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THE BORDERLINE DIAGNOSIS II: BIOLOGY, GENETICS, AND CLINICAL COURSE

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ABSTRACT

In Part I of this three-part article, consideration of the core features of BPD psychopathology, of comorbidity with Axis I disorders, and of underlying personality trait structure suggested that the borderline diagnosis might be productively studied from the perspective of dimensions of trait expression, in addition to that of the category itself. In Part II, we review the biology, genetics, and clinical course of borderline personality disorder (BPD), continuing to attend to the utility of a focus on fundamental dimensions of psychopathology. Biological approaches to the study of personality can identify individual differences with both genetic and environmental influences. The aspects of personality disorder that are likely to have biologic correlates are those involving regulation of affects, impulse/action patterns, cognitive organization and anxiety/inhibition. For BPD, key psychobiological domains include impulsive aggression, associated with reduced serotonergic activity in the brain, and affective instability, associated with increased responsivity of cholinergic systems. There may be a strong genetic component for the development of BPD, but it seems clear, at least, that there are strong genetic influences on traits that underlie it, such as neuroticism, impulsivity, anxiousness, affective lability, and insecure attachment. The course of BPD suggests a heterogenous disorder. Predictors of poor prognosis include history of childhood sexual abuse, early age at first psychiatric contact, chronicity of symptoms, affective instability, aggression, substance abuse, and increased comorbidity. For research purposes, at least, biological, genetic, and prognostic studies all continue to suggest the need to supplement categorical diagnoses of BPD with assessments of key underlying personality trait dimensions and with historical and clinical observations apart from those needed to make the borderline diagnosis itself.

BIOLOGY OF BORDERLINE PERSONALITY DISORDER

Advances in neuroscience present new opportunities to identify the neurobiologic underpinnings of personality disorder. The nature of the correlations between indices of brain biology and characteristics of personality disorder can provide clues to basic brain/behavioral relationships and the neurobiologic vocabulary of personality. Biological indicators may serve as external validators of diagnostic criteria or dimensions, as well as provide clues to etiologic factors involved in the pathogenesis of disorders such as borderline personality disorder. Biologic approaches, unlike genetic strategies, can identify individual differences with both genetic and environmental influences. While, in principle, all aspects of personality and its disorders must be encoded biologically in the brain, those aspects of personality disorder that are likely to be correlated with identifiable molar biologic indices are those involving the regulation of known psychobiologic domains, such as affects, impulse/action patterns, cognitive organization, and anxiety/inhibition. As individual variability in these domains is likely to be distributed continuously in populations, with perhaps, a skewed distribution in the personality disorders, they lend themselves to dimensional conceptualization, measurement, and investigation. For borderline personality disorder (BPD), key dimensions include impulsive aggression and affective instability.

Impulsive Aggression

Impulsive aggression is a central characteristic of a number of the "cluster B" personality disorders, particularly borderline and antisocial personality disorders. While impulsive aggression may manifest itself in Axis I disorders, such as intermittent explosive disorder, pathological gambling, or kleptomania, a propensity to aggressive behavior often has critical implications for interpersonal relationships and coping styles resulting in disorders of personality. Impulsive

aggression is heritable, as demonstrated by twin and adoption studies (Coccaro et al 1993), can be measured by laboratory tests (Cherek 1997a; 1997b; LeMarquand et al 1999), and has been consistently correlated with biologic indices, particularly those associated with serotonergic activity (Siever & Trestman 1993; Coccaro et al 1989). Thus, the descriptive, genetic, and biological domains of validation converge in suggesting that impulsive aggression is an important trait underlying disorders such as borderline personality disorder.

The evidence for serotonergic involvement in impulsive aggression rests on studies of serotonergic metabolites, such as 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF), both for self-directed aggression, exemplified by suicide attempts in depressed patients (Asberg et al 1976), and externally-directed aggression found in armed forces personnel, forensic populations, and volunteers (Brown et al 1989; Linnoila et al 1983; Coccaro 1998). Neuroendocrine responses to agents that enhance serotonergic activity have been demonstrated rather consistently to be blunted in psychiatric populations, including patients with BPD, who display impulsive aggression. These blunted responses are attributable to those criteria of BPD that reflect impulsive aggression: angry outbursts, self destructive behavior, and impulsiveness, (Coccaro et al 1989). Similar results have been demonstrated with intermittent explosive disorder, which is frequently comorbid with borderline personality disorder, using d-fenfluramine as a serotonergic agent (Coccaro et al 1996).

