP among high- and low-hostile adults. Hostility refers to a group of cognitive, behavioral, and affective traits that have been shown to be associated with an increased risk for cardiovascular disease (Smith, 1992). One of the major models explaining the links between hostility and increased disease risk cites the potential role of recurrent patterns of social interaction that characterize hostile individuals as playing a contributing role (Smith, Glazer, Ruiz, & Gallo, 2004). The notion is that stressful social interactions may contribute to exaggerated sympathoadrenal activation during daily life in a manner that may hasten the development of disease. Previous work had shown that hostility is, indeed, associated with exaggerated responses to social conflict (Davis, Matthews, & McGrath, 2000). Because hostile individuals are low in interpersonal trust (Gallo & Smith, 1997), we hypothesized that they may also show physiological differences in responding during positive interactions, interactions that, during daily life, tend to be experienced on a somewhat more frequent basis (see also Guyll & Contrada, 1998). Using self-report EMA measures in conjunction with ABP monitors in an

adult community sample, we showed that high-hostile individuals showed unexpected increases in blood pressure, a potential marker of sympathoadrenal activity, when they were engaged in daily life social interactions that were rated as high on social support (e.g., "someone gave you positive feedback"). This paradoxical pattern of response was not apparent among low-hostile individuals. Conversely, low-hostile individuals demonstrated declines in blood pressure during interactions that were rated as high on openness or intimacy (e.g., "feeling close to person"), a pattern that was not apparent among the high-hostile group. These moderation findings illustrate once again how EMA methods can elucidate patterns of stress-related processes unfolding in a real-life setting, with potential implications for health (Vella, Kamarck, & Shiffman, 2008).

One major premise for the use of EMA methods in the assessment of psychosocial stress is that chronic life demands may leave a "signature" on the behavioral and biological events in our daily lives. It is assumed that the study of "proximal" daily events will have implications for helping us to understand more distal processes involved in psychosocial stress. For example, chronic marital stress may alter the nature and pattern of social interactions with our spouses (indeed, such patterns may be the defining feature of a distressed marriage), and the study of chronic occupational stress may be informed by examination of one's daily experiences in the workplace. A number of studies do support the assumption that differences in daily experience may be driven, in part, by chronic stressors and conditions such as low socioeconomic status (SES) (Gallo, Bogart, Vrancenanu, & Matthews, 2005; Matthews et al., 2000), marital distress (Janicki, Kamarck, Shiffman, & Gwaltney, 2006), and job strain (Johnston, Beedie, & Jones, 2006; Kamarck, Muldoon, Shiffman, Sutton-Tyrrell, & Gwaltney, 2004; but see also Serido, Almeida, & Wethington, 2004).

WHAT ARE THE RELATIVE ADVANTAGES OF USING MOMENTARY MEASURES WHEN COMPARED WITH END-OF-DAY REPORTS?

Daily (i.e., once-a-day) diaries can be considered a special case of EMA, insofar as they are administered repeatedly and provide a dynamic look at daily experience, although with less resolution than within-day assessments and with some remaining potential for recall bias. Moreover, the relatively large literature on measures of "daily stress" (discussed elsewhere in this volume) illustrates the utility of assessments collected once a day in the convenience of the home environment (Almeida, Wethington, & Kessler, 2002; Serido et al., 2004) or the laboratory (Kahneman, Krueger, Schkade, Schwarz, & Stone, 2004). In this light, it is reasonable to ask whether the true momentary (i.e., near real time) quality of within-day assessments collected throughout the day provide incremental benefits when compared with the substantially less costly alternative of daily diaries.

While daily diary assessments are likely to be preferable to traditional assessments as markers of the occurrence, frequency, and duration of daily events, summarizing an entire day's experience can, unfortunately, carry with it some of the limitations of retrospective recall. Research on autobiographical memory suggests that biases due to heuristic recall strategies operate even over short time frames. For example, summary memories of pain reported even an hour after medical procedures appear to be associated with systematic biases (differential weighting of recent and salient events) when compared with pain reports that are collected in real time (Redelmeier & Kahnemann, 1996). The timing of daily diaries (typically end of the day) may present an additional source of error; to the extent that subjects are more likely to be fatigued at this time, their recall of the day's experiences may be systematically biased (Shiffman et al., 2008).

We examined the correspondence between momentary and daily diary reports of stress using data from one of our recent studies. In a group of 365 healthy older adults (the Pittsburgh Healthy Heart Project; Kamarck et al., 2004) we administered an electronic diary interview every 45 minutes throughout the waking day for two 3-day periods, 4 months apart. One of the items in the diary, inquiring whether participants were currently feeling "nervous/stressed," was administered by paper questionnaire once again at the end of each monitoring day. For the latter item, subjects were asked to summarize, in general, the degree to which they had felt nervous or stressed throughout the day. We examined the extent to which, for this one measure of stress that they contained in common, these two formats of administration (within-day and end-of-day interviews), may have produced corresponding results.

Analyses examining this question were conducted in two ways—first, we essentially averaged all responses at the person level, yielding one data value for each person and, second, we essentially averaged all responses at the level of the day, yielding one day value for each day. Multilevel modeling was used for these analyses, with between- and within-person correlations derived from multilevel covariance matrices. At the person level, the correlation was moderate in magnitude, but somewhat lower than might be expected considering that the items were identical in content ($r = 0.64$). At the day level, however, the average between-day correlation (i.e., the correspondence between the rank order of the 6 days using each of the two methods of measurement) was only modest ($r = 0.39$).

These findings suggest that within-day and end-of-day measures yield additional, useful information for this type of stress measure, especially when there is interest in within-person questions (e.g., concerning triggers or consequences of stress over time). These data suggest that the two types of report cannot be assumed to correspond

empirically. Although this is the first published comparison of within-day and end-of-day measures of stress of which we are aware, results are largely consistent with those that have been reported for other types of outcomes, such as frequency of alcohol use and pain intensity (Broderick et al., 2008; Shiffman et al., 2008).

More research is needed to examine the circumstances under which within-day and end-of-day reports may show greater convergence. For example, this may be the case when individuals are asked to recall events that may be less frequent, more salient, and less variable over time (e.g., Stone, Schwartz, Broderick, & Shiffman, 2005). It may turn out that there are certain types of stress measures, such as the reporting of discrete or major events, for which correspondence is higher and for which the convenience of end-of-day assessment outweighs the loss of fidelity associated with retrospective report. It may also turn out that there are certain circumstances under which retrospective summary measures provide better predictors of future behavior than averaged momentary ones. Data suggest, for example, that retrospective judgments of the pain associated with colonoscopy are negatively correlated with the probability that patients will return for a repeat procedure, but averaged momentary ratings are not (Redelmeier, Katz, & Kahneman, 2003), presumably because the former are more accessible than the latter when the patients are making their decision about whether to return for follow-up.

In any case, limitations of temporal resolution are likely to set limits on the utility of end-of-day reports under many circumstances. There are a number of research questions, especially those that pertain to the topography of the stress process, which call for near real-time assessment. For example, momentary effects of stress on biological activity such as ABP or cortisol variations during daily life are not likely to be recoverable at the end of the day. Because daily diary measures are covered elsewhere in this volume, we restrict our discussion in the rest of the chapter to within-day assessments of stress.

HOW DO WE TRANSLATE STRESS ASSESSMENT INTO A FORMAT COMPATIBLE WITH EMA?

As has been discussed elsewhere in this volume, challenges associated with the measurement of stress are inextricably linked with divergent definitions of the stress construct (see Dougall & Baum, 2001; Herbert & Cohen, 1996). A "stimulus-based approach" to stress, which attempts to capture the environmental demands facing the organism, can be translated into real time by identifying and assessing problematic daily life circumstances (e.g., social conflicts, goal frustration events) on an ongoing basis. A "response-based approach," which defines stress in terms of a common set of responses evoked in the organism, can be translated into an EMA self-report format by identifying and assessing affective response patterns triggered by daily events (e.g., anger, depression, or anxiety, and their physiological correlates). And finally, an "appraisal-based approach" defines stress in terms of cognitive appraisals of demands and resources, which are thought to mediate the effects of a stressful transaction on adaptive outcomes (e.g., perceptions of task overload and lack of perceived control) (Cohen, Kamarck, & Mermelstein, 1983).

In the following section, we review and evaluate examples in which each of these three approaches to the measurement of psychosocial stress have been implemented in real time in the natural environment and we discuss what is known about the utility of such measures in terms of their association with relevant behavioral, biological, and health outcomes.

STIMULUS-BASED MEASURES

Because of the large number of types of daily life events that can tax adaptation, developing a real-time method for assessing stressors can present some challenges. The threshold for identifying stressors that occur during daily life is inevitably lower than that which is applied, in the context of other measures, for defining major life events, and the definitional burden is usually placed on the shoulders of the participants for determining the types of episodes that may qualify (i.e., subjects are frequently asked to identify recent ongoing "stressors" or "problems"). The data reviewed below suggest that such methods, although seemingly imprecise, do seem to yield meaningful effects as assessed by self-report and biological criteria. Whether more stringent definitions would yield stronger effects is an empirical question worthy of future research.

There have been two approaches taken toward the real-time assessment of stressful stimuli. The first approach, adopted for example by Suls and colleagues (Marco & Suls, 1993; Suls, Green, & Hillis, 1998; Suls & Martin, 2005), takes a closed-ended approach, involving the use of one or two items, administered during each momentary interview, inquiring about whether or not a problem has occurred in the past 30 minutes (or since the last diary entry), and whether this was a new problem or the continuation of an old problem. Two studies involving momentary reports of problems by community samples of men have been published by this group; both of these studies have shown that problems are reported in 25–30% of the assessments. The endorsement of a current problem, in these studies, has been shown to be associated with greater negative mood, especially among those who scored higher on measures of neuroticism or negative affectivity (Marco & Suls, 1993; Suls et al., 1998).

A variation on this approach is represented in the work of Arthur Stone, Saul Shiffman, and others (Stone et al., 1998). These investigators identified individuals

who reported chronic work or marital stressors. Every 40 minutes during a 2-day period, they were prompted to consider whether they had recently experienced manifestations of these problems ("Since the last report, did you think about, discuss, or do something about a [work/marital/other] issue or conflict?") and they were asked to select from a list of problem categories within each one of these areas that might be most applicable to the present problem (e.g., within marital, conflict over children or conflict over finances) (see also Engel et al., 2005; Smyth et al., 2007).

A second approach to the momentary measurement of stressful events in daily life involves a more open-ended strategy, in which subjects are asked to describe stressful events that are occurring at the time of each assessment. Using this method, response content can be coded after the fact using predesignated criteria. This method provides a greater level of detail with respect to the content of daily life stressors, but it also involves greater response burden for both participants and researchers because of the use of open-ended material.

Van Eck, Nicolson, and Berkhof (van Eck, Nicolson, & Berkhof, 1998) for example, asked 85 employed males (selected on the basis of high or low perceived stress) to record the occurrence of events and mood states 10 times a day over 5 consecutive days, using questionnaire booklets and a wrist-watch prompt for timing each assessment. At each beep, participants were asked to "describe any stressful event that may have taken place in the interval since the last . . . report." These events were subsequently coded according to the activity context (work, other) as well as according to their relevance to task demands (e.g., overload, deadlines) and social interactions, categories that were selected based upon previous work suggesting that these are among the contexts in which daily events are most likely to be associated with negative mood states (Bolger, Delongis, Kessler, & Schilling, 1989; Stone, 1987). A measure of perceived stress (Cohen et al., 1983), containing items such as, "In the last month, how often have you felt that you were unable to control the important things in your life?" was found to be associated with the frequency of within-day stressor reports in this study. For work events, this effect persisted even after adjustment for trait negative affect. This finding is consistent with the assumption that the experience of daily life stressors represents, at least in part, an instantiation of chronic stress burden.

As expected, the experience of events was associated with an increase in negative mood as well as a decrease in positive affect, and these effects were greater among those who scored higher on perceived stress (van Eck et al., 1998). In another report based on the same sample, the occurrence of these daily events, especially those that were ongoing at the time of assessment, were also reported to be associated with momentary increases in salivary cortisol, a measure that was collected in conjunction with each interview (van Eck, Berkhof, Nicolson, & Sulon, 1996). Notably, cortisol assessments were subjected to stringent covariate controls to adjust for the effects of diurnal rhythms, pharmacological influences, consummatory behaviors, and physical activity. Negative affect and "agitation" appeared to mediate the effects of stressful event occurrence on cortisol. In a replication sample by the same investigators, subjects were asked to describe "any positive and any negative event that may have taken place since the last ESM report." Cortisol changes in response to negative events were shown by nondepressed individuals, but not by subjects who met criteria for current major depressive disorder (Peeters, Nicholson, & Berkhof, 2003).

Smyth et al. (1998) published an extension and replication of these findings in a sample of employed and unemployed participants who completed a monitoring booklet six times per day on 2 consecutive weekdays. In this study, participants were asked the following: (1) Since the last beep has something significant happened? (2) Were you dealing with a problem within the last 5 min? (3) Are you anticipating any stressful occurrences in the next hour? Open-ended descriptions of the problem were solicited in each case, followed by severity ratings (0 "not at all stressful" to 100 "as stressful as you can imagine") and ratings of other dimensions (previous experience with problem and controllability). Interestingly, employed and unemployed individuals did not differ in the frequency with which they reported significant events or problems during daily life in this study. However, employed individuals reported *more* instances of anticipated problems (28% of the interviews), compared with those who were unemployed (17%) (Ockenfels et al., 1995).

The presence of a "current problem" as well as the anticipation of a stressful event were both associated with momentary increases in salivary cortisol when compared with periods during which no problems were reported in this study, and there were significant additive effects of endorsing two or more of these questions when compared with endorsement of a single stressor. As in the previous study, controlling for concurrent negative mood ratings reduced the effects of stressor endorsement on cortisol response; in this case, neither negative affect nor stressor reports were significant when both terms were entered in the model, suggesting a high degree of collinearity but no mediation per se. As with the previous study, time of day effects and other confounding behaviors (e.g., caffeine, smoking) were statistically adjusted in these models.

In summary, two different types of research models have been employed for the assessment of stressful "stimuli" using an EMA format. The first model involves the use of closed-ended questions inquiring about recent "problems" during daily life and the second involves an open-ended problem description as well. Various different monitoring frequencies and time intervals for reporting have been employed. Current problems seem to be reported about 30% of the time, on average. Interestingly, the closed-ended data appear to be sufficient, in the sense that these are associated with concurrent measures of

negative affect and salivary cortisol as well as cumulative assessments of negative affect and stress, even when event content or severity is not taken into account. Most of the analyses in this literature have involved within-person assessments (e.g., asking whether the presence of a current stressor is associated with a momentary change in mood or cortisol) rather than between-person assessments (e.g., asking whether individuals who experience more frequent daily stressors show a decrement in mood or enhanced stress responding relative to those whose daily stress profile is more benign). Interestingly, to the best of our knowledge, all of the existing published work examining stimulus-based measures of daily life stressors in an EMA context relies upon time-based rather than event-based sampling approaches (asking subjects to identify stressors at the onset of their occurrence; see discussion on design issues, below).

RESPONSE-BASED MEASURES

Research traditions emphasizing the importance of response-based measures of stress have usually been based upon models of stress physiology, and have emphasized the activity of the sympathoadrenal system and the hypothalamic pituitary adrenocortical axis and their downstream effects as markers of stress (Dougall & Baum, 2001). Because the focus of this chapter is on self-report methods, we will primarily discuss the role of negative affect as a response to environmental stressors. Although psychosocial stress and negative affect are conceptually separable (with stress placing greater emphasis on environmental precipitants of mood or emotion), increases in negative affect are recognized as an essential component of the phenomenology of stress, and some models posit that negative affect may even constitute one of the primary mediators of the effects of stress on health (Herbert & Cohen, 1996). When studying the effects of negative affect using an EMA approach, it is important that the analysis allow the investigator to distinguish negative affective "states" from enduring "trait" characteristics (i.e., negative affectivity or neuroticism).

In selecting a measure of negative affect for use in EMA studies of stress, it is useful to consider which conceptual model of affect, on which the negative affect measurement tool is based, may be most relevant to one's area of research. There are two leading circumplex models of affect that specify the relationship between negative affect and other affective states in semantic space. The first model, sometimes referred to as the Russell model (Russell, 1980), designates Negative Affect and Arousal as the primary orthogonal dimensions of affect and characterizes other emotional states as combinations of these two essential axes (for example, Anger is typically described as an affective state that is high on both Negative Affect and Arousal, whereas Sadness is high on Negative Affect and low on Arousal). In this model, negative affect and positive affect are located on opposite ends of the Negative Affect axis in semantic space.

