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PERSONALITY DISORDERS (C SCHMAHL, SECTION EDITOR)

# Gene-Environment Studies and Borderline Personality Disorder: A Review

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**Abstract** We review recent gene-environment studies relevant to borderline personality disorder, including those focusing on impulsivity, emotion sensitivity, suicidal behavior, aggression and anger, and the borderline personality phenotype itself. Almost all the studies reviewed suffered from a number of methodological and statistical problems, limiting the conclusions that currently can be drawn. The best evidence to date supports a gene-environment correlation (rGE) model for borderline personality traits and a range of adverse life events, indicating that those at risk for BPD are also at increased risk for exposure to environments that may trigger BPD. We provide suggestions regarding future research on GxE interaction and rGE effects in borderline personality.

**Keywords** Borderline personality disorder · BPD · Psychopathology · Gene-environment interaction · GxE · Gene-environment correlation · rGE · Impulsivity · Emotion sensitivity · Suicidal behavior · Aggression · Anger · Adverse life events · Environmental factors · Personality disorders · Psychiatry

## Introduction

Borderline personality disorder (BPD) is a severe mental disorder characterized by dysfunction in emotional, interpersonal, and behavioral realms. BPD is present in 1 - 3 % of the general population and, clinically, is the most commonly diagnosed personality disorder [1, 2•, 3]. It is commonly comorbid with other disorders, especially other personality disorders, substance use disorders, and mood disorders [4]. Although an increasing amount of attention has been paid to the disorder in recent years, its etiology and development remain largely shrouded in uncertainty. A genetic predisposition seems to play a role, but the contribution of genetic factors is modest [5, 6], at least when compared to the heritability of other psychiatric disorders such as schizophrenia or bipolar disorder [7].

According to Linehan's biosocial model [8•], BPD develops in the context of both biological vulnerabilities and environmental risk factors. Impulsivity and emotion sensitivity are thought to be the two main products of biological risk, which then interact with the environment. In particular, individuals who go on to develop BPD are believed to be exposed to an invalidating familial environment. Linehan [9] associates three broad family types with increasing the likelihood of developing BPD: chaotic families, in which there is little time or attention for the child, perfect families, in which there is little tolerance of displays of negative emotion, and, less commonly, typical families, which may provide a poor fit for an emotionally sensitive and impulsive child. The result of this interaction, then, is that a child with a predisposition toward certain behavior develops more and more extreme patterns of dysfunction in an effort to cope with a difficult and invalidating environment. An enormous complication in explaining associations such as these is, of course, that children inherit both their genes and their environment from their parents: a chaotic family environment may be a marker for a set of genes that was transmitted from parents to offspring that leads both to chaos in the environment and increased risk of BPD.

As Kendler and Eaves [10] note, there are three major ways that genes and environment can jointly influence the

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overall vulnerability to psychopathology. First, an individual's liability for a disorder may be the sum of the contributions of genes and environment (the additive model). Second, genes and environment may interact, such that genes control the sensitivity to the environment or, alternatively, one can say the environment controls gene expression (the gene-environment interaction model; GxE). Third, genes and environment can be correlated such that genes influence environmental exposure (the gene-environment correlation model; rGE).

Given the emphasis of the biosocial model on the importance of the interaction of biological and environmental factors, gene-environment interaction (GxE) studies of BPD would seem to be particularly pertinent. In this case, models of GxE interactions posit that specific "susceptibility genes" to borderline personality disorder or major features of BPD may be expressed under certain environmental conditions or in response to certain adversities. Note that GxE does not simply reflect that both genes and environment are required for the expression of a trait or a disorder. An additive model such as the vulnerability threshold model (Fig. 1), which is often employed in genetic studies, also incorporates genes and environment, stating that risk of disorder increases with increased environmental exposure, so that in those who already score high on the vulnerability scale because of genetic reasons a small environmental insult may lead to disorder.

Since the publication of initial results from the influential Dunedin study [e.g., 11], there have been hundreds of publications examining the evidence for GxE effects in the manifestation of a range of psychopathology, with mixed results. There are two general types of GxE interaction studies: those that examine genetic influences modeled latently (i.e., examine the aggregate effects of genes rather than any one specific gene; behavior genetic studies) and those that focus specifically on measured genotypes (i.e., focusing on one specific gene of interest at a time) [12••]. Both approaches require large sample sizes–often much larger than those used in current research projects.