Imaging studies of people with impulsive aggressive personality disorders allow regional localization of reduced serotonergic responsiveness to cortical inhibitory areas that may dampen limbic release of aggression, including orbital frontal cortex and related ventral medial cortex, and cingulate cortex, which is prominently involved in evaluating incoming affective stimuli (Siever et

al 1999; New et al in press). Prefrontal metabolic activity, particularly in the orbital and medial prefrontal cortex, has been reported to be reduced in association with impulsive aggression in patients with borderline and antisocial personality disorders (Brown et al 1982; Goyer et al 1994; Raine et al 1994; 1997). Orbital frontal and cingulate cortex show decreased activation in response to serotonergic probes (Siever et al 1999; New et al in press). Reduced serotonergic modulation of these key cortical inhibitory areas may result in disinhibition of aggression. Studies pointing to reduced serotonergic activity in borderline patients associated with impulsive aggression have led to studies of serotonergic candidate genes. Examples are tryptophan hydroxylase (TPH), the serotonin transporter, the 5-HT_{1b} receptor, 5-HT_{1a} receptor, and the 5-HT_{2a} receptor among others. The TPH "L" allele and serotonin transporter "S" allele have been associated with impulsivity and neuroticism (Lesch et al 1996; New et al 1998), while the $5HT_{1b}$ receptor gene has been associated with suicide attempts (New et al 2001). These promising initial findings suggest that the association between reduction of serotonin and impulsive aggression may be contributed to in part by individual genetic differences and point to the need to assess impulsive/aggression, suicide attempts, and traits of neuroticism or novelty-seeking (TPQ) (Cloninger et al 1991) in patients with BPD.

However, clinical data also suggest environmental experiences play an important role in the genesis of BPD. For example, trauma is a frequent antecedent of BPD (Herman et al 1989), although trauma is certainly not restricted to BPD and may be comparably prevalent in other personality disorders in clinical samples (Steinberg et al 1994). In personality disordered patients, the trauma is often sexual or physical abuse. Abuse may reset "stress systems", such as the Hypothalamo-Pituitary-Adreno (HPA) Axis, and their relationships to serotonin (Yehuda et al 1991; Siever et al 1998; Heim et al 2001).

The biologic correlates of reduced serotonergic activity in impulsive aggression converge with treatment response data suggesting that impulsive aggression improves with treatment with selective serotonin reuptake inhibitors (SSRIs), independently of depression (Coccaro et al 1997; Cornelius et al 1990). It appears that reduced serotonergic capacity, however, requires longer duration (New et al 1999b) or higher dose interventions (Coccaro et al 1997) for treatment to be successful, consistent with the results of higher dose trials of SSRIs in BPD (Markovitz et al 1991).

An alternative theoretical framework to understand impulsive aggression is provided by Cloninger (1988), who suggests that what is observed clinically as impulsive aggression is a combination of high novelty seeking and low harm avoidance. Since he postulates that harm avoidance is associated with serotonergic activity, low harm avoidance would be characterized by reduced serotonergic activity, as has been described above. He hypothesizes that novelty seeking is associated with increased dopaminergic activity. Evidence in support of this view derives from studies of the D_4 receptor gene in volunteer populations associated with novelty seeking behavior (Ebstein et al 1996; Benjamin et al 1996), although this association has not been replicated in all studies (Gelernter et al 1997; Malhotra et al 2000). However, most studies of serotonergic indices have not found the hypothesized significant positive correlations between these indices and harm avoidance. Impulsive aggression may be a product of the interaction of brain systems, for example the interaction of reduced serotonergic activity and increased dopaminergic activity.

Other dimensional systems, such as those of Eysenck (1987) or Costa & McCrae (1990), have not been extensively studied using a biologic model. However, impulsive aggression could be viewed as related to increased extraversion on the NEO (Costa & McCrae 1990) and numbers of studies have suggested that extraversion is associated with reduced cortical arousal (Zuckerman

1990). Sensation seeking is another dimension closely related to novelty seeking. Sensation seeking has been associated with reduced platelet monoamine oxidase activity (MAO), which can result in increased catecholamine activity, including dopaminergic activity.

In summary, while the precise genetic and environmental antecedents and most appropriate clinical definition of the impulsive aggressive dimension need to be more definitively characterized, a dimension of behavior characterized by stimulus seeking, reactivity, and excessive aggression appears to have neurobiologic correlates, the most prominent of which is reduced serotonin activity.

Affective Instability

Another important dimension underlying borderline and related personality disorders is affective instability, that is, marked emotional reactivity to environmental events, particularly events such as separations, frustrations, or loses. However, while this dimension can be evaluated by semistructured interviews for DSM-IV, as well as by self-report scales, it has not been extensively investigated.