Some of the most commonly used tools for EMA assessment of negative affect involve ratings of mood adjectives derived the Russell model (e.g., Larsen & Diener, 1992). One of the coauthors of this chapter (SS) has used an eight-item Negative Affect scale in his EMA work, including the following items (italicized items are reverse scored): *contented,* frustrated/angry, *happy,* irritable, miserable, sad, tense, and *overall feeling.* Participants used these items to characterize their current emotional state (e.g., when smoking and not smoking), rating each adjective on a four-point scale ranging from NO!! to YES!! (Meddis, 1972). When such items are included in a measurement instrument along with items varying in Arousal, factor analyses recover the hypothesized structure, whereby the Negative Affect factor is bipolar and includes ratings of both positive as well as negative mood (Shiffman, 2005; Shiffman & Waters, 2004). This scale has been shown to be internally reliable, and ratings on this scale during daily life have been shown to be associated with risk for smoking episodes among ex-smokers who have recently quit (Shiffman & Waters, 2004; see also the following).

Brief EMA measures of Negative Affect and Arousal have also been used by the first author (TK) as part of a research program investigating daily life correlates of ambulatory cardiovascular activity (Kamarck, Janicki, et al., 2002; Kamarck, Muldoon, Shiffman, & Sutton-Tyrrell, 2007; Kamarck et al., 2004). These scales have been shown to be reliable both within- and between-subject, as well as on retest (Kamarck et al., 1998), and have been associated with momentary fluctuations in blood pressure during daily life (Kamarck, Janicki, et al., 2002; see also Jacob et al., 1999).

A second conceptual model of affect, referred to as the Watson model (Watson & Tellegen, 1985), stands in contrast with the Russell model insofar as it posits that Negative Affect and Positive affect are two orthogonal dimensions (the two major axes of the circumplex) rather than being subsumed under a single bipolar scale. In this model, Arousal is represented as an intensity feature which is associated with each of these two primary affects (i.e., strong negative or positive affect of any sort is considered to be high in arousal). The primary measurement tool associated with this model is the Positive and Negative Affect Scale (PANAS), a 20-item adjective rating scale that has been associated with extensive psychometric and validation research (Watson, Clark, & Tellegen, 1988). The PANAS has been examined in conjunction with a number of different response time frames, having been used to characterize one's current mood state as well as one's propensities to experience positive and negative mood in general (Watson, 2000). Several investigators have made use of the original 20-item version of the PANAS in EMA protocols that involved multiple

assessments per day, with some success (Beckham et al., 2005; Engel et al., 2005; Shrier, Shih, & Beardslee, 2005). Short forms of the PANAS have also been developed (Kercher, 1992; Thompson, 2007). A strength of the Watson model is that it has been shown to correspond to major dimensions of personality. Most would argue that Negative Emotionality or Neuroticism is a key personality trait, and some variant of Positive Emotionality or Extraversion is featured in most personality models. This model has been associated with some neurophysiological validation evidence as well (Watson, Wiese, Vaidya, & Tellegen, 1999). A major weakness of the PANAS scale is that it was developed to correspond to the Watson model, so that it somewhat artificially underrepresents some of the low arousal states associated with negative and positive affect (such as sadness and contentment) which tend to behave less consistently as part of the model (see Barrett & Russell, 1999; Larsen & Diener, 1992). A revision of the PANAS (the PANAS-X) includes several specific emotion subscales (Watson & Clark, 1994) that can be used to address this problem.

Drawing from the Profile of Mood States (McNair, Lorr, & Droppleman, 1971) and other sources, Usala and Hertzog (1989) have developed a 61-item measure that assesses 9 positive and negative affective states, including those that comprise the major axes of the Russell and Watson models (anxiety, fatigue, depression, well-being, vigor, guilt, calm, fear, elation). Some investigators of daily mood have employed selected items from this measure as a means of capitalizing on the strengths of the Watson model (i.e., its emphasis on positive affect as a potentially distinct dimension of experience) while maintaining the breadth of emotion adjectives that have traditionally been seen to be an important feature of affect (Cohen, Alper, Doyle, Treanor, & Turner, 2006; Janicki-Deverts, Cohen, Doyle, Turner, & Treanor, 2007). Data suggest that the relationship between negative and positive affect may vary as a function of the units of time over which affect is assessed, such that while happiness and distress may coexist over longer intervals, they do appear to be negatively correlated—as the Russell model asserts—in a particular moment (Diener & Emmons, 1985) and to a greater extent during ongoing stressful events (Zautra, Berkhof, & Nicolson, 2002). For more discussion about the relative merits of the two circumplex models of emotion, see (Barrett & Russell, 1998, 1999).

APPRAISAL MEASURES

Real-time appraisal-based measures of stress involve measuring the characteristics of current activities and one's resources for coping with them. Three types of diary items or scales have been employed for these purposes: measures of activity demand appraisal (assessing difficulty or valence of present task), social demand appraisal (assessing demands, obstacles, or valence associated with present social interactions), and performance effectiveness appraisal (assessing the effectiveness of one's own coping behavior in interaction with current activities or social events; e.g., the extent to which one's efforts are deemed successful or valued).

Drawing upon previous reviews that have demonstrated significant effects of motivated performance on cortisol in the laboratory, Schlotz, Schulz, Helhammer, Stone, and Hellhammer (2006) designed two simple diary items to assess the appraisal of motivated performance during daily life. In a small (n =77) sample of individuals who were assessed three times per day during 2 weekdays, participants were asked to rate their agreement (0–3 scale) with two statements pertaining to situations that may have occurred within the past 60 minutes: "(1) I performed tasks that allowed no mistake" and "(2) I performed my tasks inadequately." These two ratings correspond to the "activity demand" and "performance effectiveness appraisals" described above. Ratings on the first item were related to within-person increases in salivary cortisol (after adjustment for reported activity levels and substance use), with significantly larger effects among those who scored high on trait anxiety. Aggregated ratings on the second item were related, on a between-subjects basis, with reductions in salivary cortisol.

A report from one of the research teams that has previously employed stimulus-based methods for daily stressor assessments used an alternative appraisal method in a more recent investigation. In a sample of 556 female Belgian twins, EMA reports were collected 10 times daily over a 5-day period using paper-and-pencil forms in conjunction with a wristwatch prompt (Jacobs et al., 2007). In this study, mood ratings as well as salivary cortisol were also collected at each assessment. Two appraisal measures of stress were administered during each assessment and were scored as continuous scales: a two-item measure of activity demand appraisal ("I would rather be doing something else" and "This activity requires effort," each rated on a seven-point Likert scale), and a two-item measure of social demand appraisal rated when others were present ("I don't like the present company" and "I would rather be alone"). These measures were compared with a stimulus-based assessment of stress, which involved reporting the "most important recent event" and rating its valence on a seven-point scale (very pleasant to very unpleasant). All three stress measures were related to within-person fluctuations in positive and negative affect, as expected. Fluctuations in cortisol (corrected for diurnal pattern and recent food or drug consumption) were significantly associated only with the two appraisal-based measures of stress, and not with the stimulus-based assessment. Negative affect appeared to be a mediator of the stress–cortisol relationship, consistent with previous reports (Peeters et al., 2003; Smyth et al., 1998; van Eck et al., 1996).

Brondolo, Karlin, Alexander, Bobrow, and Schwartz (1999) have used EMA measures of negative social interactions (social demand appraisal) in a series of studies

examining stress and hostility in relation to ambulatory cardiovascular activity. In one study, social interactions that were rated as more "negative" in real time were shown to be related to acute ABP responses among New York city traffic agents. This finding was replicated in a second study of healthy adults, in which negative social interactions (ratings of "uncomfortable," "tense," "confrontational," "openly angry," or "about something upsetting") were more frequent and were related to larger ABP responses among hostile individuals when compared with their less hostile counterparts (Brondolo et al., 2003). In a third study by this group, daily social interactions were rated more negatively ("ignored," "harassed," and "treated unfairly") among those who scored higher on a measure of perceived discrimination (Broudy et al., 2006; see also Taylor, Kamarck, & Shiffman, 2004).

Hanson, Maas, Meihman, and Godaert (2000) described the development of a momentary measure examining work-related stress, used as a means of characterizing the Effort-Reward Imbalance model (Siegrist, 1996) in daily life. This measure contained three items pertaining to perceived activity demands: Since the last beep (a) "I was interrupted a lot," (b) "I was under time pressure," and (c) "I experienced physical demands," and two items pertaining to performance effectiveness: Since the last beep (a) "my actions were worth the trouble," and (b) "my input was acknowledged." Each item was answered using yes/no response options and was also rated with respect to distress on a 1–4 scale. In a sample of 104 employed health professionals and office clerks, these momentary measures of work stress were not associated with fluctuations in salivary cortisol over a 2-day period, whereas momentary measures of negative affect were positively linked with cortisol, after adjustments for time of day and other covariates.

In summary, various appraisal-based measures have been described assessing activity demand, social demand, and appraised performance effectiveness. These measures have been shown to be associated with fluctuations in salivary cortisol, ABP, and other global self-report assessments. In the few studies that have compared stimulus-based, response-based, and appraisal-based assessments, response-based assessments (measuring negative affect) appear to be most strongly related to salivary cortisol fluctuations, appraisal-based measures appear to be somewhat more consistent in their effects, and the stimulus-based assessments may be the weakest or least consistent correlates of within-person changes in salivary cortisol. In our own work, we have found that both appraisal-based as well as response-based assessments are independently related to ABP (Kamarck, Janicki, et al., 2002; see also the following).

Each of these three types of measures, stimulus-based, appraisal-based, and response-based, tend to travel together within-person throughout daily life. One intriguing approach that is gaining currency involves examining individual differences in the relationships between these measures, that is, differences in the slope of the within-person association between daily stressor occurrence (as assessed using stimulus-based or appraisal-based assessments) and acute changes in affective response (within-subject changes in negative affect or positive affect). Using the measures described above, such individual differences in "emotional reactivity" during daily life have been shown to be associated in the expected direction with gender (Myin-Germeys, Krabbendam, Delespaul, & van Os, 2004), recent life events (Myin-Germeys, Krabbendam, Delespaul, & van Os, 2003), childhood trauma (Glaser, van Os, Portegijs, & Myin-Germeys, 2006), neuroticism (Suls & Martin, 2005), current psychopathology (Myin-Germeys, Peeters, et al., 2003), and genetic liability to depression (Wichers et al., 2007).

Although a number of studies have shown associations between self-report EMA measures and biological markers of stress, the extent to which existing assessments are optimal in terms of capturing the psychological triggers of biological responding is unknown. Future work in the EMA assessment of psychosocial stress should strive to continue to build upon some of the laboratory and epidemiological evidence that attempts to characterize the types of adaptational demands most likely to elicit stress-related biological responding. Recent meta-analyses (Dickerson & Kemeny, 2004) suggest that performance situations involving *social-evaluative threats* may be salient stimuli for acute cortisol responding in the laboratory, especially when they involve *uncontrollable* elements (negative outcomes not contingent on one's response). Continued translation of these types of findings into the content of EMA-based measures of daily life stress should be expected to strengthen the sensitivity of these assessments.

PSYCHOMETRIC AND DATA ANALYTIC CONSIDERATIONS

EMA-based tools, like all measurement methods, require psychometric evaluation, and they need to be designed for, and evaluated within the context of the research questions and the populations for which they will be applied. For EMA research, as with traditional methods, items or measures that are retrofitted from studies designed for other purposes or for different populations need to be evaluated to ensure that the modifications have been successful. Items initially administered with a nonmomentary response set may have a different meaning, may be associated with insufficient variability, or may be difficult to interpret when administered in a momentary format. For example, the Job Content Questionnaire, a standard measure of occupational stress (Karasek, Pieper, Schwartz, Fry, & Schrier, 1985), includes a subscale that measures Skill Discretion, in which respondents are asked to evaluate the extent to which their job enables them to "learn new things" and "develop skills." We have attempted to translate aspects of this instrument to a

momentary assessment format, to assess how work stress affects daily work experiences, but pilot tests have led us to conclude that Skill Discretion items do not translate well, and are associated with insufficient within-person variability, when applied to the moment-to-moment evaluation of daily activities. Thus, initial piloting and psychometric evaluation is always advised.

Because EMA measures can be relatively intrusive, there is a valid concern about measurement reactivity, or the potential for behavior or experience to be affected by the act of assessment. Efforts to systematically examine this concern have shown little or no evidence for reactive effects in nontreatment samples (Hufford & Shields, 2002; Hufford, Shields, Shiffman, Paty, & Balabanis, 2002; Shiffman et al., 2008). For example, in one of the most well-controlled studies in this area, Stone et al. (2003) manipulated monitoring density, assigning subjects with pain syndromes to complete pain ratings 0, 3, 6, or 12 times daily. There were no main effects of the monitoring schedule on pain ratings, nor were there trends over time suggesting that the experience of repeated ratings affected pain reports.

A related concern involves the effects of repeated EMA assessments on respondent burden. This consideration dictates a need to be economical with respect to interview length as well as in the wording of individual items. However, it must be balanced against the increased reliability that may be obtained with the use of multiple item scales, particularly in the evaluation of subjective states.

The evaluation of internal reliability of multi-item scales, in turn, presents a particular challenge for those interested in EMA research. In evaluating the reliability of an instrument, we are accustomed to examining between-person data, that is, determining the extent to which items on the same scale "travel together" across persons. In EMA research, most research questions are within-subject, involving relationships between dynamic activities or states (e.g., the extent to which changes in perceived stress throughout the day are accompanied by commensurate alterations in the quality of social interactions). For these types of questions, *within-person* reliability is also an important concern. In contrast to between-person reliability, the issue here is with the extent to which items on the same scale are intercorrelated consistently, *over time*, on repeated administration (Kamarck et al., 1998). This is to be contrasted with item stability or unchanging responses; scale scores may change over time and yet the scale may be internally reliable on a within-person basis, just as scale scores may vary across person in the context of high between-person interitem reliability. There have been few efforts to evaluate within-person reliability of EMA scale scores in the contemporary literature, just as there have been few efforts to evaluate within-person item correlation matrices for EMA scales (the reader is referred to the literature on P-factor analysis and other within-person techniques, e.g., Cattell, 1952; Michela, 1990).

Although items in EMA research are designed for evaluating temporal variability, it is important not to lose sight of the fact that, when aggregated over time, such items may, in fact, provide valid assessments of stable individual differences as well. Some, for example, have proposed that the major personality traits can be reliably extracted from measures of individual difference in everyday behavior as assessed using an EMA format (e.g., "During the past hour, how well does 'talkative' apply to you"; Fleeson, 2001). For such purposes, as well as for measuring individual differences in environmental exposure, aggregation of items over time is called for. Such time-averaged items need to be evaluated, for example, using generalizability analyses (Cronbach, Gleser, Nanda, & Rajaraham, 1972; Llabre et al., 1988) to determine the minimal number of observations required within the aggregated set to achieve conventional standards of internal reliability in between-subjects analyses. Generally speaking, however, repeated assessments make for reliable composite estimates, much as adding (appropriate) items to a scale will boost its internal consistency.

When aggregated items are used, as above, one may examine the extent to which the aggregated measures are stable over time. For example, in one sample, we conducted two monitoring periods of 3 days each, interposed by a 4 month interval, allowing us to determine the extent to which the 3-day aggregated data produced scores that represented relatively stable characteristics of the individual for this time period (Kamarck et al., 2002). When interpreting such data, it is important to keep in mind the degree to which high test-retest stability is, in fact, assumed to be a property of the measure in question. It is not necessarily to be expected that measures of psychosocial stress should be stable characteristics of the individual, especially over prolonged intervals.

It is unusual to see criterion or construct validity data presented for EMA-based instruments in the literature, but we contend that these data should be expected, in the same manner that they are expected for traditional measures. The distinction between EMA data used for evaluating within-subject questions and between-subject questions, again, is paramount. If the scale in question is to be used for evaluating diurnal fluctuations in perceived stress (a within-subject question), relevant validity data should examine the extent to which the instrument is sensitive to within-subject variability in stress (e.g., comparisons between the workplace and the home environment), whereas if the scale is to be used to evaluate group differences in stress, validation data should compare groups of people (e.g., comparisons between individuals in different occupational groups) or should compare the instrument to standard retrospective self-report questionnaires. One of the important limitations of most of the EMA literature is the fact that it is based upon self-report. In this respect, observational data or informant self-reports are useful standards of comparison, and should be considered as potential validation measures. We were impressed, in some of our earlier work, at the

extent to which subjective states, such as mood, may be largely corroborated by spousal reports about inferred participant experience that are collected at the same point in time (Kamarck et al., 1998).