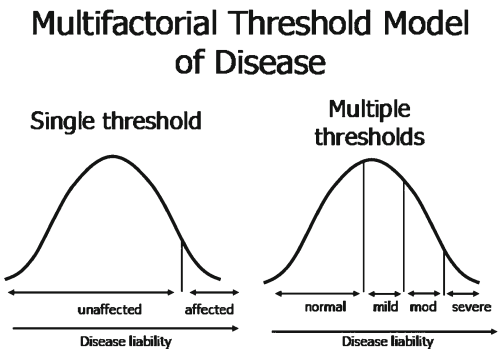


**Fig. 1** A threshold model [61] assumes a normally distributed liability (or vulnerability) underlying a disorder or an ordered-category trait. The left figure shows a single threshold model with subjects scoring below the threshold on the, unobserved, liability scale being unaffected and subjects scoring above the threshold being affected. The right figure shows a model with multiple thresholds. Individual differences in the liability distribution are a function of genetic and non-genetic differences between people. Tetrachoric (for binary data) or polychoric correlations (for ordered-category data) estimate the correlations between family members on such liability scales. A subject scoring high on the liability scale because of genetic vulnerability only would need a 'mild' environmental insult to cross the threshold whereas someone scoring low on the liability scale would need to experience a major environmental insult to cross the threshold

The current article reviews the existing literature on gene-environment studies in BPD. This, however, is still an area of emerging interest and, as such, there are relatively few studies available on the topic. Furthermore, as highlighted below, almost all existing studies we present here suffer from problems that ultimately prohibit any strong conclusions regarding evidence for GxE effects. As Boomsma and Martin [13] note, often the term GxE is used to indicate that genes and environment are important, rather than in the true statistical sense (i.e., demonstrating that different genotypes respond differently to the same environment or that some genotypes are more sensitive to environmental changes than others). In general, many studies purporting to find GxE effects on a phenotype are unable to do so definitely for one or more of the following reasons: (1) the number of participants is much too small to reliably detect GxE effects (effects which are notoriously small); (2) factors that are considered "environmental" may actually be under some degree of genetic influence (i.e., a gene-environment correlation); (3) "environments" are measured retrospectively and imprecisely; and (4) the inadequate scaling of environments (i.e., how these are quantified) can lead one to conclude that a GxE effect exists when in fact it does not [14].

As will become apparent, our position is that, to date, there is no empirical evidence yet supporting a gene-environment interaction (GxE) model of liability to borderline pathology. To begin, we review the literature of purported GxE interactions in domains relevant to BPD, focusing especially on domains highlighted by Crowell et al. [8•]: impulsivity and emotion sensitivity, but also suicidal behavior and anger and aggression. Next, we discuss the few studies that have focused on a borderline personality phenotype. Following this, we summarize the limitations of these studies and then make some recommendations for future work in this area.

## Impulsivity

There have been several gene-environment studies on impulsivity, primarily focusing on the DRD4 gene. Sheese et al. [15] and Keltikangas-Järvinen et al. [16] examined the relations between DRD4 and early childhood environment in the context of increased sensation seeking and novelty seeking, respectively, in young children. Lahti et al. [17] reported a

significant interaction effect of DRD4 and parental drunkenness on impulsivity. However, the sample sizes of all these studies were quite small, and larger studies that examined aggregate genetic effects have been mixed [18, 19].

Two more recent studies reported on purported GxE interactions for impulsivity. Sweitzer et al. [20] investigated an interaction between socioeconomic status (SES) and presence of the 7-repeat allele of the VNTR polymorphism of DRD4 on delay discounting, a behavioral measure of impulsivity. Using data from 546 middle-aged community volunteers, they found that individuals with the 7-repeat allele who were raised in lower SES environments discounted future rewards more steeply than individuals without the allele, while individuals with the allele but who were raised in a high SES environment discounted less steeply than individuals without the allele. Reif et al. [21] examined the interaction between NOS1 ex1f-VNTR and stressful life events (e.g., poor health, parental alcoholism, suicide attempt) on impulsivity. NOS1 is a gene that is linked to the serotonergic system and has been previously found to be associated with impulsivity in animal studies [22]. Additionally, previous findings linked the presence of homozygous short-short (s/s) genotype with Cluster B personality disorders [23]. They used data from a longitudinal sample of 435 Estonian students, collecting multiple measures of impulsivity. Both stressful life events (SLEs) and an adverse family environment interacted with s/s genotype to lead to increased scores on all measures of impulsivity. However, it should be recognized that their results were found primarily for males only. As noted by Patsopoulos et al. [24], in a systematic appraisal of 432 sex-difference claims from 77 studies, findings that pertain to only one sex tend to be insufficiently documented or spurious. Claims with documented good internal and external validity are uncommon and rarely based on a priori, clearly defined, and adequately powered subgroup analyses.