In one study, patients with BPD responded to the cholinesterase inhibitor, physostigmine, with an increased depressive response on the BPRS compared to normal controls (Steinberg et al 1997). In contrast, patients with a non-borderline personality disorder showed no differences in response compared to controls in this study. The degree of depressive response to physostigmine was correlated with borderline traits related to affective instability (Steinberg et al 1997). Procaine will induce dysphoric and dissociative symptoms in patients with BPD (Kellner et al 1987) and this response may in part be mediated by cholinergic systems in paralimbic regions. These regions may be critical in the evaluation of incoming stimuli and generation of responses and are also regions that are activated by emotionally charged stimuli. But, interestingly,

procaine-induced emotional responses in limbic regions are blunted in mood disorder patients compared to controls (Ketter et al 1987). This paradigm has not yet been utilized in patients with BPD to see if greater paralimbic activation occurs in response to emotionally charged stimuli than in controls. Furthermore, dissociative symptoms are not always assessed in BPD.

The noradrenergic system may play a critical role in modulating reactivity to the environment and also may be contributory to the affective instability seen in BPD patients. A number of studies suggest alterations in noradrenergic activity associated with dimensions of risk taking and sensation seeking (Zuckerman et al 1983) in populations such as gamblers and criminal offenders and with increased irritability on the Buss-Durkee Hostility Inventory (BDHI) (Coccaro et al 1991). While noradrenergic activity does not appear to mediate directly the release of disinhibited aggression as the serotonergic system does, the combination of increased adrenergic responsiveness with reduced serotonergic activity may be synergistic in heightening irritability and aggressive reactivity.

Anxiety

The biologic basis of anxiety in BPD is not well understood. However, there have been studies suggesting that panic attacks may occur upon lactate infusion in some borderline individuals (Silk et al 1994) and increased noradrenergic reactivity might also be related to anxiety (Bremner et al 1996). And, while many borderline patients are quite anxious, their propensity to act rather than delay in response to anxiety triggers may tend to diffuse the conscious experience of anxiety. SSRIs may be useful for the treatment of anxiety in BPD.

Psychotic-like Symptoms

Patients with BPD are prone to paranoid decompensations in which they may become

referential, display magical thinking, and become suspicious of others. These episodes, sometimes termed "mini psychotic episodes", usually occur in the context of some interpersonal crisis or sense of abandonment and may precipitate hospitalization or require other forms of crisis intervention. However, sustained psychotic-like symptoms are unusual in BPD in the absence of comorbid schizotypal personality disorder (STPD).

There is some evidence that enhanced dopaminergic activity may be associated with psychotic-like symptoms in personality disorder patients, particularly schizotypal personality disorder, a diagnosis that is sometimes comorbid with BPD. Increased dopamine concentrations have been reported in plasma and CSF of schizotypal patients, some of them comorbid with BPD, and controls, although the dopamine metabolite increase was not associated with the borderline diagnoses per se (Siever et al 1991). However, there was a correlation across diagnostic categories with psychotic-like symptoms for both plasma and CSF HVA, suggesting that higher dopaminergic activity may be associated with more psychotic-like symptoms. Amphetamine also induces psychotic-like symptoms in patients with BPD, particularly if they have comorbid STPD (Schulz et al 1985; 1988). These findings are consistent with the efficacy of antipsychotic medications for the psychotic-like symptoms of BPD.

Assessment from the Perspective of Biologic Studies

Biologic validators suggest that certain psychopathological dimensions should be assessed in patients with BPD. Furthermore, comorbid impulsive disorder diagnoses and behaviors relevant to BPD should be assessed. Impulsivity/aggression can be assessed by use of the relevant BPD criteria, the Assault and Irritability subscales of the Buss-Durkee Hostility Inventory (BDHI) (Buss & Durkee 1957) and the Barratt Impulsiveness Scale (BIS-11) (Barratt

& Standford 1995), increases on which have been associated with reduced serotonergic responsivity. A research diagnostic category based on intermittent explosive disorder (IED) has been developed that appears to reliably assess patients with aggressive outbursts (Coccaro 2000); new criteria have been developed for impulsive aggression disorder, which represents a potential comorbid diagnosis that should be assessed in BPD. A history of suicidal behaviors and parasuicidal behaviors should also be assessed, for example, by the Linehan scale of parasuicidal behaviors (Linehan et al 1993), again because of studies that support an association between suicidal acts and reduced serotonergic activity. A history of trauma, including abuse, should also be assessed.

Affective instability can be assessed using the criterion for BPD from semistructured interviews, as well as by self-report scales including the Affective Intensity Scale (AIS) (Larsen & Diener 1985) and the Affective Lability Scale (ALS) (Harvey et al 1989). The presence of dissociative symptoms can be assessed using the TPQ (Cloninger et al 1991), Eysenck Personality Questionnaire (Eysenck & Eysenck 1975), and the NEO (Costa & McCrae 1985), which generate measures of personality traits that may have important correlates biologically within the borderline realm. Another relevant scale is Zuckerman's Sensation Seeking Scale (Zuckerman et al 1964). The convergence of self-report scales and diagnostic interviews is likely to enhance our understanding of the biologic underpinnings of BPD.