Whether based upon self-report or upon other sources, when traditional retrospective measures are used to evaluate the validity of EMA, some caution is in order. Our previous discussion should lead us to conclude that aggregated EMA data need not necessarily be expected to be perfectly correlated with global self-report instruments even when comparable items are used. We recommend that traditional assessments as well as end-of-day assessments be used in EMA research that involves time-aggregated data, to permit us to determine the extent to which EMA measures provide *incremental validity* with respect to predicting criterion outcomes.

Multilevel models that use maximum likelihood (ML) estimating techniques have been recommended for analysis of EMA data, including the calculation of within-person and between-person coefficients such as those described above (Schwartz & Stone, 1998, 2007). Advantages of the multilevel approach include its ability to handle time-varying phenomena, its ability to model autocorrelation effects, and its tolerance of unbalanced designs, all important considerations in EMA studies, which involve longitudinal data collection and are apt to involve a lot of missing data. Another advantage of these models is that they permit accurate and efficient effect estimation when scores derived from unequal numbers of observations (i.e., differences in variance; the condition referred to as heteroscedasticity) are compared. More complete discussion of the theory behind multilevel models and associated analytic techniques is provided elsewhere (Bryk & Raudenbush, 1992; Hox, 2002; Snijders & Bosker, 1999). Various novel analytic approaches are also described in Walls & Schafer (2006).

Psychometric analysis of EMA measures has been rather cursory and unsystematic in the existing literature. Given the brevity of assessments that can be afforded when interviews are conducted in the natural environment, it would appear that this field would benefit from the use of more effective item selection methods in the development of EMA scales. In this light, item response theory (IRT) (Bjorner & Ware, 1998; Hambleton & Swaminathan, 1985) would merit some consideration. In contrast with classical test theory, IRT models do not assume that all items on a scale are equally valid measures of the construct that the scale is designed to measure. Instead, IRT models attempt to characterize the properties of each item, for example, the degree to which its inclusion increases the precision of latent trait estimation or the extent to which it provides equivalent information about those under low, moderate, or high stress. Because of its emphasis on individual item properties, the application of IRT permits the development of computerized adaptive testing (CAT). CAT uses IRT algorithms to maximize the information gained from each item response, using this information, in turn, to alter the items presented in accordance with one's individual response patterns. This permits us to characterize a given person's score along any given dimension (such as psychosocial stress) with administration of as few items as possible. Because efficiency is an important consideration in real-time assessment, EMA and CAT would appear to be a natural marriage, and the palm top computers that are increasingly common in this literature would appear to increase the feasibility of such applications.

RESEARCH DESIGN AND SAMPLING DECISIONS

In addition to psychometric considerations, the development of EMA measures involves decisions that are inextricably linked with those pertaining to research design. In contrast to global assessments, such as personality questionnaires, EMA assessments capture moments or periods of time, raising the issue of how to ensure that the moments assessed provide an adequate representation of the phenomenon under study. Designing an EMA protocol, therefore, amounts to designing a sampling scheme. Sampling in an EMA study can be roughly characterized as either event-based or time-based (Bolger et al., 2003; Shiffman, 2007; Wheeler & Reis, 1991). Event-based approaches aim to characterize particular discrete events, such as social interactions (Reis & Wheeler, 1991), headaches (Niere & Jerak, 2004), or drinking episodes (Todd, Armelis, Tennen, Carney, & Ball, 2005); they may be particularly well suited, in some instances, for the application of stimulus-based measures of stress. Time-based sampling, on the other hand, involves a greater concern for capturing a representative "slice of life" for the individual, with less regard for thorough coverage regarding specific types of behaviors. This sampling scheme may be a better match for appraisal-based measures of stress, in which the concern is for the ongoing daily burdens that may be less closely tied to discrete events.

When event-based assessments are used to examine the frequency of or characteristics associated with specific events, such as eating episodes, medication use, or craving for cigarettes, these are usually initiated by the respondent. This requires, first, that subjects be provided with clear definitions of the event, and second, that they remember to respond. With respect to event definitions, these can sometimes be surprisingly difficult to negotiate (for example, what constitutes a stressful event, or a marital argument?), so care is in order in designing protocol instructions and in training. With respect to subject compliance, there is often no way to independently verify the validity of event-related entries in EMA research, that is, there is no way to know whether events occurred that were not entered or (less likely) entries were made for events that did not occur, so this needs to be taken into

consideration in interpretation of the data (see Shiffman et al., 2008).

As with event-based assessments, time-based designs require a number of design decisions. Different types of research questions may drive differences in the schedule, frequency, and timing of time-based assessments (see Delespaul, 1995, for more detail). For example, the degree of temporal "resolution" required will depend upon the goal of the study, what is known about the behavior in question (particularly its rate of variability over time), and the theoretical framework that guides the study. Some administer time-based assessments at fixed intervals, which allow the time block to serve as the unit of analysis and support analyses that require evenly spaced assessments, such as simple autocorrelation analysis, and time series analysis. Other studies use somewhat irregular intervals, for example, requiring an assessment in the morning and evening of each day (Hensley et al., 2003). There is the potential for bias in this type of design, insofar as subjects may wait to conduct assessments until it is most convenient for them, during periods during which mood may be systematically more relaxed, or, alternatively, subjects might remember to complete mood assessments only when they experience extremes of mood.

An alternative to fixed intervals is a variable schedule, which involves random assessments to ensure that a representative sample is obtained. Stratified random sampling may also be used, as when random samples are taken within strata defined by blocks of time within a day (Affleck, Tennen, Urrows, Higgens, & Abeles, 1998). This assures that different periods of the day will be adequately represented, and allows time block to serve as the unit of analysis.

Decisions about sampling frequency will be based upon considerations of subject burden as well as the temporal variability of the variable to be assessed. Sampling frequencies of three to five times per day are common, but some studies have succeeded with as many as 15 or more (Goldstein, Jamner, & Shapiro, 1992; Kamarck, Shiffman, Muldoon, & Sutton-Tyrrell, 2007). In any case, it is recommended that samples be scheduled throughout the waking day. When a range of hours is specified, missed data in the early morning and late evening hours may be systematically different, resulting in bias. For example, in a study that involved collection of ABP during all waking hours, we compared data collected within a standard 12-hour window (9 a.m. to 9 p.m.) to the data collected outside of this window (before 9 a.m. and after 9 p.m.). "Out-of-window" data (representing evenings and early mornings) constituted 16 percent of valid observations for the average person. ABP was significantly lower during out of window times when compared to the standard interval (Kamarck et al., 2007), indicating that an assessment limited to the time window would have been biased. In a parallel analysis of self-report data collected over weeks of monitoring (Shiffman, unpublished data), we found that negative affect and arousal were both significantly lower within the 12-hour daytime window when compared with the morning and evening hours, indicating that this phenomenon may also apply to self-report assessments.

In making decisions about sampling for an EMA study, the investigator should not neglect the option of combining sampling approaches, an option that may represent the optimal strategy for testing certain hypotheses. For example, when a researcher is interested in the circumstances that are associated with a target event, it can be particularly helpful to combine time- and event-based assessments to provide some context for interpreting event data (Greeno, Wing, & Shiffman, 2000; Paty, Kassel, & Shiffman, 1992). Time-based assessments can also be used to document the antecedents and consequences surrounding the target event (Shiffman, Balabanis, Gwaltney, Paty, & Gnys, 2007). In short, the research question and the natural history of the target behavior should both be considered in formulating the sampling design for an EMA study.

An additional decision that will drive the design of the questionnaire and the sampling frame for EMA research involves the extent to which intermittent versus complete coverage is the desired goal. When momentary assessments are assessed intermittently throughout the day (e.g., momentary perceptions of stress are reported 12 times per day), it is usually understood that the sample of experience, while representative, may not be complete. It is always possible in an individual case that events occurring between sampling intervals may have altered the result, had these intervals been included in the sampling frame. In lieu of a sampling strategy, investigators sometimes opt for a coverage strategy, which aims to cover every moment of the day. For example, if the assessment of minor life events rather than perceived stress is the target (in the 12 times per day interview example), one might ask subjects to report on all events that have occurred since the prior interview. Besides being vulnerable to biases introduced by recall, this strategy requires subjects to accurately maintain a timeline of experience and to be able to extract those experiences that have occurred since the last assessment. Because people do not tend to be proficient at such tasks (Sudman & Bradburn, 1973), measurements reflecting this approach need to be treated with caution. For this reason, sampling strategies are typically preferred to coverage strategies; if absolute estimates or counts of events are needed, these can be imputed from the representative estimates provided from momentary reports.

Most of the types of sampling designs discussed here will generally require some sort of electronic assistance. EMA is most closely associated with the use of palm-top computers (Hufford & Shields, 2002), although a number of devices ranging from beepers to cell phones may be employed. The use of a hardware platform that can not only manage prompting schedules, but can also present

assessment content to subjects, manage assessment logic such as branching, accept and store data, and time stamp entries, should be considered (Shiffman, 2007). Verifying the timing of each assessment, in particular, turns out to be critical, given the potential distortions associated with retrospective report, and the difficulties with obtaining prompt and reliably timed data when paper-and-pencil diary records are used (Stone, Shiffman, Schwartz, Broderick, & Hufford, 2002). Whatever device is used, its suitability to the population in question is an important consideration. For example, a small screen may be difficult to negotiate for a visually impaired group, and a system relying on auditory prompts or questions may be less suitable for those with hearing impairments.

Approaches using electronic devices require software for basic system functionality as well as to design the interview in accordance with the requirements of the study. There are a growing number of options in this area. Le et al. (Le, Hat, & Beal, 2006) have reviewed a number of freely available EMA software programs, and a number of commercial vendors also provide programming assistance and support.

THE PITTSBURGH EXPERIENCE

In this section of the paper, we describe some of our previous work using EMA-based measures of psychosocial stress, as a means of illustrating some of the types of scientific problems that may be elucidated with such tools.

STUDIES OF STRESS AND CARDIOVASCULAR DISEASE

In some of our work, we have been particularly concerned about the role of stress in cardiovascular disease risk. We have adopted the assumption, based upon previous literature, that alterations in sympathetic nervous system (SNS) activation may be the feature that characterizes psychosocial stressors most strongly associated with cardiovascular disease, and that hemodynamic changes (increased heart rate and blood pressure) may be taken as a marker of SNS responding. As a result, we have selected dimensions for measurement for this research based upon their demonstrated association with acute hemodynamic changes (usually based upon laboratory evidence) as well as with cardiovascular disease. Drawing from the response-based as well as the appraisal-based traditions, five primary dimensions of *psychosocial demands* have been characterized in our work, and assessed repeatedly over the course of daily living using a series of multi-item scales: Social Conflict, Task Demand, Decisional Control, Negative Affect, and Arousal (Kamarck, Janicki, et al., 2002; Kamarck et al., 1998, 2005).

The Diary of Ambulatory Behavioral States (DABS) was developed for repeated assessment of daily experiences relevant to cardiovascular activity and health risk (Kamarck et al., 1998). In addition to measuring the five dimensions described above, we also included in this diary items assessing various social interaction characteristics, as well as other behaviors (postural changes, physical activity, and substance use) known to be associated with cardiovascular activation in the natural environment. For a depiction of the items on the DABS, see Kamarck et al. (1998) and Kamarck, Schwartz, Janicki, Shiffman, & Raynor (2003).

THE PITTSBURGH HEALTHY HEART PROJECT

The Pittsburgh Healthy Heart Project (PHHP) (Kamarck et al., 2004) was designed to examine the links between daily experience, ABP, and subclinical cardiovascular disease. A sample of 337 healthy older adults (age range of 50–70, 51% female, 16% nonwhite) completed 6 days of ABP and DABS assessments over two 3-day periods, 4 months apart. During each of these monitoring periods, assessments were collected every 45 minutes throughout the waking day using an electronic diary (see Kamarck et al., 2007).

Examining the "Stress Signature" Assumption

Earlier we discussed the "stress signature" assumption, which posits that momentary experience represents the instantiation of chronic stressors. Some of our own data are consistent with this assumption. In a subset of the PHHP sample, we administered the Chronic Stress Scale, a self-report questionnaire inquiring about the presence of life stressors, over the past 6 months, across seven life domains (Marital, Parental, Filial, Financial, Occupational, Ecological, and Physical; Norris & Uhl, 1993). Sample items include (Marital) "In the past 6 months, how often did your spouse expect more from you than he or she was willing to give back?" (Occupational) "In the past 6 months, how often were you treated unfairly by others on the job?" To equate participants for participation in comparable life roles, we selected only those who were currently married and employed for the following analyses ($n = 95$). We averaged each of our five measures of momentary psychosocial demands across the 6-day monitoring period for each participant. We used multiple regression models to predict each of the five EMA measures, with the seven chronic stress subscales as predictors, along with covariates for age and sex. Below, we report only those effects that were significant in these multivariate models.

Marital stress was shown to be the major correlate of negative affect during daily life That is, global Marital Stress scores were the only measures of chronic stress that were independently associated with mean momentary ratings on the EMA Negative Affect scale, $p = 0.005$. Physical stress (i.e., the presence of physical disabilities) predicted the experience of low energy throughout the day ($p = 0.04$ for EMA Arousal scale). Filial Stress (i.e.,

caretaking responsibilities) as well as Occupational Stress were both associated with the experience of a demanding psychosocial environment (for EMA Task Demands measure, $p = 0.002$ and 0.01, for Filial Stress and Occupational Stress, respectively). Occupational Stress was associated with a perceived lack of control over daily activities (as measured by the EMA Task Control scale, $p = 0.04$). And finally, both marital stress and parental stress were independently associated with daily experiences of social strain (mean ratings on EMA measure of Social Conflict during social interactions) ($p = 0.0001$, $p = 0.05$, respectively). While causal direction in this pattern of cross-sectional findings is difficult to discern with certainly, these results are consistent with the assumption that the effect of chronic stressors on our daily experience is discernable using EMA methods, and the relatively specific patterns of effects shown here are not consistent with an interpretation that emphasizes response bias or a "negative halo" phenomenon as the major reason for the observed effects.

Examining Psychosocial Demands as Correlates of Hemodynamic Responding During Daily Life

One of our goals in developing the DABS scales was to help us to characterize the effects of psychosocial exposures on SNS responding during daily life. For this purpose, we examined acute changes in ABP and heart rate associated with each of our five dimensions of psychosocial stress. Posture, activity, substance use (e.g., caffeine, alcohol), and various other potential confounds were used as time-varying covariates in each case. We used a multilevel modeling approach for this purpose (Schwartz & Stone, 2007).

Fluctuations in each of these psychosocial dimensions during daily life was significantly and independently associated with changes in systolic and diastolic blood pressure (SBP and DBP) in the expected direction even after adjusting for posture, physical activity, and other incidental behaviors (Kamarck, Janicki, et al., 2002). In related work, we showed that the magnitude of hemodynamic perturbation in response to fluctuations in daily psychosocial demands varies across individuals, and that such differences are related to relatively stable traits of psychophysiological responding, as assessed in the laboratory (Kamarck et al., 2003). Findings support our contention that there are measurable classes of everyday experience that are linked with SNS activation. To the extent that SNS activity may mediate the effect of psychosocial stress on cardiovascular disease, these same dimensions of everyday experience might be relevant to disease risk. Notably, these types of within-person analyses, which examine the covariation of behavior and physiology in the natural environment, are not possible with traditional retrospective questionnaires or with end-of-day reports.

Examining Individual Differences in Exposure to Daily Psychosocial Demands

In addition to their role in evoking SNS responding during daily life, another property that makes these dimensions of experience important is that they are unequally distributed: Some individuals are exposed to these experiences more frequently or intensely than others. In the PHHP sample, we averaged momentary ratings on each of these dimensions across all observations to attain summary scores for each subscale. These scores were only moderately intercorrelated across these five dimensions (Social Conflict, Task Demand, Decisional Control, Negative Affect, Arousal, average intercorrelation of 0.42 (Kamarck, Janicki, et al., 2002) suggesting that they represent relatively independent dimensions of daily experience.

Because PHHP participants were administered the DABS over two 3-day periods, 4 months apart, we were provided with an opportunity to examine the stability of such differences over time as well. Momentary ratings on each of these subscales were averaged separately across each of the two 3-day monitoring periods in this study, and the corresponding pairs of summary scores were correlated across time. Results (test-retest correlations of 0.70 to 0.76) suggest that each of the five dimensions are relatively stable over time and may be used to characterize stable differences in the experience of psychosocial stress.