## Emotion Sensitivity

Fewer gene-environment studies have directly examined emotion sensitivity. However, several have reported gene-environment interactions predicting increased negative affect [25, 26], and decreased positive affect [27]. Sugden et al. [28] reported that children with the s/s genotype of 5-HTTLPR were more likely to develop emotional problems following bullying. The s-allele of the 5-HTTLPR gene is related to greater amygdala activity (an area of the brain associated with attention and emotion processing) in response to emotional cues. Therefore, the authors argued that these findings support the idea of genetic vulnerabilities that leave emotions more susceptible to environmental influence (i.e., heightened emotional sensitivity). There have been attempts to examine components of emotion sensitivity directly, as well. For example, Hayden et al. [29] found that children with the s/s genotype of 5-HTTLPR were more likely to engage in negative schematic processing following a negative mood induction. Negative schematic processing was measured by the likelihood of participants ascribing negative adjectives to themselves. However, their sample included only 39 participants.

More recently, Gibb et al. [30] investigated the effects of 5-HTTLPR and maternal criticism on children's attentional biases toward emotional information. Participants consisted of 74 mother-child pairs. Approximately half of the mothers had a history of major depressive disorder ($n$=40). Maternal criticism was operationalized as the level of expressed emotion criticism during a five minute speech made by the mother about the child. To assess attentional bias, children participated in a dot-probe task involving facial expression. There was a significant three-way interaction between child 5HTTLPR gene, maternal criticism, and facial expression. Children with the s-allele who experienced maternal criticism showed an attentional avoidance toward angry, but not sad or happy, facial expression.

Related to emotion sensitivity is the concept of distress intolerance, or the inability to continue goal-directed behavior while experiencing negative affect [31]. Distress intolerance is linked both theoretically and empirically to BPD [9, 32]. Amstadter et al. [33] examined the effects of 5-HTTLPR l/s and COMT Val158Met and emotional abuse on distress intolerance in a sample of 218 adolescents. Distress intolerance was measured by (lack of) persistence on an aversive behavioral task. They found that both the s-allele of 5-HTTLPR and the Val allele of COMT predicted poorer performance on the behavioral task. The effect for 5-HTTLPR was moderated by emotional abuse, such that individuals with the s-allele and a history of emotional abuse showed more distress intolerance.

## Suicidal Behavior

Recurrent suicidal behavior is one of the DSM-IV symptoms for BPD. It is estimated that one in ten BPD patients completes suicide [34], 60 - 70 % make at least one attempt [35], and the incidence of suicidal ideation and threats is higher still [36]. There is good evidence that suicide ideation, suicide attempts, and suicide completion are genetically influenced [37, 38]. Three recent gene-environment studies have investigated suicidal behavior.

Perroud et al. [39] examined the interaction of childhood physical and sexual abuse and the BDNF $Val^{66}Met$ polymorphism on 813 suicide attempters. Suicide attempts were categorized as violent (hanging, use of firearms or knives, throwing oneself under a train, and jumping from heights) or nonviolent (drug intake and superficial wrist cutting). Childhood sexual abuse, but not physical abuse or neglect, was

associated with violent suicide attempts in Val/Val individuals. All measures of maltreatment, with the exception of physical neglect, predicted an increased number of suicide attempts and a younger age of suicide attempt.

Ben-Efraim et al. [40] investigated an interaction between single nucleotide polymorphisms (SNPs) in corticotrophin-releasing hormone receptor-1 (CRHR1), associated with hypothalmic-pituitary-adrenal (HPA) axis functioning and physical assault, rape, and cumulative stressful life events (SLE) on suicide attempts. The authors focused on the HPA axis because of its role in cortisol release as a result of stress and they focused on the CRHR1 gene in particular because previous studies indicated a relationship between childhood maltreatment and dexamethasone non-suppression [41, 42], a partial predictor of suicide attempt [43, 44]. They found that rs4792887 interacted with cumulative SLEs to predict suicide attempt in males, rs7209436 interacted with physical assault during childhood or adolescence to predict suicide attempts among females, and rs16940665 interacted with physical assault in adulthood to predict attempted suicide among males. These latter two SNPs were also associated with increased anger and aggression.

## Aggression and Anger

Although BPD is generally associated with negative affect [45], anger is singled out in particular by DSM-IV, citing 'inappropriate, intense anger or difficulty controlling anger' as a symptom of BPD. Although internalized anger is sufficient to meet this criterion, individuals with BPD may also engage in aggressive behavior. The area of anger and aggression has been the topic of a number of gene-environment studies.

