BIOLOGICAL PSYCHIATRY
IN PRESS

THE BORDERLINE DIAGNOSIS III: IDENTIFYING ENDOPHENOTYPES FOR GENETIC STUDIES

Running Title: ENDOPHENOTYPES/GENETICS OF BORDERLINE PERSONALITY

Larry J. Siever, M.D. [1]

Svenn Torgersen, Ph.D. [2]

John G. Gunderson, M.D. [3]

W. John Livesley, Ph.D., M.D. [4]

Kenneth S. Kendler, M.D. [5]

1) Department of Psychiatry, Mount Sinai School of Medicine, 1 Gustave L. Levy Place, Box 1230, New York, New York 10029

2) Center for Research in Clinical Psychology, Department of Psychology, University of Oslo, P.O. Box 1039- Blindern, N-0317 Oslo, Norway

3) McLean Hospital, 115 Mill Street, Belmont, MA 02178

4) Department of Psychiatry, University of British Columbia, 2255 Wesbrook Mall, Vancouver BC, Canada V6T 2A1

5) Medical College of VA, VA Commonwealth University, Department of Psychiatry, Box 980126, 800 East Leigh Street, Suite 100, Room 1-123, Richmond, VA 23219

Supported in part by the Borderline Personality Disorder Research Foundation

Key words: borderline, endophenotype, genetic, familial

Address correspondence to: Larry J. Siever, M.D., Department of Psychiatry, Mount Sinai School of Medicine, 1 Gustave L. Levy Place, Box 1230, New York, New York 10029, Phone: (718) 584-9000 x5227; Fax: (718) 364-3574 ; E-mail: Larry.Siever@med.va.gov

Abstract

While it is generally acknowledged that borderline personality disorder has a complex, multifactoral etiology with interacting genetic and environmental substrates, the specific genetic underpinnings of this disorder have not been extensively investigated. Family aggregation studies suggest the heritability for borderline personality disorder as a diagnosis, but the genetic basis for this disorder may be stronger for dimensions such as impulsive/aggression and affective instability than for the diagnostic criteria itself. Family, adoptive, and twin studies also converge in supporting an underlying genetic component to the disorder. An endophenotypic approach to defining the genetics of this complex disorder may be called for. Twin studies in an epidemiologic non-clinically ascertained sample using both diagnostic measures and laboratory measures that can be operationalized including neuropsychologic, psychophysiologic, and operationalized behavioral tests may be useful. Large-scale family studies of clinically ascertained samples with careful diagnostic demarcation and measurement of endophenotypes in probands and relatives may also prove to be a promising approach. The use of laboratory paradigms for measures of aggression and affective instability are discussed in the context of such endophenotypic approaches.

Introduction

While there is general consensus that borderline personality disorder has a multifactorial etiology including both genetic and environmental influences, there has been little systematic research into the specific genetic and environmental antecedents to this disorder. In part, the interpersonal and psychodynamic considerations that provided the original impetus to define this disorder and address its treatments may not lend themselves as easily to classic genetic approaches as more simply defined disorders. However, if the borderline personality disorder diagnosis is reframed in terms of more specific, measurable, presumably biologically-based endophenotypes, the possibilities of identification of genetic predisposing factors might be considerably improved. Such a reframing that might generate fruitful genetic investigation into this disorder might then encourage more rigorous research, attracting investigators to what has heretofore seen as a somewhat "fuzzy" diagnosis from a genetic point of view. A better understanding of the genetics of this disorder might improve the prospects of targeted interventions for more homogeneous subsets of borderline patients characterized by specific genetic vulnerabilities.