In sum, each of the five dimensions of experience is associated with significant within-person fluctuation day-to-day as well as substantial between-person variability. The importance of these latter findings lies in the potential utility of such scores as reliable markers of the extent of exposure to autonomically relevant stressors during daily life. To the extent that EMA assessments of stress can be used to characterize individual differences in stress exposure, we might expect these measures to be related to important health outcomes.

Examining Daily Psychosocial Demands as Correlates of Cardiovascular Risk

ABP has been shown to be an important predictor of risk for cardiovascular risk; for example, it was noted earlier that blood pressure measures taken during daily life are stronger predictors of cardiovascular morbidity and mortality than are traditional resting blood pressure measures assessed in the clinic setting (Janicki & Kamarck, 2008; Verdecchia, 2000). By virtue of their ability to capture the effects of daily life psychosocial processes with a potential effect on autonomic function, we reasoned that EMA assessments of stress could help to explain, in part, the unique predictive value of ABP. As such, in the PHHP sample, we examined the cross-sectional association between momentary scores on each of the five scales described above, averaged across 6 days of monitoring, and averaged measures of ABP. People who

rated themselves as higher in Task Demand and lower in Decisional Control during daily life tended to have higher ABP over the 6 days of monitoring in the study. In contrast, average measures of momentary Demand and Control were not associated with blood pressure assessments that were taken in the laboratory, under standard doctor's office conditions; as such, associations with ambulatory pressure persisted even after adjustment for laboratory pressure assessments. Daily experiences of Demand and Control do not appear to be linked with differences in resting blood pressure, but only with differences in blood pressure that emerge in the course of daily living.

We next examined the relationship between our EMA measures of stress and carotid artery intima-medial thickness (IMT), a marker of systemic atherosclerosis (Pignoli, Tremoli, Poli, Oreste, & Raoletti, 1986; Wong, Edelstein, Wollman, & Bond, 1993) as assessed using ultrasonography. We hypothesized that, to the extent that they might trigger excessive or prolonged SNS responding, cumulative exposure to these daily sources of psychosocial stress might contribute to increases in the risk for early cardiovascular disease. After adjusting for relevant demographical and risk factor covariates, we did, indeed, observe significant associations, once again, involving the measures of Task Demand, and Decisional Control. Those individuals who rated their daily lives as more demanding, by EMA report, tended to show greater carotid IMT thickness, suggestive of more extensive atherosclerosis. An inverse association between ratings of Decisional Control and atherosclerosis was marginally significant (Kamarck et al., 2004). Neither of these associations was accounted for by traditional biological or sociodemographic markers of risk. Moreover, the effects were shown to be partially mediated by the effects of Demand and Control on ABP that was reported above (Kamarck et al., 2004).

Three years after initial enrollment in the PHHP, additional measures of carotid artery atherosclerosis were assessed in the participants, allowing us to examine whether baseline measures of daily psychosocial demands were significant predictors of subclinical atherosclerotic progression in this sample. EMA-based measures of Task Demand and Decisional Control were, indeed, significant predictors of atherosclerotic progression, an effect, however, that was significant only among the men in this sample. This time, effects were partially accounted for by elevated ambulatory heart rate among those men with low baseline ratings of Task Control. As with the cross-sectional findings, neither demographical nor biological risk factors could be shown to explain the observed effects (Kamarck et al., 2007).

We had expected that our EMA measures, when compared with traditional self-report questionnaires, would be more powerful tools for characterizing the excess SNS burden associated with psychosocial stress. We compared our aggregate EMA measure of Task Demand with global questionnaire reports examining the same construct. The subset of the PHHP sample who were employed had also been administered a traditional questionnaire, the Karasek Job Content Questionnaire (Karasek et al., 1985), which elicits a global appraisal of demand ("Psychological Demands") and control ("Decision Latitude") associated with the job environment. In this employed subsample, as in the sample as a whole, EMA measures of Task Demand were significantly associated with carotid atherosclerosis and, among the men, atherosclerotic progression. In contrast, in comparable samples, scores on the globally-assessed, non-EMA Karasek scales showed no associations with carotid disease outcomes (Kamarck et al., 2004, 2007).

Furthermore, among those who were employed, associations between average momentary ratings of demand and IMT did not differ as a function of whether such ratings were taken in the workplace or in nonwork settings. Interestingly, this finding is contrary to the job strain hypothesis articulated by Karasek and Theorell (1990), which implies that the observed effects of task demand and decisional control on health involves the operation of characteristics that are specific to the work environment.

In sum, momentary diary ratings of Task Demand appeared to be associated with enhanced carotid atherosclerosis and atherosclerotic change whereas traditional self-report assessments of the same constructs were not predictive in this sample. These results comply with our expectation that EMA measures of daily experience, because of their measurement fidelity and their proximity to behavioral and biological events, may be expected to outperform global measures of psychosocial stress as markers of disease risk. Our findings showing that ambulatory physiology may partially mediate the relationship between daily psychosocial stress and disease risk illustrate the potential for EMA-based research for the evaluation of biological or behavioral mechanisms linking stress and health. Finally, our comparisons of the effects of demand and control inside and outside of the workplace illustrate another hypothesized strength of EMA discussed earlier, involving the facility it lends us to explore setting differences in the relationship between stress and health risk.

STUDIES OF STRESS AND THE SMOKING RELAPSE PROCESS

Another illustration of the use of EMA measures of psychosocial stress involves our work on the role of stress in the relapse process among ex-smokers. Methodologically, this line of work is complementary to that described above, insofar as it involves a greater emphasis on the ability of EMA measures to capture longitudinal or sequential processes over the course of daily life, and it includes a different set of sampling strategies as well, as outlined below.

Among smokers, behavior change is a significant hurdle, with most of the attempts to quit smoking ending up in failure. It is estimated that 95–99% of all unaided quit attempts end in relapse (Jarvis, 2003), most within the few weeks of quitting. A high rate of relapse is also characteristic of other addictions (Marlatt & Gordon, 1985) such as gambling, alcoholism, and drug use, and is seen in weight loss efforts as well (Brownell, Marlatt, Lichtenstein, & Wilson, 1986). In this respect, lessons learned about the relapse process are thought to have general implications for understanding health-related behavior change.

Because relapse consists of real-world events, driven in part by complex environmental and situational influences, it seems essential to study relapse processes in people's natural environments. Moreover, the processes that lead to relapse seem to play out over time, suggesting the importance of repeated sampling to capture temporal variation. The resumption of smoking is viewed, in part, as a punctate event, as the ex-smoker's experience is characterized by periodic challenges to abstinence in the form of episodes of intense craving (Shiffman, 1982; Shiffman et al., 1997) that tend to occur in the context of specific situational and affective cues (Shiffman, 1982; Shiffman, Hickcox, et al., 1996). At the same time, the relapse process is also viewed as the outcome of a longer term struggle, in which the cumulative effects of coping efforts and challenges gradually reduce resolve (Shiffman, 1989). Thus, attempts to study the relapse process may benefit from use of EMA methods with longitudinal assessments, and use of measures that involve momentary as well as longer term temporal parsing.

Psychosocial stress is thought to be one of the major drivers of relapse, and negative affect is considered to be one of the important mechanisms of its effects (Kassel, Stroud, & Paronis, 2003). In the study of the relapse process, we have made use of a negative affect scale administered in real time to assess one's momentary state, and we have averaged such assessments over time to assess background conditions of affect or mood, which are thought to vary more slowly, and to represent more tonic influences on behavior. Given the interest in relapse as the response, in part, to a single discrete event (the "relapse crisis" during which one is tempted to resume smoking, and in which a momentary state of negative affect may play a part), an event-based sampling strategy is called for. Given the interest in background conditions of affect and the need to characterize baseline differences in mood, event-related assessments are supplemented by signal contingent interviews, initiated on a random basis, and designed to capture a representative sample of background affect during each monitoring day.

THE UNIVERSITY OF PITTSBURGH SMOKING RELAPSE STUDY

Three hundred smokers embarking on a quit attempt were recruited to participate in a behaviorally based smoking treatment program. Following treatment, 214 of these were deemed to be successful in quitting initially (defined as at least 24 hours of abstinence) and were followed for up to 4 weeks to examine the relapse process. During this 4-week period, subjects were asked to carry electronic diaries that administered time-stamped assessments of three sorts: First, subjects were asked to self-initiate interviews each time they encountered a "relapse crisis" in which they were tempted to smoke or had smoked, recording, in each instance, the acute situational and affective cues associated with the event, their attribution for the cause of the episode (stress, bad mood, smoking cues, and so forth), and the resolution (whether the event resulted in a mere "temptation" or a smoking "lapse"). Second, we also beeped subjects for assessment at random times throughout the day, at which point additional questions about negative affect and other states were assessed. Third, subjects were asked to respond to a series of end-of-day questions, summarizing their experience (for example, their perceptions of stress) across the day.

Examining the Role of Negative Affect in Relapse Crises

Previous work examining the association between lapse episodes and negative affect has been largely based upon retrospective self-report. In this study, we used momentary data to address this question by comparing, among those who lapsed, negative affect at the time of the lapse to negative affect during other points in the day. All of the subjects in this analysis had lapsed, and all of the comparisons were within-subject. The comparison observations were taken only a day or so before the lapse. Results showed that both types of relapse crises were associated with significantly higher levels of negative affect than were the random occasions, and that negative affect in the lapses was also significantly higher than during the temptation episodes (Shiffman, Paty, Kassel, & Hickcox, 1996).

In addition to considering the role of momentary negative affect in the relapse crisis, we also hypothesized that lapse risk might be exacerbated by negative mood and stress in the days preceding the lapse episode. Despite previous evidence suggesting that prevailing stress may predispose smokers to relapse, this hypothesis was not borne out by our data. It is possible that previous data addressing this question implicitly confounded between-person differences with within-person differences over time by comparing subjects with high versus low stress, rather than periods of high versus low stress (Cohen & Lichtenstein, 1990). The use of EMA sampling with repeated assessments, in this case, permitted us to rule out important confounds that are difficult to examine using traditional measurement methods.

Although our methods of data collection and analysis permitted us some advantage over previous treatments

of this topic, we were concerned that our assessment of momentary negative affect during relapse crises might have been contaminated by retrospective bias, despite the relatively short lag between the lapse episode and subjects' responses (estimated to be on the order of 6–8 minutes (Shiffman, Paty, et al., 1996). To address this problem, we analyzed the trend in momentary affect in the hours preceding lapses on the lapse day itself. We restricted these analyses to those who attributed the cause of their lapse to stress or negative affect, to reduce the heterogeneity of the episodes sampled. We showed that stress-triggered lapses were in fact preceded by significant increases in negative affect beginning about 6 hours before the episodes themselves (Shiffman & Waters, 2004). These data suggest that negative affect builds up gradually in the hours preceding lapses, and that the earlier findings could not be attributed to retrospective bias alone (since they were consistent with prospective trends).

In sum, our work with the University of Pittsburgh Smoking Relapse Study supports the role of stress and negative affect as precipitants of relapse crises, while helping us, at the same time, to develop a more sophisticated view of the temporal sequence by which stress may trigger the relapse process. Contrary to the conclusions of previous research, it appears that relapse crises and lapses are driven by relatively "local" changes in affect, over the course of hours or minutes, rather than by tonic changes or background levels of stress and mood over days or weeks. These data are consistent with evidence from other work from this laboratory and elsewhere implicating relatively local cues (e.g., presence of other smokers) associated with the lapse crisis in the relapse process (Shiffman, Hickcox, et al., 1996). The temporal resolution required to detect and explore such processes exemplifies the unique strengths of EMA methods in helping us to study the precipitants and consequences of psychosocial stress.

FUTURE DIRECTIONS

There are two broad goals that we would like to see pursued in the years to come. First, we would like to encourage the research community to develop an increased expertise in the methodological and technical aspects of EMA-based measures of psychosocial stress. And second, we would like to see these methods more widely applied where they appear to have specific merit in addressing conceptually important issues pertaining to stress and health.

New Developments Needed on the Methodological and Technical Fronts

We need to make more widely available relevant psychometric data for the instruments discussed here, addressing both the reliability and validity of these tools, and oriented both toward addressing trait (between-person) questions as well as state or stress-as-process (within-person) issues. What will be particularly useful in this area will be the availability of *incremental validity* data, examining the extent to which EMA measures of psychosocial stress are better suited for some purposes than existing methods of measurement. We have attempted to address such issues to some extent in our own work, as discussed above (Kamarck et al., 2004). We make no claims in doing so, however, that our measures are the best available for the purposes toward which they were developed, and we can certainly conceive of other purposes for which other measures may be a better match. Only increased availability of psychometric data and further measurement development work will allow us to make further advances in this area. It is important to recognize that the increased face validity provided by the collection of data in real time and in the natural environment does not *necessarily* translate into improved criterion validity, and that the novelty of EMA per se does not obviate the need to pursue the hard work of measurement development.

On the technical end, an important direction that we would like to see pursued involves the enhancement of user-friendly assessment features designed to augment compliance for protocols involving EMA-based measures of psychosocial stress. Although EMA study methods appear to be quite promising for large scale application (e.g., in social epidemiological research), they are relatively untested for these purposes at present. Their application has been limited, in part, because of the significant burden that they place on the respondent. When data collection takes place in "real time," it typically requires ongoing interruption of daily routines, an inconvenience with a potential effect on subject recruitment and retention. Indeed, EMA methods typically do exclude those whose daily routines cannot handle interruption, such as fast food vendors, assembly line workers, or surgeons, and, in our experience, many of those who do enroll but drop out of such studies cite time demands as a major obstacle to their participation.

Electronic diary methods appear to be effective in enhancing the attractiveness of and compliance with EMA research, and compliance among study participants who agree to use such methods tends to be quite strong, as illustrated in our own work and the work of others (Anderson et al., in press; Drummond, Ghosh, Ferguson, Brackenridge, & Tiplady, 1995; Hufford & Shields, 2002; Kamarck et al., 2007; Stone et al., 2003; Tiplady, Crompton, & Dewar, 1997). There may be limitations with the typical palm top computer, however, in terms of its ability to help participants surmount the burden associated with EMA research. Respondents are required to open the device, to hold the device with one hand, to remove a stylus from the case with the other hand, and to press the stylus on the appropriate spot on a small screen. These are tasks which may not be easily performed during a number of common activities of daily living, such as driving, riding a bicycle, carrying

groceries, participating in a conversation, or standing on a crowded bus.

Although the precise effects of such sampling biases have never been systematically evaluated, it would appear that the development of strategies to diminish the burden of EMA methods—on both participants and investigators—could facilitate their use on a mass scale in unselected populations. The application of new technologies for streamlining the process of question presentation and response acquisition (e.g., text-to-speech software, remote response devices equipped with Bluetooth wireless communication capabilities, and machine learning algorithms) might be expected to reduce the cognitive and motoric load associated with EMA assessment. We are currently exploring such options with our collaborators, Dan Siewiorek and Asim Smailagic, from the Human Computer Interaction Institute at Carnegie Mellon University, and we hope that such developments may enhance the prospects for real-time assessment methods as a tool for social epidemiological research.

FUTURE APPLICATIONS FOR EMA-BASED MEASURES OF PSYCHOSOCIAL STRESS

In addition to furthering the technical performance of EMA-based measures of psychosocial stress, we suggest that additional consideration be given more broadly to the potential uses of such measures in the context of the research on stress and adaptation. As noted earlier, one of the important features of EMA methods involves their facility for capturing a representative "slice of life" of the individual. As such, we should expect such methods to enable us to characterize the implications of ongoing psychosocial stress on individuals' daily routines; their moods, their activities, and their social interactions. In general, more work is needed characterizing the specific activities and interactions that may distinguish individuals who score high on measures assessing conditions that have been associated with psychosocial stress, including job strain (Hanson et al., 2000; Johnston et al., 2006; Kamarck et al., 2004; Teuchmann, Totterdell, & Parker, 1999), SES (Gallo et al., 2005; Grzywacz, Almeida, Neupert, & Ettner, 2004; Matthews et al., 2000), and anger or hostility (Brondolo et al., 2003; Guyll & Contrada, 1998; Vella et al., 2008). Such research would appear to have important implications for setting behavioral intervention targets as well as for theory development in these literatures.