Simons et al. [46] found, in a sample of 689 African-Americans, that the l-allele of DRD4 and the s-allele of 5-HTTLPR both increased aggression in the presence of an adverse environment, but led to decreased aggression in a supportive one. McDermott et al. [47] found that individuals with the low activity (l-) allele for the monamine oxidase A (MAOA) gene were more aggressive than those with the high activity (h-) allele when proximally provoked. However, their sample consisted of only 78 male participants.

Three recent studies have examined aggression and anger expression in psychiatric patients. Frazzetto et al. [48] examined the interaction of early SLEs and the MAOA gene on adult violent and aggressive behavior in a combined sample of 235 healthy volunteers and 90 psychiatric outpatients. Thirty-four percent of adults endorsed one or more early SLEs, although psychiatric outpatients were more likely to be exposed to a traumatic event than healthy controls. Individuals exposed to early traumatic events were more likely to exhibit aggression. Kinnally et al. [49] found l-MAOA was a risk factor for antisocial behavior among women. Female participants, either healthy controls or diagnosed with MDD or bipolar disorder, ($n$=159; 12.6 % with a diagnosis of BPD) reported retrospectively on the presence of early SLEs and on parental bonding with the parent that they spent the most time with. A three-way interaction was evident such that l-MAOA, low parental care, and early stress interacted to predict higher impulsivity and aggression scores on self-report measures.

Using the same sample as Perroud et al. [39] described above, Perroud et al. [50] investigated nine candidate genes for an interaction with CSA on anger expression in 875 adult suicide attempters. These genes included COMT, TPH1, MAOA, 5-HTR1B, 5-HTR2A, TPH2, 5-HTR1A, BDNF and 5-HTTLPR. Interaction-level effects were found only for COMT Val$^{158}$Met. A three-way interaction between gender, COMT Val$^{158}$Met, and CSA was found, such that presence of the Val allele and CSA predicted increased levels of self-reported anger. There was also a main effect for COMT Val$^{158}$Met, with presence of the Val allele predicting higher scores of self-reported anger.

## BPD Studies

We now turn to the small group of studies that examined gene-environment effects within a BPD sample or focused on GxE on a borderline personality phenotype [see 51••]. Of the existing gene-environment studies of BPD, only two treated BPD features as a dependent variable. The remainder, consisting of a series of studies by Wagner and colleagues, tested for the presence of an interaction on personality traits relevant to BPD in BPD samples. In these studies, they tested whether a history of SLEs (i.e., physical maltreatment, rape, and CSA) interacted with gene polymorphisms believed to be involved in serotonergic (e.g., 5-HTTPLR ss/sl, BDNF Val$^{66}$Met) and dopaminergic (e.g., COMT Val$^{158}$Met) functioning to produce aggression and/or impulsivity. Wagner et al. [52] tested the interaction of SLEs and the 5-HTTPLR ss/sl polymorphism on impulsivity as measured by an impulsivity questionnaire in individuals with BPD. They found that presence of CSA and self-report of functional impairment by SLEs both predicted lower impulsivity scores. These effects were specific to ss/sl carriers. Additionally they found that, in ss/sl carriers, physical maltreatment and number of SLEs predicted lower impulsivity scores. Using the same sample, Wagner et al. [53] tested an interaction of SLEs and the BDNF Val$^{66}$Met polymorphism on impulsive aggression in BPD individuals. Presence of childhood CSA was associated with lower levels of impulsive aggression and this effect was found to be specific to BDNF Val$^{66}$Val carriers.

Again using the same sample, Wagner et al. [54] examined the role of SLEs and COMT Val$^{158}$Met on BIS scores and found no effect. However, Wagner and colleagues published another study around the same time reporting significant results relating COMT Val$^{158}$Met to impulsive aggression in individuals with BPD [55]. In Val$^{158}$Val carriers, presence of

CSA and the cumulative number of SLEs were associated with decreased scores of impulsive aggression. There was also a main effect in the same direction for CSA on impulsive aggression.

An initial study by Wilson et al. [56] found that polymorphisms in the tryptophan hydroxylase I (TPH1) gene were significantly associated with a diagnosis of BPD but not with a history of suicide attempt(s). In a follow-up study, Wilson et al. [57] tested whether the strength of the association between childhood abuse and BPD was moderated by TPH1 polymorphisms. Specifically, 98 BPD patients and 300 non-BPD patients with either major depressive disorder or bipolar disorder were genotyped, and childhood abuse was assessed via direct interview. Results indicated that TPH1 risk allele carriers (A alleles at both loci) were significantly more likely to be in the BPD diagnostic group. Furthermore, TPH1 polymorphisms significantly moderated the strength of the association between childhood abuse and BPD status as an adult. These latter results were independent of Axis I status and a history of suicide attempt(s).