Family Aggregation Studies of Borderline Personality Disorder

Currently there is substantial evidence for familial aggregation of borderline personality disorder or traits as a greater frequency of the diagnosis of borderline personality disorder or borderline traits are seen in the relatives of probands with borderline personality disorder than in comparison groups (Baron et al, 1985, Links et al 1998 Loranger et al, 1982, Pope et al, 1983,

Reich 1989, Silverman et al, 1991, Soloff & Milward, 1983, Zanarini et al, 1988, Torgersen, 2000). The frequency of borderline personality disorder features among first degree relatives of borderline personality disorder probands varies from study to study, possibly because the definitions of borderline personality disorder vary somewhat from study to study. With the exception of Links and colleagues (1998), Baron and colleagues (1985) and Reich (1989), relatives were not interviewed directly. Only Loranger and colleagues (1982), Zanarini and colleagues (1988) and Silverman and colleagues (1991) found statistically significant differences between relatives of individuals with borderline personality disorder and relatives of controls. Loranger and colleagues (1982) did not interview the probands but only reviewed the medical records. The information about the relatives stemmed from the proband's therapist and social worker. The criteria for borderline personality disorder among the relatives was closer to antisocial personality disorder and to substance abuse than to borderline personality disorder, and only 2 of 9 criteria were required for receiving a positive diagnosis, so that whether they had a DSM-III borderline personality disorder more often than controls is unknown. The study of Zanarini and colleagues (1988) represents the strongest proof of a familial transmission of borderline personality disorder. However, it is important to note that all information about the relatives was derived from the borderline personality disorder patients themselves. Soloff and Millward (1983) did not really study borderline personality disorder among relatives, but rather what they called «eccentric or peculiar behavior», in other words, personality features more similar to schizotypal personality disorder than borderline personality disorder.

Baron and colleagues (1985) are often cited for having found that borderline personality disorder breeds true in families. However, they only obtained significance when they included

probable borderline personality disorder, and in addition «corrected» upward the frequency as a compensation for not having interviewed the relatives directly. Links and colleagues (12) show that this may be wrong as they found a frequency of 3.4% when the relatives were interviewed directly and 15.1% based on information from the patient. Thus, it is just as possible that the borderline personality disorder probands exaggerate the borderline features among their relatives. This group (1985) also showed that the frequency of borderline personality disorder is especially low when the probands have mixed borderline personality disorder plus schizotypal personality disorder.

Silverman et al. (1991) made the interesting observation that among the relatives, *either* impulsive *or* affective personality traits (not mood disorders) were found, not *both* sets of personality traits. Thus, the familial relationship may be stronger for dimensions such as impulsive/aggression and affective instability which are transmitted partially independently than for the diagnostic category, borderline personality disorder, itself (Silverman et al, 1991).

While familial aggregation studies do not separate genetic from environmental factors in the etiology of the disorder, twin and adoption studies provide better evidence of a genetic contribution to the development of borderline personality disorder. One study of 7 MZ and 18 DZ twin pairs showed a concordance of zero in MZ and 11% in DZ pairs (Torgersen, 1984). As the frequency of BPD is between 2 and 3% in the population (Stone, 1998; Widiger and Frances, 1989) the study suggest that common environment, but not heredity is of importance in the development of BPD. However, the small number of twins limits the interpretability of the finding . A more recent larger Norwegian twin study (Torgersen et al, 2000) investigated the

range of personality disorders diagnosed by an operationalized interview in a sample of 92 monozygotic and 129 dizygotic twin pairs derived from crossing twin and patient registries in Norway. The results could be interpreted that the genetic effect in the development of BPD is below .60, while the common environmental effect may be above .10. However, the most likely interpretation from the models used in this study, from the principle of parsimony, is that the effect of heredity is close to .70 and there is no effect of common family environment.

Heritability of Personality Disorder

A number of studies have examined heritability of different facets of personality, although most have not focused on the personality disorder diagnoses. Studies of twins reared together and apart suggest a strong genetic influence on personality dimensions such as neuroticism and extraversion (Tellegen et al, 1988; Pedersen et al, 1991). Adoption studies of samples with diagnosed personality disorders have demonstrated a genetic influence on the development of antisocial personality disorder (Cadoret & Stewart, 1991) while twin studies have demonstrated a genetic underpinning for schizotypal personality disorder (Torgersen et al, 1993). An early twin study of borderline personality disorder suggested that the diagnosis was largely environmentally determined, although the core symptoms (including impulsivity and affective instability) were shown to be substantially heritable (Torgersen, 1984). Other studies have confirmed the heritability of impulsive aggression. These include twin studies showing heritability of "irritable impulsiveness" with heritability scores of 41% (Coccaro et al, 1993), and in a different population, heritability scores for different forms of self-reported aggression ranged from 53-72% (Coccaro et al, 1997).