In addition to its value for facilitating representative sampling, we have argued that EMA methods may help us to better understand the stress process, testing mechanistic hypotheses linking stress with health outcomes. Traditional methods for examining mediation make use of associations that are measured between persons (comparing those who are high and low on stress to those who are high and low on mean levels of ABP) and are frequently subject to alternative explanations for observed effects (What other characteristics may be shared among those who are high on stress and ABP?). When such analyses can be complemented by associations that are measured within persons over time (comparing temporal variations in stress and ABP), this should assist us in ruling out spurious explanations and establishing plausible causal links, especially when complementary between-person and within-person (daily life) effects can be demonstrated in the same sample. In addition to the research on job strain, additional literatures that might benefit from this type of treatment include work on the role of stress in contributing to pain symptoms (Stone & Broderick, 2007), in triggering problems in diet or exercise adherence (Grilo, Shiffman, & Wing, 1989; Jeffery et al., 2000), and in facilitating proinflammatory processes (Marin, Martin, Blackwell, Stetler, & Miller, 2007).

A distinction is sometimes drawn between *distal* risk factors, such as sociodemographical and historical influences, and *proximal* risk factors, involving the more specific social and physical events (e.g., specific types of social interactions or current emotional responses) that are likely to mediate the effect of distal variables on the individual (Moffitt, Caspi, & Rutter, 2005; Wachs, 2000). Some have characterized proximal risk factors as most relevant to gene-environment research, to the extent they lend themselves to the development and testing of biologically plausible hypotheses linking environmental exposures to health outcomes (Moffitt et al., 2005). By their nature, EMA methods are particularly well suited for assessing proximal risk factors, thus these types of measures may be particularly well suited for research related to gene–environment interactions involving psychosocial stress.

Finally, we also noted the virtue of EMA methods for characterizing situational or individual difference effects that may moderate the relationship between psychosocial stress and health. We discussed, for example, the potential role of setting effects (home vs. work) in moderating the effects of "demand" and "control" on cardiovascular health. Additional literatures that might continue to benefit from this type of treatment include work on the moderating role of social support or social relationship quality in contributing to stress-related health outcomes (House, Landis, & Umberson, 1988; Robles & Kiecolt-Glaser, 2003) and the moderating role of setting characteristics (e.g., exposure to health-impairing habits or high risk situations) in contributing to maintenance of health behavior change (Shiffman, 2005; Witkiewitz & Marlatt, 2007).

Our goal in this chapter has been to characterize the types of contributions that might be made by EMA-based self-report measures of psychosocial stress, to document the range of methods that have been developed to date, and to summarize current research needs in this area. Our sense is that this is a methodology that is well suited to the assessment of psychosocial stress; existing research bears this out, and, based upon the specific strengths of

this approach, we have been able to generate a number of topics to which these methods would appear to be productively applied. We hope that this chapter serves as an impetus to the research community to continue to validate these methods in a wider array of populations in order that we may learn more about their utility and limitations, and, potentially, as a result, to accelerate their productive use in the literature examining psychosocial stress and health.

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43 Multilevel Analysis of Stress

Greg J. Norman, A. Courtney DeVries, John T. Cacioppo, and Gary G. Berntson

INTRODUCTION

> One of the most highly developed skills in contemporary Western civilization is dissection: the split-up of problems into their smallest possible components. We are good at it. So good, we often forget to put the pieces together again.
>
> *—Alvin Toffler*

As is apparent from the broad range of topics covered in this volume, the scientific study of stress has developed into an expansive enterprise encompassing both psychological and biological levels of analysis. Given the recent unprecedented growth in scientific understanding of biological process, the breadth of scope is fitting. Remarkably, only 50 years after the elucidation of the double helix structure of DNA, scientists have succeeded in decoding the three billion base pairs constituting the human genome. We now have a basic understanding of the molecular basis of inheritance and how certain diseases are caused by changes in the action of one or more proteins caused by mutations in the genes encoded by DNA. Such developments represented a significant milestone in what is considered by many to be the ultimate goal of biological research, namely, the ability to explain biological processes in terms of physics and chemistry (Crick, 1966).

Similarly, advancements in psychology and neuroscience have begun to unlock the mysteries of the human mind. Imaging technology has made it increasingly possible to investigate the differential activation of particular brain regions in normal and disordered thought, capturing the imagination of the public and the scientific community alike. Additionally, brain–machine interface technology has advanced to the state where surgically implanted microchips are capable of translating thought-generated brain activation into movement in external devices (see Donoghue, Nurmikko, Black, & Hochberg, 2007). These and other developments represent a new era in the understanding of both the biological and psychological underpinning of human existence. However, it has become increasingly apparent that conventional models in both biology and psychology are inadequate in explaining the complexity of human behavior.

Dating back to the initial discovery of the structure of DNA in 1953, a motivating principle within molecular genetics has been that detailed knowledge of the physical and chemical properties of individual genomes would allow for the prediction of phenotypic characteristics (Dipple & McCabe, 2000a). Indeed, this anticipated predictive capacity was central to arguments used to garner funding for the Human Genome Project. However, as data accumulated, it became clear that various firmly held beliefs within molecular biology were inaccurate. Based on the assumption that biological complexity was directly proportional to the number of genes within a genome, initial predictions suggested that no fewer than 100,000 genes were necessary to produce the complexity necessary to account for human behavior (Pennisi, 2005). Therefore, many scientists were surprised when it was discovered that the human genome contained only a quarter of that number, less than half the amount contained within the genome of rice (Goff et al., 2002). Additionally, as increasing numbers of mutations have been identified, it has become increasingly clear that the correlation between genotype and phenotype is often incomplete, even for relatively simple Mendelian traits (Dipple & McCabe, 2000b). Emerging from such discrepancy in theoretical prediction and empirical observation has been the recognition that the application of strict unidirectional reductionist approaches, while powerful, does not apply equally well to all domains of biological complexity. Recent developments in systems biology and scale-free networks have begun to shed light on many of the emergent properties of biological phenomena and have provided insight into the benefit of interdisciplinary studies even within a given level of analysis (Barabasi & Oltvai, 2004; Boyer et al., 2006; Bray, 2003)

The approach of social scientists throughout most of the 20th century was similarly constrained. Two world wars, a great depression, and civil injustices made it clear that social and cultural forces were sufficiently imperative that they could not await the full explication of their cellular and molecular mechanisms. Thus, biological events and processes were routinely ignored within most social scientific disciplines. Despite this historical independence of biological and social sciences, evidence for a "social brain" in nonhuman primates and humans has

began to accumulate (Brothers, 1990; Dunbar & Shultz, 2007). Individuals with damage to the amygdala display decreased emotional activation to threatening stimuli and increased ratings of the trustworthiness of faces (Adolphs, Tranel, & Damasio, 1998; Tranel, Gullickson, Koch, & Adolphs, 2006). Additionally, bilateral damage to specific regions of the temporal lobe leave individuals with the inability to recognize previously familiar faces (Prosopagnosia; see Damasio, Damasio, & Van Hoesen, 1982). The multilevel nature of the neural processing of social stimuli, however, is illustrated by the fact that the brain's of such individuals are capable of facial recognition outside of conscious awareness, as they show larger skin conductance responses to familiar faces (Tranel & Damasio, 1985). Such insights into the neural substrates of social process have led to the development of disciplines such as social neuroscience (Cacioppo & Berntson, 1992) and affective neuroscience (Davidson & Sutton, 1995) and have demonstrated the necessity of accounting for physiological processes when modeling mental phenomena.

As a result, it is now evident that integrative multilevel analysis is necessary when attempting to model complex psychological phenomena. Multilevel analyses represent a subset of interdisciplinary approaches where the measures, constructs, and theories extend across levels of organization. Efforts to integrate information across levels of analyses are especially challenging given the inherent complexity of biological and social systems, but it is only through such research that a complete understanding of mind–body issues will be possible.

Although multilevel analyses can provide a more comprehensive understanding of human behavior, they can be problematic, as the terms, constructs, and measures at different levels of analyses often develop largely independently of those of other levels, and hence moving across levels rarely involves simple one-to-one relations. In some cases, such differences have resulted in a mutual suspicion between disciplines and a division of labor within the scientific community, which has posed impediments to cross-disciplinary collaborative efforts to bridge these boundaries. The divergent paths have created distinct theoretical constructions and methodological approaches between social and biological levels of analysis that have fostered what has been termed the *category error*, wherein seemingly parallel concepts from different levels of analysis may reflect only partially overlapping domains, rather than representing a one-to-one isomorphism. One instance of the category error arises from early work on the neurobiological substrates of mental phenomena in which complex psychological processes were thought to reflect activity in a single, localized brain region. Psychological processes (e.g., memory) commonly present themselves as singular theoretical entities leading many to postulate the existence of localized neuronal sites responsible for distinct psychological processes. As the science has matured, it has become clear that mental states rarely reflect the processes of single localized brain structures, as psychological processes are typically associated with distributed, interconnected sets of neuronal regions. Although the inherent complexity of psychophysical relations can be overwhelming at times, multilevel analysis capitalizes on such complexity and reduces category errors through the utilization of knowledge at one level of analysis to refine and inform another.

An illustrative example of how knowledge at the one level can refine and constrain theories operating at another emerges from work on the neural substrates of evaluative processes (see Cacioppo & Berntson, 1994; Cacioppo, Gardner, & Berntson, 1999; Larsen, McGraw, & Cacioppo, 2001). The physical constraints imposed on behavioral manifestations (inability to simultaneously approach and avoid a goal object) have lead some to characterize the evaluation of a stimulus as a point along a bipolar (positive to negative) valence dimension (Posner, Russell, & Peterson, 2005). Although useful in many contexts, models of evaluative processes that assume reciprocity among positive and negative valence are likely too simplistic. The recognition of distinct positive and negative neurobiological substrates mediating evaluative processes allows for the expansion of models to include bivariate modes of activation that are better able to account for patterns of reciprocity or coactivity (e.g., in ambivalence). The bivariate nature of evaluative space provides organisms with more flexible behavioral responses, such as cautious approach during anxiety-like states (McNaughton & Corr, 2009). Therefore, through an understating of the neurobiological components mediating evaluative systems, one is better able to explain processes operating at a social psychological level (and vice versa).

Fundamentally, multilevel analysis entails reductionism: the ability of events or processes at lower levels of organization and analysis to inform or explicate higher level phenomena. Although reductionism is a central foundation in most scientific disciplines, it has been a source of controversy within the realm of the social sciences, primarily because of two distinct meanings of the term. The first formulation, as described earlier, is a conceptual approach that strives to understand complex phenomena through understanding the interaction of their parts. This approach is neutral with regards to the "ontological status" of high-level phenomena (i.e., mental states) and is entirely compatible with multilevel analysis. Conversely, a radical form of reductionism, which we have referred to as *substitutionism*, dictates that all the properties of complex phenomena will ultimately find a proper explanation solely in the terms of lower level analyses. This approach holds that all high-level systems (i.e., cognition, social interaction) are mere epiphenomena, exerting no causal agency on the fundamental phenomena used to explain it, and are thus subject to replacement via reference to increasingly lower levels of analysis. However, emergent properties appear from combinations or interactions among the elements (e.g., properties of crystalline sodium and chloride–salt) that are not

predictable from the known properties of the elements. A substitutionist may concede that many complex phenomena are unpredictable through reference to their constitutive parts but argue that so-called emergent properties are nothing more than constituent properties of the parts that only become apparent through the study of their interactions. Although this proposition *may* be true in a metaphysical sense, the inability to know such facts independent of the study of their interactions means that in no meaningful sense could the lower level properties be said to "explain" or account for emergent properties.

In rejecting substitutionism, multilevel analysis embraces the ability of information derived from distinct levels of analysis to mutually inform one another. Multilevel analysis is a reciprocal process, as higher level analyses can also inform lower level processes (extensionism). Important in this reductionism–extensionism process is the tuning and calibration of concepts to enhance cross-level mappings and minimize category errors. Central to such efforts is the development and refinement of meaningful theories of the relations between levels. This is especially important because of the intricacies and multiple mappings across distinct levels and the associated need for model constraints.

The primary aims of this chapter are twofold. First, some principles pertaining to multilevel analysis that have been applied to various interdisciplinary projects will be described and used to frame issues and organize research perspectives relevant to stress research. Second, examples of multilevel analysis will be discussed in an attempt to demonstrate the benefits of converging lines of evidence from multiple levels of analysis.

CONCEPTUAL FOUNDATIONS OF MULTILEVEL ANALYSIS

Basic principles of multilevel analysis, which frame issues and organize research efforts, have been articulated (Cacioppo & Berntson, 1992). These include the following.

The principle of *multiple determinism* stipulates that a target event at one level of organization, especially at more molar levels, will have multiple antecedents within and across levels of analysis. The response to perceived stress, for example, has both genetic and social determinants (see McCaffery, Uchino & Birmingham, chapters 6 and 9) that interact in complex ways to produce distinct phenotypes. Consequentially, although measures of stress (i.e., glucocorticoids) may provide information about the end-point stress response, the precise causes of such a response are not necessarily inherent in end-point measures, as similar stress responses can derive from multiple determinants. Indeed, day-to-day variance in diurnal cortisol activity, routinely treated as a trait variable, can also result from the inherent variance in everyday social and emotional experience (Adam, Hawkley, Kudielka, & Cacioppo, 2006). Because of the multiple antecedents across even proximal levels, the mappings across more divergent levels of analysis become increasingly complex. Although the ultimate goal of multilevel analysis is to bridge levels of analysis, the *corollary of proximity* suggests that this effort may be more straightforward for more proximal levels. As bridges are built among adjacent levels, those integrations will facilitate the superordinate mappings across progressively more disparate levels. This is not to say that bridging across broader levels of analysis is not possible or desirable, rather, it is a realization that the establishment of smaller bridges may be more efficient and practical and can facilitate subsequent efforts for more expansive bridge building efforts.

The principle of *nonadditive determinism* reflects the fact that the properties of the whole cannot always be predicted by knowledge of properties of the parts. The sources of variance from higher level processes are often broader than those for lower levels of organization, and as such, higher level systems tend to be more complex. Molecular biology has taught us that, in many cases, knowledge of a genotype is necessary but not sufficient when predicting phenotype, which in critical ways depends on environmental interactions, including the social environment (Meaney, 2001; Trainor, Lin, Finy, Rowland, & Nelson, 2007). This principle reflects the increase in relational complexity with higher levels of organization and introduces the final corollary. The *corollary of asymmetry* states that the definition of a phenomenon of interest should include observations at the highest level of organization at which it manifests, as it may not be understood by appealing exclusively to lower levels of analysis. That is, higher level analyses can identify and characterize phenomena (e.g., social stress) that may be explicated in part by lower level organizations, but these phenomena may never be known from analyses limited to the lower level processes. Therefore, although physiological and endocrinological contributions to social stress may be identifiable and help explicate the stress response, neither may be sufficient to account for the context, occasion, or conditions that give rise to that stress. These determinants may be more efficiently studied at a higher level of analyses. The corollary of asymmetry is not a proscription against strictly lower level (e.g., molecular) analyses, but it does assert that a single level of analysis does not universally provide the optimal description of scientific phenomenon.

The principle of *reciprocal determinism* asserts that there may be mutual, reciprocal influences among levels of organization—that is, the direction of causation or explanation need not always flow from lower to higher level phenomena. One may be tempted to view causation as an entirely bottom-up process where lower level operations (e.g., genes) strictly determine activity at higher levels (cellular, organ system, or behavior). Although such bottom-up strategies have provided countless scientific breakthroughs, they do not provide a complete picture. Environmental influences are not just capable of

altering gene expression and hence complex system outputs but can "reprogram" the expression of specific genes in a fashion that extends into subsequent generations through nongenomic inheritance (Weaver et al., 2005). Therefore, because causal influences among levels can be bidirectional, the *corollary of interdependence* states that a single level of analysis may not yield a comprehensive account of multilevel phenomena and that no single, preferred level of analysis applies uniformly. Importantly, this is not to suggest that research conducted within individual levels is not important as multilevel research is necessarily dependent on the work done within single-level analysis. The corollary does, however, indicate that multilevel analysis is necessary when the primary goal is obtaining a comprehensive understanding of complex phenomena.

The principles and corollaries outlined above are intended as conceptual guidelines rather than rigid prescriptions and proscriptions. Moreover, we wish to emphasize that merely mapping concepts from one level to another, although informative, does not in itself constitute an explanation of those relations. The latter will require well-developed theories that can foster prediction, and permit hypothesis testing and theoretical refinements.