GENETICS OF BORDERLINE PERSONALITY DISORDER

Until recently, accounts of the etiology of personality disorder have tended to emphasize the role of psychosocial adversity, particularly abuse and trauma, and to neglect biological contributions. This is surprising because the importance of constitutional factors in development

of personality pathology has been discussed repeatedly by clinical observers and the genetic underpinnings of normal personality traits have long been established (Plomin et al 1990). Recently, however, interest in genetic influences has increased, leading to changes in our ideas about the nature of borderline personality disorder and its treatment.

Research Designs

Early investigations of the genetics of BPD relied heavily on family studies, although this design does not disentangle genetic from environmental factors. Confounding of etiologic factors is particularly a problem because both genetic and psychosocial theories of causation predict an increased incidence in family members. To separate genetic and environmental effects, it is necessary to conduct adoption or twin studies.

Studies vary according to whether personality phenotypes are specified using categorical diagnoses or specific dimensions. Although categorical diagnoses are appealing to the clinician, the complexity and reliability of the phenotype has been a major problem. Perhaps more than other DSM-IV personality diagnoses, BPD is multidimensional. For example, statistical analyses show that the criteria form three clusters: identity problems and interpersonal difficulties, affective dysregulation, and impulsivity and self-harm (Sanislow et al 2000). These components may have different etiologies and responses to treatment. For this reason, some investigators have focused on evaluating specific traits dimensions. As McGuffin and Thapar (1992) note in their review of the genetics of personality disorder diagnoses, however, controversies about the classification of PD and the lack of clearly defined and reliable phenotypes has not prevented research on the genetics of personality disorder.

Genetics of the BPD Category

The concept of borderline personality disorder has roots in both psychoanalytic theory and classical phenomenology. The Danish adoption studies included a borderline condition in the schizophrenia spectrum. Following the distinction between borderline and schizotypal personality disorders in DSM-III, family studies suggested that BPD did not have a familial relationship to schizophrenia (Nigg & Goldsmith, 1994). This led to the alternative suggestion that it was related to mood disorder (Stone et al 1981; Akiskal 1981; Andrulonis et al 1981; Schultz et al 1989; Soloff & Millward 1983).

The high comorbidity of depression and BPD has been noted in several studies (Akiskal 1981). Besides the possibility of a genetic relationship, other explanations of this association include the inclusion of affective items in the BPD criteria set. Moreover, comorbidity with depression may not be specific to BPD. It may simply reflect the high base rates of both BPD and depression in clinical samples (Alnaes & Torgerson 1988; Coryell & Zimmerman 1989; Oldham et al 1995).

In an early study, Stone et al (1981) provided preliminary evidence of familial aggregation. They used Kernberg's concept of borderline organization, however, which is a broader concept than borderline personality disorder and hence their findings cannot be generalized readily to the DSM diagnosis. They also failed to control for schizotypal personality disorder: some relatives were schizotypal and others had BPD with an affective component. Several studies have, however, provided evidence of a link with mood disorders (Loranger et al 1982; Links et al 1988; Soloff & Millward 1983; Schultz et al 1989). Unfortunately, several of these studies did not control for comorbid mood disorder. When this is controlled, depression is

found only in the relatives of depressed borderline probands (Pope et al 1983; Zanarini et al 1988). Moreover, some studies have failed to find an increase of BPD in the families of depressed probands (Coryell & Zimmerman 1989; Maier et al 1992). Nigg and Goldsmith concluded that "the evidence overall is therefore unconvincing for a familial-genetic link between borderline personality disorder and affective disorders" (p.361). They raise the possibility of two kinds of BPD, one of which is related to mood disorder. It may be, however, that the relationship is due to chance because mood disorder is relatively common.

Familial transmission of BPD has been reported in several studies (Loranger et al 1982; Baron et al 1985; Zanarini et al 1988; Reich 1989). Other studies, however, only found a familial relationship for probands with BPD and depression (Pope et al 1983). Nigg and Goldsmith (1994) pointed out that studies of familial aggregation rely heavily on chart review and family history, often lack appropriate control groups, and many fail to control for comorbid mood disorders. These factors along with the multidimensional nature of the diagnosis make it difficult to draw firm conclusions. Nevertheless, Nigg and Goldsmith concluded that when all family studies are combined, the morbid risk of BPD in first degree relatives is 11.5%. Although this finding is consistent with a genetic component, psychosocial theories also predict a familial relationship. Twin and adoption studies are required to estimate the size of genetic and environmental factors. Unfortunately, few such studies are available.