Strategies for Genetic Studies of Borderline Personality Disorder

Ideally, the most definitive study would identify a large number of twins in an epidemiologic non-clinically ascertained sample but with a sufficient prevalence of probands with the diagnoses of borderline personality disorder to achieve substantial power for genetic studies. The twins could then be systematically identified and recruited for the study. In this kind of study, subjects would be evaluated with regard to clinical phenotype by diagnostic interview, self-report measures of personality traits, and laboratory measures including neuropsychologic, psychophysiologic, or operationalized behavioral tests that address endophenotypic dimensions likely to have a genetic basis. However, the sample sizes for such a study might be prohibitively large, especially if clinical assessment for personality disorders with operationalized interviews (and ideally informants) were utilized. A compromise strategy might consist of determining the overlap between clinically ascertained borderline personality disorder patients with a twin registry as was done by Torgersen and colleagues (2000).

Genetic studies of clinically ascertained samples which may be representative of the disorder as diagnosed in clinical samples might also represent a viable strategy if carried out on a large enough scale to allow for analyses of factors such as gender, ethnic heterogeneity, diagnostic heterogeneity within the borderline diagnosis, and correlation between measures, as well as determination of underlying genetic structures. Such studies provide less definitive information about specific genetic contributions to the development of borderline personality disorder than twin studies, but may be more feasible. Association studies of a clinical sample

may be valuable insofar as the demonstration of genetic association with one or more components of the borderline diagnosis may allow for a clearer definition of the phenotype for more definitive studies. This would then inform the way phenotype might be assessed for more definitive studies. Twin studies might then focus on personality dimensions related to borderline personality disorder, which would not depend on identifying a substantial number of individuals with borderline personality disorders. All of these strategies depend on the identification of relevant clinical phenotypes for borderline personality disorder and its possible underlying dimensions.

Endophenotypic/Dimensional Approaches

If borderline personality disorder is conceptualized as a personality disorder emerging from the interaction of underlying genetically based traits (Siever & Davis, 1991; Livesley et al, 1992), the prospect for identifying underlying endophenotypes becomes potentially more feasible. Endophenotypes represent measurable characteristics that reflect an underlying genotype that may be more closely related to that genotype than the diagnostic category itself. The endophenotype approach is being successfully applied to the schizophrenic disorders, for example, using psychophysiologic measures (Erlenmeyer-Kimling et al, 2000; Waldo et al, 1988; Braff et al, 2001; Paulus et al, 2001) or affective disorders, for example, using neurochemical measures (Leboyer et al, 1998b). Impulsivity or impulsive aggression is generally considered to be an underlying fundamental dimension or trait in borderline personality disorder by a number of investigators (Siever & Davis, 1991; Zanarini, 1993; Links et al, 1999). As a partially heritable basis has been established for impulsive aggression as outlined above,

impulsive aggression might represent a heritable endophenotype that would contribute significantly to the likelihood of developing borderline personality disorder.

There are now a number of laboratory paradigms that may discriminate aggressive individuals from comparison groups including the Point Subtraction Aggression Paradigm (PSAP) (Cherek, 1981) and a "go/no go" version of the Continuous Performance Task (CPT) (LeMarquand et al, 1999). For example, the PSAP involves an experimental subject and a "confederate" (a computer), and the objective of the experimental subject is to accumulate "points" that can be exchanged for money (Cherek et al., 1990). The PSAP has been externally validated in violent and non-violent male parolees, in that violent parolees emit more aggressive responses than non-violent parolees; furthermore, the number of aggressive responses correlated with other psychometric measures of aggression (Cherek et al, 1997). However, the heritability of these laboratory measures have never been systematically assessed in studies of families or sibs of impulsive/aggressive probands, a logical prerequisite to an endophenotypic approach to borderline personality disorder.