NEUROANATOMICAL BASIS FOR MULTILEVEL ANALYSIS

In his essay "*Evolution and dissolution of the nervous system*," Jackson (1884) laid groundwork for multilevel characterizations of neuronal organization. Jackson argued that the evolutionary emergence of higher levels of neuronal organizations does not involve a replacement or displacement of lower levels. Rather, evolutionary developments entail a re-representation and elaboration of function at progressively higher levels of the nervous system. Indeed, the nervous system is characterized by a hierarchical organizational pattern composed of simple reflex-like circuits at the lowest levels (brainstem and spinal cord) and distributed neural networks for more integrative computations at higher levels (for reviews, see Berntson, Boysen, & Cacioppo, 1993a; Berntson & Cacioppo, 2000; Berridge, 2004). Together, these interacting hierarchical structures allow neural systems to rapidly respond to threatening stimuli through low-level processing (e.g., startle reflex), whereas more rostral neural substrates permit more elaborate computation of potential coping strategies. Based on hierarchical interconnections, higher level systems may depend heavily on lower level systems for the transmission and preliminary processing of stressful stimuli.

The hierarchical model is compatible with the views of Walter Cannon, who significantly shaped early conceptions of autonomic control and autonomic psychophysiology (Cannon, 1928; Cannon, 1929). Cannon proposed that a primary role of the autonomic nervous system (ANS) was in maintaining the constancy of the internal mileau, a regulatory process he termed "homeostasis" (Cannon, 1929; Cannon, 1939). Cannon viewed the sympathetic branch as the primary homeostatic regulator, with the parasympathetic branch serving to fine-tune reactions across organ systems. Historically, the two autonomic branches have been considered to be reciprocally regulated by central systems (Fulton, 1945), a view that continues to be promoted in the contemporary literature (Malliani, Montano, & Pagani, 1997). There is ample evidence for a reciprocal mode of autonomic control in simple reflex responses such as the baroreceptor–heart rate reflex. Reciprocal control synergistically amplifies the actions of the end organ response and expands the dynamic range of autonomic control (see Berntson, Cacioppo, & Quigley, 1993b). The homeostatic model of autonomic function dominated early conceptions of stress, and behavioral–autonomic relations were often viewed as hierarchical extensions of homeostatic processes. In a hierarchical system, rostral levels could access a wider range of response mechanisms, but the actions of these systems would be constrained by the more primitive organizations at lower levels (Figure 43.1a). Hence, the basic reciprocal mode of control apparent in brainstem reflexes might be expected to manifest in behavioral contexts as well.

However, additional complexities exist beyond strict hierarchical patterns of organization, as descending pathways are capable of bypassing intermediate levels and directly synapse onto lower levels of the neuraxis (Porter, 1987; Wakana, Jiang, Nagae-Poetscher, van Zijl, & Mori, 2004). This organizational pattern, previously described as a neural heterarchy (Berntson & Cacioppo, 2000), contains the components of hierarchical systems, as higher levels are in continuous communication with lower level systems via intermediate levels, but have the additional capacity to interact over widely separated levels via direct connections (Figure 43.1b). In addition to the well-known anatomy of somatomotor systems (Porter, 1987; Wakana et al., 2004), this pattern of organization is also apparent in both the autonomic nervous system (ANS) (Berntson & Cacioppo, 2000; Critchley et al., 2005) and hypothalamic–pituitary–adrenal (HPA) axis (Radley, Williams, & Sawchenko, 2008; Sullivan & Gratton, 2002). Of importance to stress science, this provides a means through which higher psychological stressors can yield antihomeostatic effects (e.g., concurrent increases in blood pressure and heart rate) on the ANS and HPA axis. For example, although baroreflex responses may entail tightly regulated reciprocal patterns of autonomic control, the autonomic branches may change reciprocally, independently, or coactively in behavioral contexts (Berntson et al., 1993b; Berntson et al., 1994). This has necessitated an expansion in the simple reciprocal bipolar model of autonomic control (Figure 43.2a), in which autonomic states are considered to lie along a single continuum with maximal sympathetic (and minimal parasympathetic) activity at one end and maximal parasympathetic (and

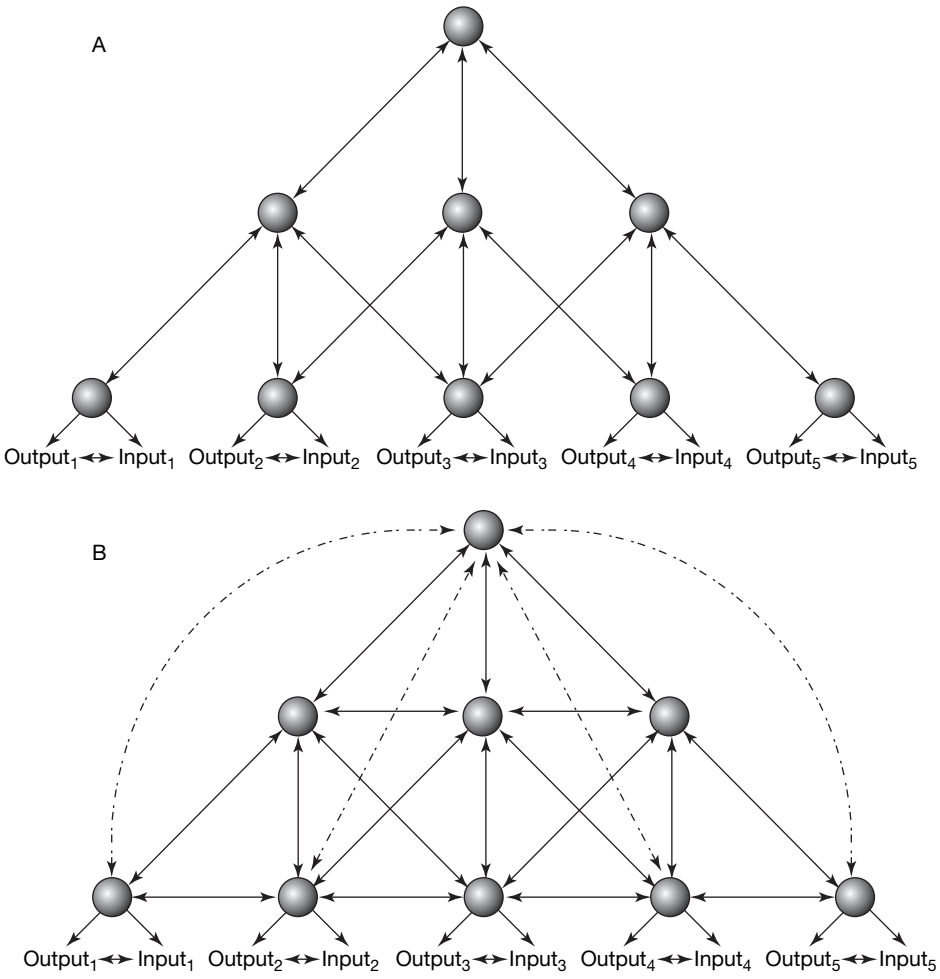

Figure 43.1 ■ *Organizational structure*: **(A)** Classical hierarchical organization, with sensory inputs and motor outputs associated with lowest levels, and maximal convergence/divergence at the highest level. **(B)** Heterarchical organization, with long ascending and descending pathways (dashed arrows). Not illustrated are additional complexities associated with the presence of lateral interactions.

minimal sympathetic) activity at the other. Although this model may apply to reflexive brainstem circuits, the greater output flexibility of higher neural systems necessitates a bivariate model of autonomic space with sympathetic activity along one axis and parasympathetic activity along the other.

In addition, there may be far greater individual differences in autonomic responses arising from the operations of rostral neural systems in psychological contexts. At a group level, the heart rate responses of human subjects to orthostatic stress and to standard psychological stressors (mental arithmetic, speech stress, reaction time task) are similar (Berntson et al., 1994; Cacioppo et al., 1994). Analysis of the separate contributions of the two autonomic branches by the use of single and dual pharmacological blockades revealed that the orthostatic stress (transition from sitting to standing) yielded a rather consistent response across subjects, characterized by a highly correlated sympathetic activation and parasympathetic withdrawal. In contrast, psychological stressors yield a more varied pattern of response across subjects, with no overall correlation between the responses of the autonomic branches. In this study, some subjects showed a predominant sympathetic activation, others a predominant parasympathetic withdrawal. Although there were considerable individual differences in the responses, individual response patterns were stable across the three psychological stressors (Berntson et al., 1994; see also Malarkey, Lipkus, & Cacioppo, 1995).

Extending such findings, Berntson, Norman, Hawkley, & Cacioppo (2008) derived two distinct metrics of autonomic control, based on two models of cardiac autonomic regulation. Both metrics utilized high-frequency (HF) heart rate variability and preejection period (PEP) as measures of parasympathetic and sympathetic control. Based on bipolar measures of autonomic control, a cardiac autonomic balance (CAB) metric was derived as a scale extending from maximal sympathetic activation on one end of a continuum to maximal parasympathetic activation at the other extreme (i.e., along the reciprocity diagonal of Figure 43.2a). Although this index was not correlated with most aspects of health and disease in a population-based sample (Chicago Health and Social Relations Study, [CHASRS]), it was predictive of diabetes mellitus, independent of demographics and health behaviors (Figure 43.2b). In contrast to bipolar models of autonomic control, recent conceptualizations

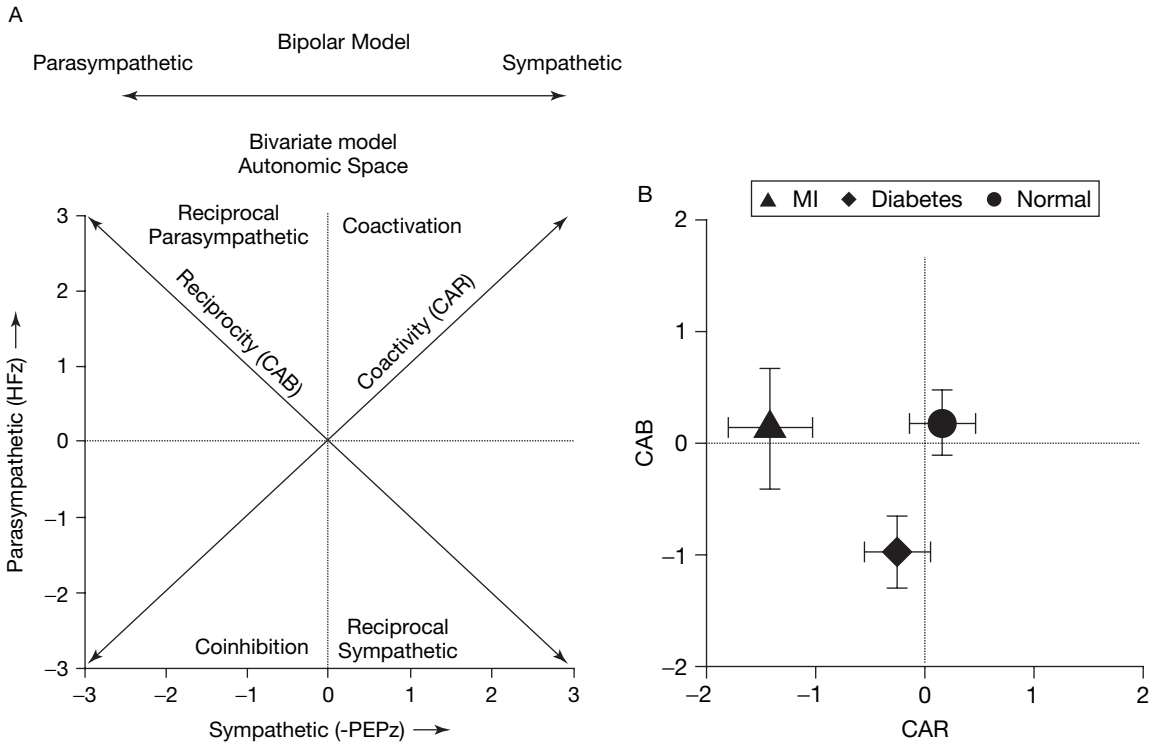

Figure 43.2 ■ *Autonomic space*: **(A)** Bipolar versus bivariant representations of sympathetic and parasympathetic control. **(B)** Cardiac autonomic balance (CAR) and cardiac autonomic regulatory capacity (CAB) in disease states. Data points illustrate means and standard errors of CAR and CAB as a function of participant group, relative to the population. Compared to other participants, subjects with a prior myocardial infarction (MI) had lower CAR scores, indicating lower overall cardiac regulatory capacity, but were not highly deviate on CAB. In contrast, those with diabetes showed a lower CAB score, reflective of a predominant sympathetic balance, but were not highly deviant on CAR.

of psychosomatic relations have emphasized the overall capacity for autonomic control as indexed by autonomic flexibility and variability (Friedman, 2007; Friedman & Thayer, 1998; Hoehn-Saric & McLeod, 2000; Thayer & Sternberg, 2006). This concept, together with the demonstration of the basic bivariate structure of autonomic control, provided an alternative metric to CAB. An index of cardiac autonomic regulatory capacity (CAR) was derived as the sum of activities of the autonomic branches again based on normalized HF and PEP measures. In contrast to the reciprocal diagonal represented by CAB, CAR is a metric that captures the coactivity diagonal of Figure 43.2a. Analysis of the CHASRS sample revealed that CAR was a better predictor of overall health status and was a significant predictor of the occurrence of myocardial infarction, whereas the reciprocity metric (CAB) was not (Figure 43.2b). These results suggest that distinct patterns of autonomic control may be associated with distinct health dimensions. A bipolar conception of autonomic control, however, admits theory and measurement only of CAB and would occlude the relationships between CAR and health. In contrast, the broader and more comprehensive bivariate model of autonomic control subsumes CAB as one diagonal (reciprocal diagonal of Figure 43.2a) and captures CAR as the coactivity diagonal. Such findings illustrate the fact that theories are constrained by the measurements used to describe the phenomena they attempt to explain, and specious or oversimplified theories may obscure lawful relationships.

The richness of central neural control of the stress response and the reciprocal interactions among the central and peripheral nervous systems are only now being fully appreciated. As described later, the nervous system is a potent modulator of immune function through both the neuroendocrine and individual branches of the autonomic system (see Glaser & Kiecolt-Glaser, 2005; Sternberg, 2005; Tracey, 2002). Appreciation of the integrated nature of autonomic, neuroendocrine, and immune systems continues to be biased by reflexive depictions of the ANS and HPA axis function. The heterarchical organization of the central nervous system allows for more rostral neuraxial systems to increase the complexity of neuroendocrine and autonomic regulation of immune parameters. As mentioned earlier, there is significant interindividual variability in autonomic and neuroendocrine response that may have important implications for health that would not be readily apparent when the systems are

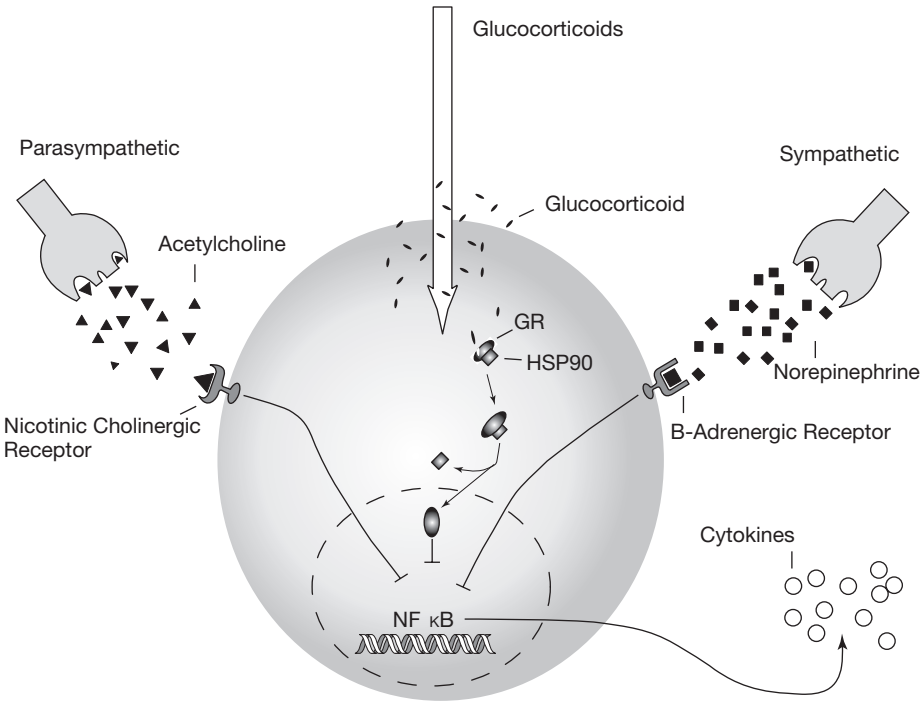

Figure 43.3 ■ *Molecular pathways for neural regulation of immunity*: Glucocorticoids bind to glucocorticoid receptors displacing heat-shock protein 90 (HSP90), which allows for movement into the nucleus and binding of the glucocorticoid–glucocorticoid-receptor complex to DNA. This leads to a decreased ability to activate transcription of proinflammatory cytokines. Norepinephrine binding to β-adrenergic receptors at the cell surface inhibits cytokine production through inhibition of NF-κB. Acetylcholine binds to α-7 nicotinic cholinergic cell-surface receptors and inhibits cytokine production again through inhibition of NF-κB95.

studied in isolation. As depicted in Figure 43.3, significant convergence exists in the signaling pathways for neural regulation of immune function. This convergence does not merely represent redundancy as the individual systems have disparate effects on immunity depending on variables such as intensity as duration (Dhabhar, 2000; McEwen, 1998; Webster, Marketon, & Glaser, 2008). Moreover, despite powerful homeostatic controls over many immune parameters, even regulated dimensions of immunity are not characterized by fixed, invariant levels. Rather, it is alterations in these dimensions (e.g., proinflammatory or anti-inflammatory profile, glucocorticoid sensitivity) that permit an adaptive, immune response to environmental perturbations and immune challenges. This pattern of regulatory flexibility has been termed allostatic (McEwen & Wingfield, 2003; Sterling & Eyer, 1981) or allodynamic (Berntson & Cacioppo, 2007) regulation and is conceptualized as a means of achieving "stability through change" (Sterling & Eyer, 1981, p. 631). Thus, many of the critical dimensions involved in neural control of immunity may not be the individual contributions of the HPA axis and ANS control during a stress response; rather, it may be the flexibility of regulatory capacity that permits an organism to adaptively deal with changing demands.