Torgersen (1984) reported a small twin study of 25 probands with borderline personality disorder. Seven pairs were MZ and 18 pairs were DZ. None of the MZ pairs were concordant for BPD, but two of the DZ pairs (11%) were concordant (Torgersen 1987). More recently, Torgersen (2000) reported another Norwegian twin study of 221 twin pairs, 92 MZ and 129 DZ

pairs. "Definite" borderline personality disorder meant that the required number of criteria was fulfilled; "broad" disorder included cases with one or two criteria less. The concordance for definite BPD was 35% in MZ pairs and 7% in DZ pairs. With the broad BPD as the starting point, the concordance was 38% and 11%, respectively. The most parsimonious genetic model yielded an additive genetic effect of .69 and no shared-in-families environmental effect. However, a model with a .57 additive genetic effect and a .11 shared-in-families environmental effect could not be excluded. The larger Norwegian twin study suggests a rather strong genetic component in the development of borderline personality disorder.

A family relationship has also been reported between borderline personality disorder and other personality disorders, although the findings are inconsistent. Some studies report a familial increase in antisocial personality disorder (Pope et al 1983; Links et al 1988), but others did not find such a relationship (Zanarini et al 1988). An increase in histrionic personality disorder has also been reported (Pope et al 1983). There is also a suggestion that BPD has a familial relationship to alcoholism and substance abuse. These findings raise the possibility that the increased risk in the families of BPD probands may not be specific to borderline pathology.

Genetics of Borderline Traits

The second major research trend has been to investigate genetic and environmental contributions to the etiology of personality disorder traits using twin study designs. Before discussing these topics, however, it is necessary to consider briefly the phenotypic structure of personality disorder traits.

Phenotypic structure of personality disorder traits

Several investigators have studied the dimensions underlying personality disorder diagnoses and a consensus seems to be emerging regarding the lower order traits that compose personality disorder (Watson et al 1994; Clark et al 1996). In earlier studies, Livesley and colleagues (Livesley 1986, 1987; Livesley et al 1989) identified the traits delineating personality disorder using a combination of literature review, clinical judgment, and psychometric analyses. This procedure resulted in a set of 18 factor-based scales to assess personality disorder: anxiousness, affective lability, callousness, cognitive dysregulation, compulsivity, conduct problems, identity problems, intimacy avoidance, insecure attachment, narcissism, oppositionality, rejection, restricted expression, social avoidance, stimulus seeking, and submissiveness. BPD could be represented by such traits as anxiousness, affective lability, cognitive dysregulation, identity problems, insecure attachment, and submissiveness.

Factor analyses of the 18 traits assessed in the general population (n=939), patients with personality disorder (N=656), and twins (N=686 pairs) yielded a four factor solution that was stable across samples (Livesley et al 1992). This finding provides a strong argument for a dimensional representation of personality disorder (Eysenck 1987). The four factors were labeled emotional dysregulation, dissocial behavior, inhibitedness, and compulsivity.

Univariate studies of traits

The results of twin studies show that the heritability of traits delineating personality disorder is 35% to 56% (Livesley et al 1993; Jang et al 1996). Unique environmental effects were estimated at between 44% and 65%. Common environmental factors had little effect. The heritability of specific borderline traits is indicated in Table 1.

Multivariate genetic analyses

Phenotypic factor analyses examine the structure underlying a matrix of correlations derived from measures of multiple traits. Multivariate genetic analyses are applied in a similar way to a matrix of genetic correlations. Data from MZ and DZ twins may be used to partition the phenotypic correlation between two traits into genetic and environmental components. The genetic correlation indicates the extent to which the genetic effects on one trait predict the genetic effects on the second trait. These correlations may be subjected to factor analysis.

When this method is applied to the 18 basic dimensions assessed by the Dimensional Assessment of Personality Pathology-Baseline Questionnaire (DAPP-BQ), a four factor genetic structure emerges (Livesley et al 1998). The large first factor appears to describe a general tendency toward labile affects, unstable cognitive functioning, an unstable sense of self, and unstable interpersonal relationships. In view of the high salience of affective traits, this component was labeled emotional dysregulation. As the lists of salient loadings in Table 2 show, the genetic structure strongly resembles the phenotypic structure.

This factor strongly resembles BPD, although the component is more broadly based than the DSM-IV definition. The breadth of this component helps to explain the substantial overlap between BPD and other personality disorders – nearly 95% of patients meeting the criteria for borderline meet the criteria for at least one other disorder (Widiger et al., 1991). The remaining factors were labeled dissocial behavior, inhibitedness, and compulsivity. Estimates of the heritability of the higher-order factors were: emotional dysregulation, 47%; dissocial behavior, 50%; inhibitedness, 48%; and compulsivity, 38%.

Factor congruence between genetic and phenotypic factors was 0.97 indicating that phenotypic structure strongly resembles underlying genetic architecture.

Residual heritability of lower-order traits

These findings raise the question of whether personality and personality disorder is inherited as a small number of genetic dimensions that exert broad effects on personality phenotypes or as a larger number of dimensions with more circumscribed effects. That is, is there a genetic predisposition to BPD per se, or do a large number of genetic dimensions underlie the diagnosis?