This approach might ultimately be combined with candidate gene strategies and/or with measures of brain neurotransmitter or circuitry via imaging or pharmacologic studies. For example, biochemical, neuroendocrine, and imaging studies implicate reduced serotonergic activity associated with impulsive/aggressive trails (Coccaro et al, 1989; see review Siever & Trestman, 1993; Gurvits et al, 2000). Candidate gene studies of serotonergic related genes in relation to impulsive aggression, however, have been confined to relatively limited well-characterized clinical populations in case control studies (New 1998, 2001; Mann, 1997) or

larger volunteer populations characterized largely by self-report scales (Lesch et al, 1993). While impulsive aggression may represent an endophenotype for borderline personality disorder, it might not be specific and might also, for example, characterize people with antisocial personality disorder. However, the identification of underlying heritable factors including impulsive aggression that may interact with others to yield borderline personality disorder could conceivably be of critical importance in targeting populations whom might respond to specific pharmacologic or even psychosocial interventions. These are, however, likely to be continuously distributed rather than constituting discrete subgroups.

Another underlying dimension of borderline personality disorder that may be partially heritable is affective instability. While clinical tools including structured interviews and self report questionnaires such as the Affective Lability Scale (ALS) (Harvey et al, 1989) have been used to characterize this trait clinically, there has been no generally acknowledged laboratory measure for this dimension, although galvanic skin response or fMRI responses to affective stimuli have been measured in psychiatric populations. Other potential biologically based traits that might be relevant for borderline personality disorder include pain sensitivity, tests of information processing, or physiological reactivity.

The development of meaningful endophenotypic indicators entails a discrimination not only of the target clinical population, i.e., of borderline personality disorder from a comparison group, but also the heritability of the index of the endophenotype. This could be evaluated by family studies of relatives or of affected and unaffected sibs. The endophenotype approach has been successfully employed by Leboyer (Leboyer et al, 1998b) in studies of autism and bipolar

disorder using biologic indices (e.g. serotonin transporter binding) (Leboyer et al, 1999a; 1999b), cognitive tests (Hughes et al, 1999), and clinical characteristics (Leboyer et al, 1998a). Studies of risk markers in schizophrenia as exemplified by the work of Neuchterlein 1983; Cornblatt et al, 1988 have been extended to family studies, sib-pair, and twin studies to determine heritability of psychophysiologic and neuropsychologic measures of schizophrenia (Keefe et al, 1997; Weinberg, 1999; Egan et al, 1999, 2001a, 2001b). Biologic measures are more likely to provide useful intermediate phenotypes as they are presumably closer to genetic substrates than temperamental measures. While alterations in such measures might represent consequences of the disorder such as medication treatment or frequent stressful crises, they can ultimately be applied to unaffected populations such as sibs as well to address this concern.

In this context, candidate gene studies might be employed not simply in case control association studies of borderline personality disorder (which might require up to 500 probands to achieve adequate power) but in conjunction with more rigorously identified endophenotypes in sib-pair or transmission disequilibrium tests involving family members. Thus, while the etiologies of borderline personality disorder are likely to be multifactorial and heterogeneous with respect to genotypic influences, as has been established to be the case for mood disorder and schizophrenia, the possibility of targeting endophenotypes that reflect the genetic substrates for this disorder offers a promising way to identify genetically homogeneous subgroup within borderline samples.

At this point, it is not clear that even if appropriately large samples of twins could be identified, that the relevant endophenotypic assessments or candidate genes could be chosen with

any assurance. Smaller scale studies with clinically identified probands to "pilot" promising endophenotypes along the lines that have been suggested earlier might complement attempts to identify appropriate larger scale samples for more definitive studies. The relationship between candidate genes and relevant brain measures derived from imaging or brain neurochemistry as well as the delineation of endophenotypic markers and their relationship to treatment response may help provide the tools needed to select candidate genes for optimal larger scale studies. At the same time, development and clinical assessment of appropriate populations of twins and borderline personality disorder probands and their relatives and collection of their blood samples for future genotyping could be initiated.

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