APPLICATIONS OF MULTILEVEL ANALYSES TO STRESS SCIENCE

An important finding that has emerged over the past 50 years of stress research has been the realization that the source of the stress (e.g., physical versus psychosocial) can have different effects on the ensuing stress response. Largely shaped by the work of Hans Selye (1956) and his conceptualization of the general adaptation syndrome (GAS), the stress response has historically been viewed as a uniform response with distinct temporal dynamics thought to be consistent across individuals and stress conditions. The global features of the GAS, in turn, fostered a relatively simplistic peripheral model of psychosomatic disease (diathesis stress model), in which distinct disorders were considered to reflect specific end-organ vulnerabilities. Thus, although Selye acknowledged individual differences in stress-related disorders, these differences were considered to arise largely from peripheral end-organ dispositions. Recently, it has become apparent that the source of the stressor can have dramatic influence on pattern of neuroendocrine and autonomic activation. For example, in mice, social reorganization stress, in contrast to physical restraint stress, can lead to reactivation of herpes simplex type 1 virus (HSV1), similar to the stress-related HSV1 reactivation that causes "cold sores" in humans (Padgett et al., 1998). Similarly, social stressors, in contrast to restraint stress, are associated with an exaggerated and often lethal inflammatory response to influenza virus in mice (Sheridan, Stark, Avitsur, & Padgett, 2000). In both studies, the difference between the social and the physical stressors could not be accounted for by differences in glucocorticoids as both types of stressors yielded comparable glucocorticoid levels. Rather, it appears that social stress induced a state of glucocorticoid resistance or receptor insensitivity attributable to the impairment in nuclear

translocation of the glucocorticoid receptor complex in socially stressed animals (Quan et al., 2003). As a result, glucocorticoids failed to suppress the actions of a transcription factor (NF-κB) responsible for the upregulation of proinflammatory cytokines (see Dhabhar, chapter 4; Hash-Converse & Kusnecov, chapter 5). Thus, it is now clear that the source of the stress (social versus physical) can have dramatic influence on the phenotype of stress reactivity. Therefore, simply measuring neuroendocrine or autonomic output without taking the environmental context into account may provide an incomplete picture.

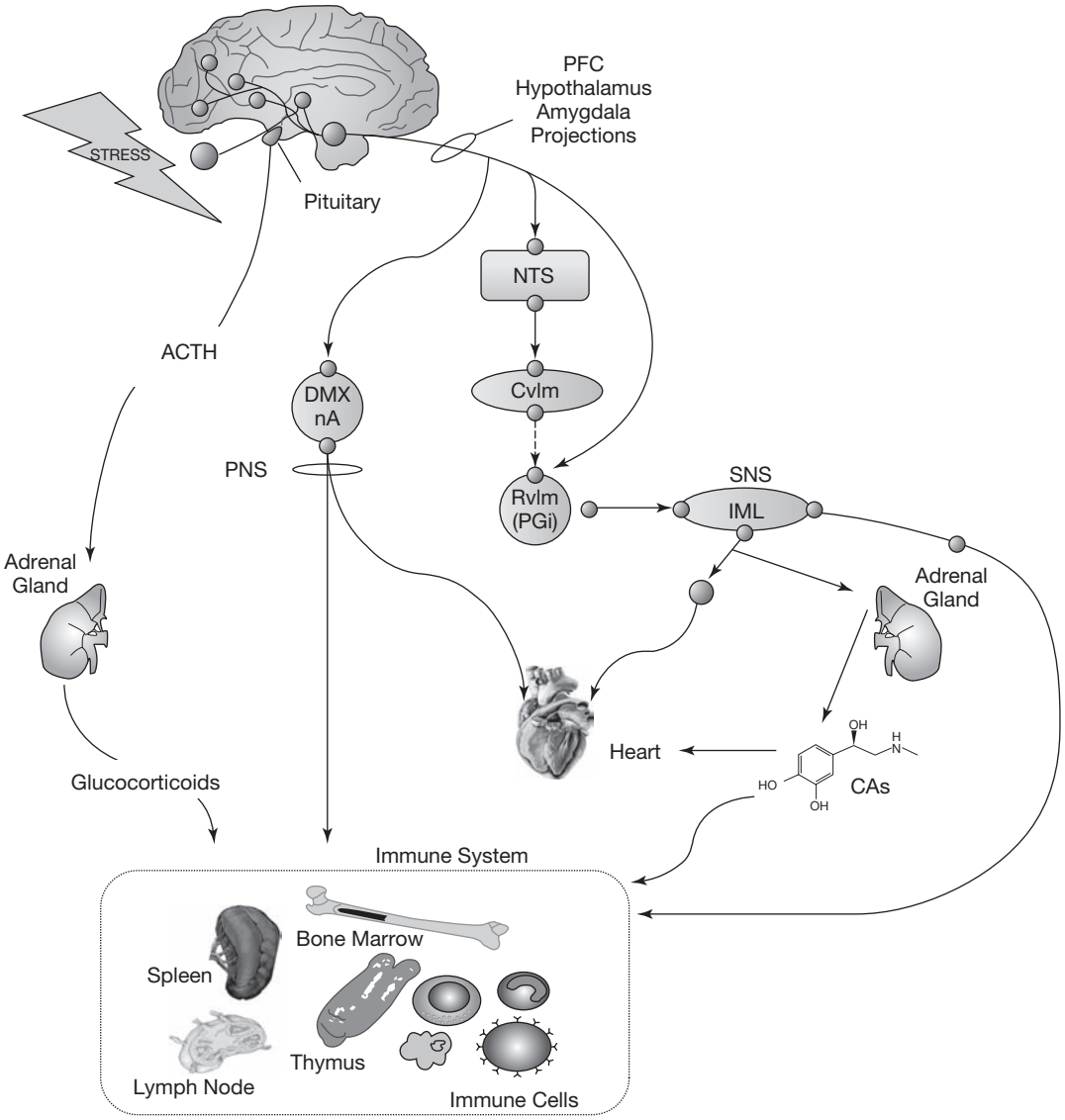

Figure 43.4 ■ *Top-down influences on physiological processes*: Rostral brain structures influence autonomic output through projections to the NTS & Rvlm. The NTS subsequently projects to the dorsal motor nucleus of the vagus (parasympathetic control) and the Rvlm to the intermediolateral cell column (sympathetic control). Sympathetic activation at the adrenal medulla results in systemic catecholamine release. Rostral brain structures influence neuroendocrine control via the hypothalamus. Activation of hypothalamic neurons via corticotrophin releasing hormone results in systemic release of ACTH. When ACTH reaches the adrenal cortex it induces the release of glucocorticoids. Both the autonomic and neuroendocrine systems influence the function of organs and the immune system. NTS, nucleus tractus solitarius; Cvlm, caudal ventrolateral medulla; Rvlm, rostral ventrolateral medulla; DMX, dorsal motor nucleus of the vagus; IML, intermediolateral cell column; ACTH, adrenal corticotrophin releasing hormone; PNS, parasympathetic nervous system; SNS, sympathetic nervous system; CAs, catecholamines.

TOP-DOWN: MOLAR INFLUENCES ON MICRO PROCESSES

The broad, multivariate nature of stress confers a particular benefit on a multilevel approach to the study of stress. Animal models have been useful in providing insights into the mechanisms of stress as the physiological substrates of the stress response (Figure 43.4) are well conserved within mammals (Feder & Hofmann, 1999; McEwen, 2000; Yao, Schulkin, & Denver, 2008). Additionally, animals that have evolved complex social groups are similar to humans in their susceptibility to stress derived from the social world (DeVries et al., 2001; Padgett et al., 1998; Sapolsky, 1989; Stark et al., 2001). For social mammals, parent–offspring interactions rank among the most essential relationships for determining reproducing fitness. The young of many species, including humans, require extended parental care to survive, leading to smaller litters and complex behavioral interactions between parent and offspring. As with all behaviors, significant variance exists in precisely how each individual animal within a species cares for its offspring (Champagne, Diorio, Sharma, & Meaney, 2001). In rats, for example, the amount of time the dam spends licking, grooming, and nursing its offspring dramatically influences the development of their biological and behavioral reactions to stress (Weaver, et. al., 2005). Poor maternal care (low licking) modifies the developmental trajectory of pups to that of a highly reactive phenotype characterized by increased fear (Caldji et al., 1998), anxiety (Weaver, Meaney, & Szyf, 2006), and HPA axis reactivity (Caldji, Diorio, & Meaney, 2000). The phenotypic variation is largely explained by epigenetic alterations of DNA methylation and chromatin structure that can dramatically alter the expression of key genes involved in stress reactivity including the glucocorticoid receptor gene (Francis, Diorio, Liu, & Meaney, 1999; Weaver et al, 2005). The plasticity in the epigenetic regulation of stress reactivity did not likely evolve by chance as the ability to tailor the stress response to environmental conditions can serve to increase survival. If dams are less attentive because of their own experience of stress, then the ability of their pups to reprogram their stress responses may allow for a more appropriate fit with their future environment.

The ability of the social world to influence physiological processes does not end after infancy. Within populations of baboons, low-ranking individuals show increased basal glucocorticoid levels, driven by higher hypothalamic release of adrenocorticotropic hormone (Sapolsky, 1989). Additionally, subordinate animals display decreased levels of hippocampal glucocorticoid receptors, meaning such animals are less susceptible to negative feedback regulation of the HPA axis. In cynomolgus monkeys, social instability leads to heightened activity of the sympathetic nervous system, which, in turn, promotes coronary atherogenesis (Manuck, Kaplan, Adams, & Clarkson, 1988). Chronic deprivation of social contact in adult rodents has equally dramatic effects on biological function and behavior (see DeVries, Craft, Glasper, Neigh, & Alexander, 2007). Social isolation results in dramatic changes in neurotransmitter systems associated with both physiological and emotional reactivity, including serotonin (Schiller, Jahkel, Kretzschmar, Brust, & Oehler, 2003), γ-aminobutyric acid (Serra et al., 2000), adrenergic function (Fulford & Marsden, 1997), and corticotropin-releasing hormone (Ojima, Matsumoto, Tohda, & Watanabe, 1995). Additionally, through the development of glucocorticoid resistance, social stress alters a broad spectrum of immune properties. Animals exposed to an aggressive intruder display splenomegaly (Avitsur, Stark, & Sheridan, 2001) and large increases in the number of CD11b+ monocytes (Avitsur, Stark, Dhabhar, & Sheridan, 2002). Additionally, isolated spleens from socially stressed animals treated with a potent activator of immune function secrete higher levels of the proinflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor alpha compared with control animals (Avitsur et al., 2003; Stark, Avitsur, Hunzeker, Padgett, & Sheridan, 2002). Stress-induced increases in sympathetic nervous system activity provide an additional pathway through which the social environment can alter immune function (Bellinger, Lorton, Lubahn, & Felten, 2001). In primates, chronic social stress increases sympathetic nervous system innervations of the lymph node, potentially leading to long-term alterations in cytokine profiles (Cole, Korin, Fahey, & Zack, 1998; Kohm & Sanders, 1999). Additionally, social stress-induced sympathetic activation produces neutrophil granulocytosis in conjunction with an increase in circulating natural killer cells independent in HPA axis function (Engler et al., 2004).

As would be expected from the work mentioned in the previous section, social stress has important implications for health. For example, social isolation increases cytokine gene expression and cell death in animal models of cerebral ischemia (Figure 43.5). Similarly, animals deprived of social contact show a decreased ability to heal wounds (Detillion, Craft, Glasper, Prendergast, & DeVries, 2004). Paralleling animal studies, both social networks and social support influence mortality and morbidity among human stroke patients (Cohen & Syme, 1985; House, Landis, & Umberson, 1988). Social isolation has also been associated with compromised immune function, including poorer natural killer cell function (Kiecolt-Glaser et al., 1984), and higher antibody levels to the Epstein–Barr virus (Glaser, Kiecolt-Glaser, Speicher, & Holliday, 1985). Furthermore, an academic exam delays wound healing by 40% compared with wounds produced at other times of the academic year (Marucha, Kiecolt-Glaser, & Favagehi, 1998). These studies demonstrate the powerful effect of top-down influences on the phenotypic expression of physiological processes.

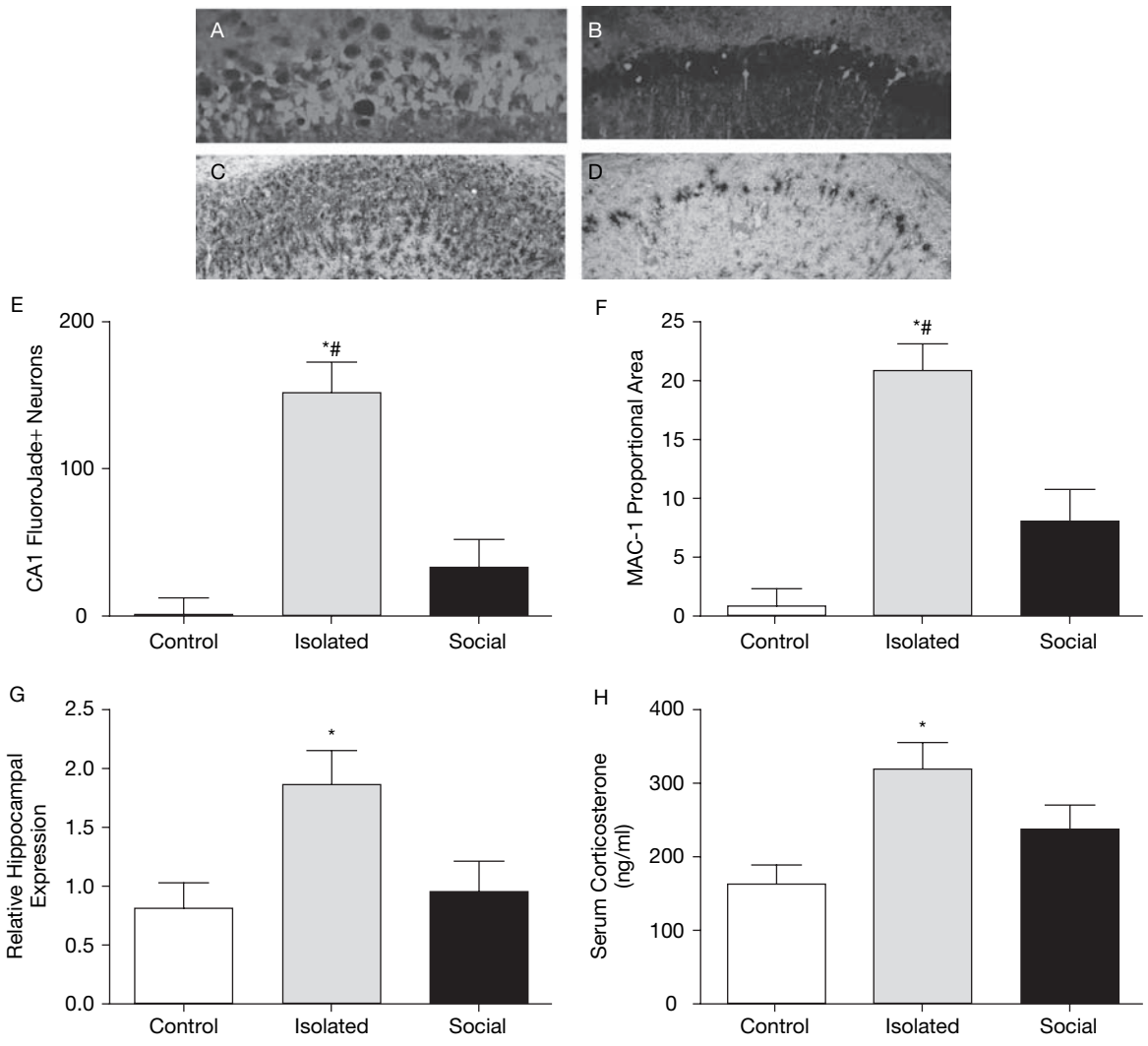

Figure 43.5 ■ *Social isolation potentiates ischemic damage*: Fluoro Jade staining of hippocampal cell degeneration in socially isolated **(A)** and socially housed mice **(B)**. Microglial activation in the socially isolated **(C)** and socially housed animals **(D)**. Summary (mean ± s.e.m.) of histological outcomes in the ischemia-vulnerable CA1 region; Fluoro Jade staining **(E)** and proportional microglial staining **(F)**. mRNA expression of the proinflammatory cytokine tumor necrosis factor-α (TNF-α; mean ± s.e.m.) 24 hour after reperfusion **(G)**. Circulating corticosterone (mean ± s.e.m.) 24 hour after reperfusion **(H)**. Adapted from Weil, Z. M., Norman, G. J., Barker, J. M., Su, A. J., Nelson, R. J., & Devries, A. C. (2008). Social isolation potentiates cell death and inflammatory responses after global ischemia. *Molecular Psychiatry, 13*, 913–915. (*See color insert.*)