As a first step in exploring this issue, the heritability of the traits with salient loadings on the emotional dysregulation component was estimated, following removal of the effects of the higher-order factors using regression techniques. Of the 9 traits salient on this component, all showed substantial residual heritability except anxiousness, cognitive dysregulation, and oppositionality. This provides supports for the multiple genetic factor hypothesis (Livesley et al 1998).

The next step was to evaluate this hypothesis using multivariate genetic techniques. Each of the 18 basic traits is defined by between 2 and 6 specific traits. For example, anxiousness consists of trait anxiety, guilt proneness, rumination, and indecisiveness, and affective lability consists of affective instability, affective over-reactivity, generalized hypersensitivity, labile anger, and irritability. Phenotypic analyses in which the specific traits defining each basic trait were inter-correlated and the resulting matrix examined by factor analysis showed that each basic trait is composed of a single factor. Multivariate analyses of the matrices of genetic correlations yielded a different picture. For some basic traits such as anxiousness a single genetic factor was identified, but for several traits two or three factors with obtained. Again the finding supports the multiple factor hypothesis.

Based on these results, it is proposed that the genetic dimensions that underlie the emotional dysregulation or borderline cluster of traits are those listed in Table 3.

Pathways analyses

Phenotypic factor analyses imply that a single latent dimension labeled emotional dysregulation underlies the cluster of traits salient on the factor. Assuming that emotional dysregulation bears a close resemblance to BPD, this suggests an underlying latent entity of "borderlineness." The genetic equivalent to this model is the common pathways model which assumes that etiological factors influence a latent structure of "borderlineness" that in turn affects the basic traits defining the pattern. The alternative model is the independent pathways model in which it is assumed that each basic trait is directly influenced by genetic and environmental factors, that is, there is not a latent structure or trait of "borderlineness." When these models were fit to the data, the fit was unsatisfactory for the common pathways model. At all levels of the trait hierarchy, the independent pathways model provided the best fit (N=695 twin pairs) (Livesley et al in press). If these findings are replicated, they suggest that the most profitable level of analysis when investigating the etiology of BPD will be at the level of the specific trait components.

The results of twin studies largely confirm genetic studies using categorical diagnosis that suggest that BPD has a heritable component. The evidence points to the importance of genetic and environmental influences on borderline personality disorder.

Assessment From the Perspective of Genetic Studies

The combinations of phenotypic and genetic analyses provide a strong evidence that emotional dysregulation and its associated basic traits are continuously distributed. The implication is that these traits are best represented by a dimensional structure.

The findings also suggest that BPD is influenced by multiple genetic dimensions that differ in their effects on the resulting phenotype. Given that multiple dimensions are involved, the phenotype is likely to be fuzzy in nature and individuals assigned to a diagnostic category based on this phenotype are likely to be heterogeneous. Thus, the results of behavioral genetic analyses are consistent with clinical and empirical observations of the heterogeneous nature of borderline patients, an observation that has prompted the idea that sub-types of BPD should be described and measured.

An important issue is whether the emotional dysregulation factor of the DAPP-BQ corresponds to BPD. Examination of the content of scales reveals considerable substantive similarity to the features of BPD. The factor also bears a strong resemblance to Linehan's description of the condition (1993). Clinical use of the scales indicates that patients meeting the DSM-IV criteria for BPD obtain high scores on the emotional dysregulation factor and associated basic traits. Additional indirect support for the similarity is provided by the finding that neuroticism scales correlate highly with emotional dysregulation ($r=0.79$). Patients with BPD score highly with neuroticism (Widiger et al 1994). It appears, therefore, that emotional dysregulation and BPD are largely the same construct. Emotional dysregulation is slightly broader in that it contains a few features that are omitted from the DSM diagnosis. Dimensions such as neuroticism and emotional dysregulation should be measured in studies of BPD.

PERSPECTIVES ON COURSE

An enduring pattern of inner experience and behavior is generally believed to be a fundamental aspect of all personality disorders (PDs). A relatively stable pattern of long duration, in contrast to an episodic course with remissions and relapses, has been one rationale

for placing personality disorders on a separate Axis II in the various editions of the DSM, beginning with DSM-III. Most semistructured interviews designed to assess personality disorders require that the traits and behaviors represented by the diagnostic criteria describe the person over at least the previous two to five years. Although the essential feature of borderline personality disorder is defined in DSM-IV as a "pervasive pattern of instability in interpersonal relationships, self-image, and affects and marked impulsivity," questions can be raised about how stable these characteristics are and which of them are associated with stability of the diagnosis -- thereby identifying the core components of the disorder.

Reviews of the Course of BPD

There are ten major reviews of longitudinal studies of course and stability of personality disorders (Paris 1998; Stone 1989; 1993; Zanarini et al 1991; McGlashan 1992; Perry 1993; McDavid & Pilkonis 1996; Grilo et al 1998; Grilo & McGlashan 1999; Grilo et al 2000). The last two are extensions of Grilo et al's 1998 review.