In the only study to date to study the role of gene-environment interactions and gene-environment correlations (rGE) on the etiology of BPD traits, Distel et al. [51••] analyzed data from twin and sibling pairs from the Netherlands and Belgium ($n$=6368). Previously, this research team demonstrated that the heritability estimates of BPD features were similar across three countries (approximately 42 % [5]), and relations among the four major components of BPD (affective instability, identity problems, negative relationships, and self-harm/impulsivity) were best explained by a common genetic pathway model. This latter finding indicates that both genetic and environmental factors influence these four major features through the same mechanism.

In the follow-up study, focusing specifically on gene-environment interactions and gene-environment correlations in this sample, Distel et al. [51••] analyzed twins' and non-twin siblings' self-reported symptoms of BPD, using the Personality Assessment Inventory-Borderline Scale (PAI-BOR) [58], and their reported experience of SLEs (i.e., divorce, car accident, assault, robbery, and job loss). In addition to evaluating evidence for gene-environment interactions (GxE), the investigators also estimated rGE, or the correlation between the genetic influence on environmental risk factors and the genetic influence on BPD traits. To limit the chance of spurious findings, two measures of rGE were used: a bivariate genetic model and a co-twin control method.

Car accidents and robberies were not significantly moderating factors and were dropped from the models. Divorce/break-up, violent assault, and job loss did not moderate the effect between genetic risk and BPD traits, but did moderate positively the effect of unique environment. Individuals with a higher number of stressful life events had lower heritability rates of BPD traits, although this was not significant. Finally, sexual assault was a significant negative moderator of genetic risk in predicting BPD traits. In fact, when sexual assault was accounted for, the impact of genes became negligible. Importantly, the authors also found significant rGE for most of the life events, suggesting that genes that are responsible for BPD risk increase risk of exposure to stressful life events.

## Conclusion

As we discussed at the beginning of this review, GxE studies are often plagued with methodological and statistical problems and most of the studies we reviewed suffer from these limitations. The ability to accurately and precisely discover and characterize a non-spurious GxE interaction effect on the liability to psychopathology is a function of many research design features. As can be seen in our review, most current studies are based on a small number of participants and do not include replication samples, may use imprecise measurements of environment (e.g., single indices based on retrospective self-report), do not address the possibility of spurious interaction effects due to improper scaling of the environment and the uncritical use of logistic regression, and do not assess for rGE effects. As is true in other areas of psychopathology, these design flaws likely conspire such that replications of any reported GxE interactions for borderline personality or its features will likely be more the exception than the rule.

So, what can be concluded from our review? At present, it appears that rGEs are especially relevant to borderline personality. Specifically, evidence suggests significant rGE for divorce/break-up, violent assault, sexual assault, and job loss and borderline personality [51••]; the genes influencing borderline features increase the likelihood of being exposed to these adverse life events. However, it is not possible to determine the direction of causality. In the Distel et al. [51••] study, there was evidence for GxE effects as well. However, given the findings of a rGE for these same events, it seems most appropriate to conceptualize this as evidence for shared genetic influence with these events on borderline personality.

We recommend that future studies of GxE interactions in BPD be guided first by well-designed, large twin and family studies that assess the aggregate effects of genes. Second, in order to reliably characterize a GxE interaction effect, it is necessary to use very large samples. Our review indicates that almost all existing studies in this area of research were based on very small samples, making replication less likely. Third, it is necessary to also evaluate rGE effects, and a failure to do so could lead to erroneous conclusions about a GxE effect [59]. Fourth, there is a great need for improved measures of environmental influences. Moffitt et al. [60] recommend that measurement of environmental stress or adversity be prospective, cumulative, and proximal in order to adequately characterize environmental risk for psychopathology in GxE studies.

We would add that investigators must pay particular attention to how environmental measures are scaled, given the demonstrations that improper scaling and transformation can lead to false conclusions regarding GxE effects in many cases [14]. Finally, in GxE studies that include measured genotypes, the genes that were considered include a relatively small range of candidate genes, whose status as risk factors for BPD is uncertain. There are no large scale genome wide association (GWA) studies yet for BPD which can supply genetic variants to be tested in a GxE context. The next generation of gene-environment studies of BPD should address the limitations of previous studies, adopt optimal research design strategies to uncover GxE interaction and address gene-environment correlation effects.

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- • Of importance
- •• Of major importance


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