BOTTOM-UP: PHYSIOLOGICAL INFLUENCES ON STRESS REACTIVITY

In addition to the afferent sensory systems covered earlier, there are important neural and chemical signals originating in the periphery that bias the operations of central networks. The vagus nerve and its terminal site in the nucleus tractus solitarius (NTS) is a critical pathway for the visceral priming of emotional memories, as this priming is blocked by either vagotomy or NTS lesions (Ferry, Roozendaal, & McGaugh, 1999; McGaugh et al., 1993; Williams & McGaugh, 1993). An important site of afferent biasing of cortical processing is the paragigantocellular nucleus (PGi). The PGi receives direct afferent projections from the NTS and is partially coextensive with the rostral medullary pressor area which directly projects to sympathetic motor neurons in the intermediolateral cell column of the spinal cord (Aston-Jones, Rajkowski, Kubiak, Valentino, & Shipley, 1996). Additionally, the PGi has extensive projections to noradrenergic neurons in the locus coeruleus (LC), an important structure associated with emotional intensity (Aston-Jones et al., 1996). The LC,

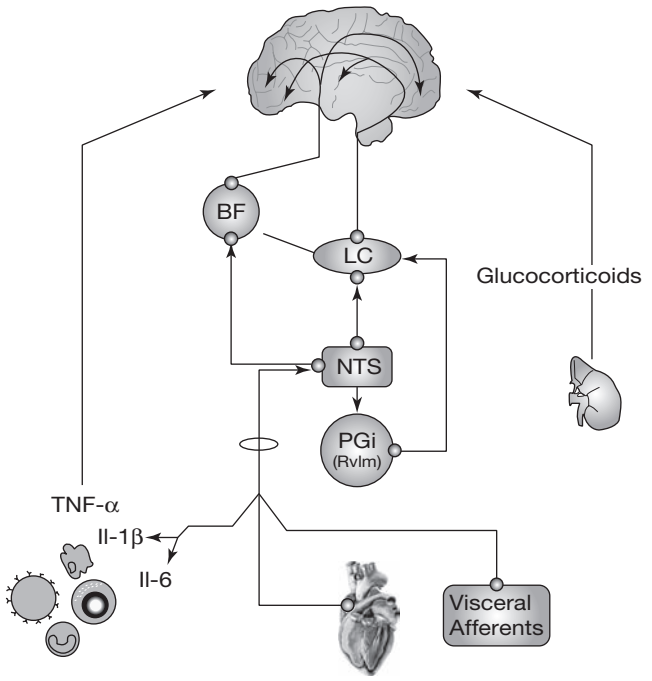

Figure 43.6 ■ *Bottom up Influences on neuronal processes*: Vagal afferents convey visceral information to the NTS, the major visceral relay nucleus of the brainstem. The NTS issues a direct noradrenergic projection to forebrain areas such as the amygdala, and via an excitatory input to the PGi can also activate the ascending noradrenergic system arising in the LC. The LC, in turn, projects to the basal forebrain cholinergic system as well as to the amygdala and the cortex. There are thus several routes (noradrenergic and cholinergic) by which ascending visceral information can impact cortical/cognitive processing. Reciprocal interactions between the amygdala and basal forebrain, together with their overlapping targets in the medial prefrontal cortex, constitute important processing substrates for emotion and cognition. NTS, nucleus tractus solitarius; PGi, paragigantocellular nucleus; LC, locus coeruleus noradrenergic system; BF, basal forebrain cholinergic system.

in turn, issues ascending noradrenergic projections to the amygdala and cerebral cortex, the former being particularly important for visceral memory priming (Clayton & Williams, 2000). As illustrated in Figure 43.6, the LC noradrenergic system provides an additional route of access to cortical systems via an excitatory projection to the basal forebrain cholinergic system (Berntson, Sarter, & Cacioppo, 1998). This may be an important route by which visceral feedback can activate cortical processing systems, including those of the medial prefrontal cortex that have been implicated in anxiety and autonomic control (see Berntson et al., 1998; Hart, Sarter, & Berntson, 1999). Similarly, cholinergic basal forebrain modulation of cortical processing may provide the conduit by which visceral activity is able to trigger panic attacks via a bottom-up activation of rostral systems.

In addition to neural afferent sensory systems, stress hormones (e.g., glucocorticoids) can exert powerful control over the operations of central networks. The most well-studied effects of glucocorticoid modulation of central networks have been on the hippocampus. The hippocampus expresses both mineralocorticoid and glucocorticoid receptors that serve to mediate many of the effects of stress hormones on brain function. The acute elevation of stress hormones does not represent a dysfunctional state as they can coordinate adaptive responses (Dhabhar, 2000; see Dhabhar, chapter 4) and facilitate functions such as novel object recognition (Okuda, Roozendaal, & McGaugh, 2004) and spatial learning and memory (Oitzl, de Kloet, Joëls, Schmid, & Cole, 1997). Chronically elevated glucocorticoid levels can have long-lasting consequences on the brain and behavior. For example, chronic stress-induced elevation of corticosterone can lead to severe deficits in hippocampus-related memory (Conrad, Galea, Kuroda, & McEwen, 1996) in conjunction with increased fear-like behavior (Corodimas, LeDoux, Gold, & Schulkin, 1994). The neural correlates of the these behavior deficits have been documented in the hippocampus, amygdala, and prefrontal cortex and include aspects of structural remodeling and cell proliferation, as well as changes in amine, neuropeptide, and receptor systems (McEwen, 1999; Mirescu & Gould, 2006; Welland et al., 1997). Chronic exposure to high concentrations of stress hormones reduces the branching and length of pyramidal apical dendrites and decreases the number of synaptic contacts (Lambert et al., 1998; Sandi et al., 2003). Chronic stress also leads to functional and structural changes within the amygdala and is known to enhance amygdala-dependent fear conditioning and aggression (McEwen, 2004). The structural remodeling in these brain regions is important for human psychiatric disorders because the altered circuitry is likely to contribute to impaired cognitive function and affect regulation. Moreover, stress is widely acknowledged as a precipitating factor in psychiatric illness (see Gutman & Nemeroff, chapter 25).

Studies in laboratory animals and humans provide compelling evidence that the immune system can have profound control over brain function. Until recently, it was thought that the brain operated largely outside of the influence of the immune system. However, it is now evident that the immune system can have profound effects on brain function, the most prominent example being the induction of sickness behavior following the increase of proinflammatory cytokines in the periphery, resulting in depressed affect, decreased activity, altered sleep patterns, anhedonia, and impaired memory and concentration (Dantzer & Kelly, 2007, see Hash-Converse & Kusnecov, chapter 5). Cytokine-induced behavioral changes have been associated with alterations in the metabolism of neurotransmitters relevant to stress science such as serotonin, norepinephrine, and corticotropin-releasing hormone (Konsman, Parnet, & Dantzer, 2002; see Dallman & Hellhammer, chapter 2). For example, innate immune cytokines, including interferon-alpha and IL-6, have been shown to deplete the amino acid tryptophan, the primary precursor of serotonin, via induction of the enzyme indolamine 2,3-dioxygenase (Capuron et al., 2002). Administration of the proinflammatory cytokine

γ-interferon to humans is associated with increased regional blood flow in the anterior cingulate (Capuron et al., 2005), a structure believed to play an important role in detecting physical and social threat and subsequent recruitment of attention and coping resources to minimize danger (Carter et al., 2000; Eisenberger et al., 2003; see Gianaros & O'Connor, chapter 39).

One mechanism through which the immune system can influence the brain is via the detection of inflammatory cytokines through visceral afferent nerve fibers that communicate with the brain through the vagus nerve (Bluthe, Michaud, Kelley, & Dantzer, 1996; Watkins et al., 1994). Vagal nerve stimulation by cytokines in turn modulates nervous system function in part through interconnected neuronal projections to the NTS which can bias rostral information processing (described earlier). Indeed, many of the physiological and behavioral responses to cytokines in the periphery (i.e., fever, HPA axis activation, conditioned taste aversion) can be blocked by vagatomy (Goehler et al., 1995; Watkins et al., 1995). Additionally, peripherally released cytokines are able to enter the CNS through active transport mechanisms or through leaky sites in the blood–brain barrier (Vitkovic et al., 2000). These studies demonstrate the powerful effect of the bottom-up biasing of neuropsychological processes.

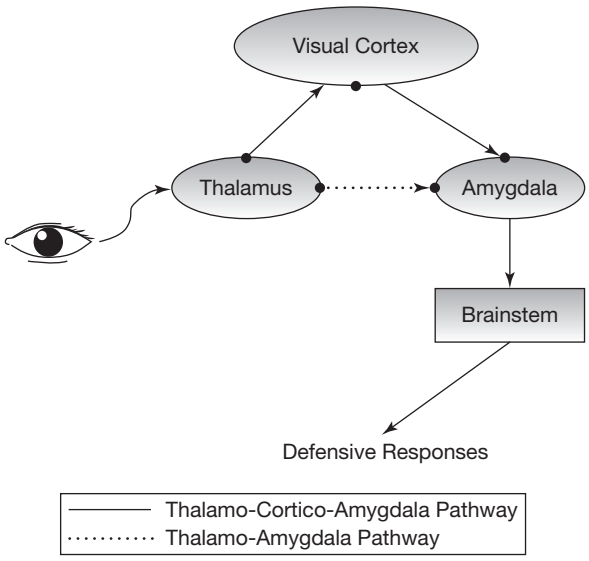

Figure 43.7 ■ Schematic representation of the multilevel visual pathway where information is transduced from photoreceptors in the eye that subsequently project to the thalamus. In the standard visual pathway this information is relayed from the thalamus to the visual cortex mediating vision (thalamo-cortico pathway). An alternative route mediating many of the nearly immediate responses to aversive stimuli has been proposed by LeDoux (2003) where information is passed directly from the thalamus to the amygdala (thalamo-amygdala pathway) which it then leads to defensive responses (i.e., startle).

MULTILEVEL ANALYSIS OF MULTILEVEL SYSTEMS: IMPLICATIONS FOR STRESS

As described earlier, evolutionary developments have led to a re-representation and elaboration of function at progressively higher levels of the nervous system. As environmental challenges grow increasingly complex, more integrated neuronal circuits are brought online to allow for higher level analytical and response mechanisms to come into play. The simpler neurobehavioral organizations are not taken offline, but instead they run alongside to promote potentially adaptive responses. Accordingly, substrates at differing levels of the brain interact in a complex heterarchical fashion, with partially distinct organizations and differential processing capacities that vary with regard to their access to sensory, perceptual, memorial, and cognitive information. A noxious stimulus, for example, may evoke a spinally mediated withdrawal reflexes while concurrently triggering higher level processes such as aggression, or acquired anticipatory reactions that may permit avoidance or control of the aversive stimulus. Even associative processes are represented at multiple levels. Simple fear conditioning to an acoustic stimulus can be mediated by a "quick and dirty" subcortical circuit (see Figure 43.7) composed of a direct projection from the auditory thalamus to the amygdala, which in turn projects to lower mechanisms for a behavioral, autonomic, and neuroendocrine response (LeDoux, 1996). In contrast, the processing of more complex, threat-related cues, more akin to anxiety, may be dependent on higher level cortical processing (Berntson et al., 1998).

Cortical systems allow for strategic organization of behavior—for anticipatory planning, cognitive simulations, and counterfactual reasoning; for establishment of self-awareness; and for adaptive, flexible, and creative responses to ever-changing environmental challenges. This re-representation and elaboration of the nervous system has extended the reach of stressors beyond immediate and obvious physical threats to survival (being chased by a lion) to more subtle threats emanating from the social world (being late for work). Humans spend relatively little time worrying about the leading causes of death (e.g., cardiovascular disease, car accidents) as compared with the daily angst and stress derived from the social world. The disruption of personal ties, whether through ridicule, discrimination, separation, divorce, or bereavement, is among the most stressful events people must endure (see Cacioppo & Patrick, 2008; Gardner, Babriel, & Diekman, 2000). The social environment we inhabit is in a state of constant flux, and the heterarchy of neural substrates mediating complex evaluations, ranging from reflexive responses to self-reflective evaluations, continuously aids us in negotiating the ebb and flow inherent in social interaction. Importantly, the rostral

circuits that serve to mediate the perception of social threats and coordinate appropriate responses are necessarily dependent on lower level neuraxial systems to implement the necessary autonomic, neuroendocrine, and motor activity to achieve such tasks. Although the multiple levels of organization entail partially independent processing substrates, they are largely integrated with systems at one level able to control, modulate, or bias processing at other levels of organization. An important aspect of this is that heterarchical structure of the brain permits both top-down and bottom-up biases, in some cases, the complete bypassing of levels. This concept is not a trivial neuroanatomical observation; it necessarily implies that to obtain a comprehensive understanding of the neurobehavioral processes underlying the perception of a stressor and the subsequent response, a multilevel approach is needed. In such instances, a strictly physiological (or social) analysis is not sufficient to reveal the orderly relationships that exist, regardless of the sophistication of the measurement technology.

SUMMARY

Recent developments in biological and social levels of analysis have made it increasingly clear that cross-disciplinary, multilevel research is necessary when attempting to understand the complexities inherent in humans. Not only is it no longer possible to think of the nervous, endocrine, and immune systems as distinct, it has become apparent that these systems have evolved to interact in complex ways depending on environmental influences. To realize the full potential of recent developments within neuroscience and molecular biology, we will require the integration of this information within the broader knowledge base concerning higher level behavioral, cognitive, and social psychological domains (Cacioppo, Berntson, Sheridan, & Mcclintock, 2000). It may appear to be a rather daunting task to integrate, for example, cellular biology with social psychology, but it is a task that must be accomplished. The principles of multiple determinism, reciprocal determinism, and nonadditive determinism, together with their corollaries, offer some strategic guidelines to organize such efforts. A deeper understanding of re-representation within the CNS and its subsequent effects on the periphery will help develop more complete models of physiological functioning. The ultimate goal of multilevel research is to promote meaningful *reductionism* and *extensionism* so that knowledge and constructs at multiple levels of organization and analysis can mutually inform, elucidate, and constrain theory and research at other levels. Importantly, multilevel research does not prescribe that all research should be conducted across all levels; rather, successful multilevel analysis is dependent on the high-resolution detail gained from such practices to help build meaningful bridges.

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