Borderline personality disorder has been by far the most commonly studied from the longitudinal perspective. Virtually all of the studies have significant methodologic limitations including small sample sizes; unstandardized assessment methods; insufficient attention to reliability and independence (i.e., blindness) of follow-up assessments; insufficient characterization of Axis I and Axis II comorbidities; variable, typically short, and one-time follow-up periods; and the absence of contrast groups to provide a context for comparisons. Overall, the results of longitudinal studies of BPD suggest that stability, at least over the longer term, is less than what standard general definitions of personality disorders would appear to require. Also, within samples of patients with a BPD diagnosis, clinical course is heterogeneous,

further emphasizing the need to look for core features of the disorder that would exhibit expected stability or for factors that would be associated with a relatively poor prognosis (and, thus, diagnostic stability) over the intermediate-term. The majority of studies have examined DSM-III or DIB defined BPD, rather than DSM-III-R or DSM-IV.

Estimates of BPD Stability Over Time

There are 13 studies that report the stability of a BPD diagnosis, made according to specified criteria and with the assistance of a semistructured interview (Gunderson et al 1975; Pope et al 1983; McGlashan 1983; Barasch et al 1985; Paris et al 1987; Kullgren & Armelius 1990; Silk et al 1990; Loranger et al 1991; Stevenson & Meares 1992; Links et al 1993; 1998; Meijer et al 1998; Shea et submitted). The range of stability is from 14% in Meijer et al's (1998) 3 year follow-up of 14 adolescents with BPD to 78% in Silk et al's (1990) 1 to 3.5 year follow-up of 9 of 30 inpatients or 90% in Barasch et al's (1985) 3 year follow-up of 10 outpatients, if both definite (60%) and probable (30%) BPD diagnoses are allowed. A weighted average of 55% stability has been found for 462 patients with pre-DSM-IV BPD. Several studies have high rates of attrition, raising the question of whether subjects lost to follow-up have higher or lower rates of BPD. Also, the follow-up periods in these studies have been highly variable, ranging from less than 6 months (Loranger et al 1991) to an average of 15 years (McGlashan 1983; Paris et al 1987). The age range of the subjects is also variable. The lowest stability rate was found in adolescent patients, when personality is often considered in flux. In general, stability of BPD has been found to have a strong negative correlation to length of follow-up period (Perry 1993; McDavid & Pilkonis 1996).

In a prospective follow-along study, the Collaborative Longitudinal Personality Disorders Study (CLPS), in which the criteria of DSM-IV BPD were assessed on a monthly basis for 1 year, Shea et al (submitted) found that 65% of BPD subjects met full criteria every month for the first 6 months and only 41% met criteria every month for the full year. The persistence of symptomatology reflected by the individual criteria for BPD was highly variable. Over 90% of subjects had persistence of intense anger, affective instability, and unstable relationships, while 77% had persistent impulsivity and only 46% had persistent self-injury or suicide attempts (Shea et al in preparation). Persistent symptoms may represent the core or central aspects of BPD psychopathology.

Prognostic Factors In BPD

There have been few studies examining negative prognostic factors in BPD. Negative prognostic factors would be associated with greater diagnostic stability and, therefore, may need to be identified and assessed to account for heterogeneity in clinical course for patients with BPD. Negative prognostic factors can be divided into two types: historical and phenomenologic.

Historical predictors of poor prognosis in BPD include history of childhood sexual abuse (Paris et al 1993) and incest (Stone 1990). Early age at first psychiatric contact (Links et al., 1993) and chronicity of symptoms (McGlashan 1992) have also been associated with greater stability of diagnosis at follow-up.

Phenomenologic factors associated with greater stability (or poorer prognosis) include affective instability, magical thinking, and aggression in relationships (McGlashan 1985, 1992); impulsivity (Links et al 1993); substance abuse (Links et al 1993; Stone 1993); and greater severity of disorder, as indicated by more BPD psychopathology at intake and greater numbers

of Axis II comorbid diagnoses on follow-up (Links et al 1998). Comorbid schizotypal (McGlashan 1985), antisocial (Stone 1993), and paranoid (Links et al 1998) features, in particular, have been associated with greater BPD stability.

Other Factors Associated with BPD Stability

Most studies of diagnostic stability of PDs have found that dimensional measures and concepts are more stable than are the categorical diagnoses (Grilo et al 1998, 1999). Lenzenweger (1999) showed that BPD criteria counts had moderate levels of stability over a four-year period, although they also declined, consistent with the data on categorical diagnoses. Five-Factor Model (FFM) (Costa & McCrae 1992) traits of high neuroticism and low agreeableness are thought to be associated with BPD on both theoretical (Widiger et al 1994) and empirical (Morey et al submitted) grounds. Agreeableness was found in the CLPS study to show little change on follow-up; neuroticism showed a relatively minor decrease over time.

Impairment in psychosocial functioning is also integral to any definition of personality disorder. Functional impairment appears to persist on follow-up of many BPD patients, even if diagnosis is unstable. Patients with BPD may show some fluctuations in psychopathology over time due to situational changes, treatment, or sampling variations, but impairment in functioning may persist. In the CLPS study (Skodol et al in preparation) only 6% of BPD patients showed a "functional remission" over 12 months of follow-up. The discrepancy between the instability of some of the diagnostic criteria of BPD (and consequently of the diagnosis itself) and the stability of impairments in functioning suggests that at least some criteria do not reflect well the stable impairments in object or interpersonal relations believed by many to be at the core of BPD.

Comorbidity on both Axis I and Axis II appears to be associated with BPD stability. For example, in the CLPS (Shea et al submitted), remission from Axis I major depressive disorder and dysthymic disorder was associated with "remission" from BPD. A diagnosis of BPD appeared to be associated with a mood disorder with an insidious onset and recurrence, chronicity, and progression in severity (Skodol et al 1999). A greater number of Axis II diagnoses at follow-up predicted BPD stability after 7 years in Links et al's study (1998); number of co-occurring Axis II diagnoses at baseline did not appear to influence the 1 year stability of BPD in the CLPS study, however.

Assessment of BPD from the Perspective of Clinical Course

BPD assessment should be embedded in a comprehensive assessment of a range of Axis I and all other Axis II disorders to account for the effects of comorbidity and continuity of disorders on BPD stability. Measures of BPD should be considered from a dimensional perspective as to the degree of prototypicality (i.e., number of criteria) manifest (Widiger 1993), as well as according to set diagnostic thresholds. Other personality traits potentially underlying BPD, such as those represented by the Five-Factor Model (FFM), should also be considered because of their manifest stability over time. Independent measures of psychosocial functioning should be included in BPD assessments, since impairment in functioning may be more stable than the diagnosis itself. A history of childhood sexual abuse, including incest, and the age at first psychiatric contact and age at first BPD diagnosis (as measures of chronicity) should be assessed because of their demonstrated effects on BPD diagnostic stability.

CONCLUSIONS

Biological and genetic studies have suggested that pathological personality traits underlying borderline personality disorder may be of fundamental importance in understanding etiology and targeting treatment. Follow-up studies also suggest that measuring personality dimensions and making other clinical observations apart from those needed to make the borderline diagnosis itself may be necessary to account for the heterogeneity of outcome in BPD.

The first two parts of this three-part presentation on the borderline diagnosis suggest that promising research advances can be made if rigorous assessment of DSM-IV BPD criteria by semistructured interview is augmented by assessment of personality traits, such as those in the three- or five-factor models of personality, or such as impulsive aggression and emotional dysregulation. Future research priorities for the borderline diagnosis should include the establishment of robust relationships between descriptive traits and pathogenetic mechanisms, such as genetics, neurobiology, childhood temperament, family environment, and life events. Improved methods for measuring and validating fundamental trait dimensions underlying BPD and its comorbid Axis I disorders are needed. It remains to be demonstrated whether dimensional models of general personality functioning can fully account for all aspects of borderline psychopathology and would prove to be more clinically useful in practice than the current diagnosis of borderline personality disorder. Finally, linking borderline patient subtypes or underlying dimensions to various psychosocial and psychopharmacologic treatments to improve treatment response could greatly improve prognosis in these disabling conditions. In Part III of this series, an endophenotype approach to identifying the genetics of this complex disorder is described.

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Table 1. Heritability of Borderline Traits

Borderline Trait	Heritability Co-efficient
Anxiousness	44
Affective lability	45
Cognitive dysregulation	49
Identity problems	53
Insecure attachment	48
Submissiveness	45

Table 2. Factor Analysis of Phenotypic and Genotypic Correlations for DAPP-BQ Factor I Emotional Dysregulation

DAPP-BQ Trait	Phenotypic Loading	Genotypic Loading
Anxiousness	89	90
Identity problems	83	75
Submissiveness	79	84
Affective lability	78	73
Cognitive dysregulation	77	70
Insecure attachment	75	70
Social avoidance	76	71
Oppositionality	69	68
Narcissism	52	49

Table 3. Phenotypic and Genetic Dimensions Underlying Borderline Traits

Phenotypic Dimension	Genetic Dimension
Anxiousness	Anxiousness
Affective lability	Reactivity
	Hypersensitivity
Submissiveness	Submissiveness
Social avoidance	Low affiliation
	Social fearfulness
Insecure attachment	Insecure attachment
Cognitive dysregulation	Cognitive dysregulation
Oppositionality	Oppositionality
	Passivity