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Gene-Environment Interaction And Borderline Personality Disorder

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GENE-ENVIRONMENT INTERACTION AND BORDERLINE PERSONALITY DISORDER

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To my parents and friends,
for all the guidance through the storms.

GENE-ENVIRONMENT INTERACTION AND BORDERLINE PERSONALITY DISORDER

ABSTRACT

Borderline Personality Disorder is a commonly diagnosed personality disorder characterized by marked emotional dysregulation, and is associated with impairments in self-functioning and interpersonal relationships. With a high mortality rate and elevated healthcare costs, this disorder has been the subject of numerous investigations in the past few years, namely concerning its etiology and development. It is somewhat established that borderline personality traits have a hereditary component of transmission, and genes involved in the serotoninergic and glutamatergic neurotransmission systems, as well as in the hypothalamic-pituitary axis, have been implicated in the disorder. On the other hand, environmental influences such as history of childhood abuse, neglect, trauma, and sociocultural variables have also been suggested to play a part in its etiology. Recent research has pointed to possible interactions between the genetic and environmental fields, either by additive effects or by modulating one another. This work intends to review the studies published in the last few years concerning this area, and to point possible directions for future research.

KEYWORDS: borderline personality disorder; gene-environment interaction; genetic predisposition to disease; environment; risk factors

INTRODUCTION

Over the last few years, there has been some controversy as to whether the diagnosis of a personality disorder (PD) should be based on categorical or dimensional criteria. A strong argument in favor of the latter is the absence, to date, of a non-arbitrary cut-off point on the continuum between normal and extreme positions on behavior dimensions.[1] The new Diagnostic and Statistical Manual of Mental Disorders (DSM-5), although retaining the categorical approach of its predecessor, also includes an alternative hybrid dimensional-categorical model for diagnosis of personality disorders in a separate chapter. The manual defines the essential features of a PD as "an impairment in self and interpersonal functioning" associated with "pathological personality traits", translating into a pattern of behavior not better understood as socially normative and which is stable across time and situations.[2]

With this in mind, Paris and Lis describe personality disorders as arising from a combination of trait vulnerability, individual experiences and social expectations. [3] However, an unusual trait profile does not necessarily mean that symptoms will develop: a key aspect of personality disorders is poor adaptation to the surrounding environment. Maladaptation can either be the outcome of a pattern of extreme, intransigent behaviors, the result of harmful environmental influences – or even an association of both.[1]

According to traditional personality theory, an individual's personality becomes somewhat stable after reaching adulthood[4], but the features that shape it may come into play before that, with early relationships serving often as a template for long-term patterns of interpersonal and adaptive (or maladaptive) behaviors.[5] A model for the development of personality disorders suggests a possible interplay between inherited

vulnerability (as expressed by personality traits) and environmental factors such as childhood abuse and neglect.[6] Social factors like family and school environment, as we will discuss later in this paper, may also exert some influence in the process.

Of all the personality disorders, Borderline Personality Disorder (BPD) stands out among the rest. With a prevalence of 1-2% in the general population, up to 10% in psychiatric outpatients and 20% in psychiatric inpatients, BPD is the most commonly diagnosed PD[7], and individuals affected by the disorder require more healthcare resources than patients with other psychiatric diagnoses.[8] According to DSM-5, the core features of BPD include an impairment of self-image or lack of self-direction, unstable and intense interpersonal relationships, and personality traits characterized by negative affectivity, antagonism, and impulsive or risk-taking behaviors.[2] Mortality among BPD patients is high because of suicide and impulsive behavior; up to 10% of BPD patients commit suicide, a percentage nearly 50 times higher than in the general population.[9] It is more frequently diagnosed in women than in men[7] and it has a substantial comorbidity with substance abuse, mood disorders, anxiety disorders, and other PDs.[10]

As other personality disorders, BPD is assumed to be the outcome of complex interactions between genetic, neurobiological and environmental factors, and a good example of the connection between the biological and psychosocial areas.[6,11] There appears to be a familial component of transmission, with estimates of hereditability around 42%[12] and a higher risk of development in relatives of BPD or major depression patients.[13,14] This genetic predisposition has been hypothesized as translating disturbances in the serotoninergic, glucocorticoid and/or glutamate neurotransmission systems.[10,11,15] On the other hand, BPD patients have been notably associated with a

childhood experience of abuse, neglect, environmental instability, poor parental care and parental psychopathology.[16,17]

The connection between these two fields has been recently discussed in the literature. Perroud *et al.* have hypothesized that long-term epigenetic changes may result from childhood abuse and neglect[18], possibly mediating the transition to psychopathology later in life. Linehan's biosocial model describes impulsivity and emotional vulnerability as biological risk factors for the child to develop BPD, which may then interact with an invalidating familial environment to develop and perpetuate a pattern of emotional dysregulation. A child with a tendency toward certain behavior, as an effort to deal with a difficult environment, develops more and more extreme patterns of dysfunction.[19]

Whether or not the genetic inheritance is sufficient to develop BPD independently of childhood conditions, or vice-versa, is still an area of debate. This work reviews the state of the art in genetic and environmental contributions to BPD etiology, as well as possible interactions between the two grounds.

METHODS

The purpose of this work was to evaluate the genetic and environmental influence in the etiology of Borderline Personality Disorder. To do so, I resorted to the US National Library of Medicine's PubMed database using Thomson Reuters' Endnote X7 software. A search was conducted for all articles published in 2000 or after which included the following combinations of terms in their abstracts: "gene environment personality disorders", "borderline personality gene" and "borderline personality environment". Additionally, I also searched for articles that included the combination of

words “gene environment personality” in the title. In total, 37 articles were collected using this method. Upon reading of the abstracts, 9 of these articles were excluded: 3 because they were in a language other than English, and 6 because they did not seem related to the work. The remaining 28 articles were included based on their relevance.

After reading the selected articles I was able to detect a number of works that were either consistently quoted or potentially important to my work. As such, an additional 19 articles were included in the study, regardless of publication date.

In total, 47 articles were reviewed for this work.

HERITABILITY: THE GENETIC INFLUENCE IN BORDERLINE PERSONALITY DISORDER

The amount of phenotypic differences between individuals in a specific population that can be due to genetic dissimilarities is called heritability. In the classical twin model, the total variance in a phenotype is divided into additive genetic influence, shared environment and non-shared (i.e., individual-specific) environment.[20] Personality traits have been reported as being influenced by genetic factors, with heritability estimates of approximately 42%.[12] Genetic effects in personality are mainly additive, with different alleles or loci acting in an additive way to increase the risk for a disorder or trait. However, non-additive contributions have also been demonstrated, with alleles interacting with other alleles in the same locus (dominance) or in other loci (epistasis). Shared environment includes all environmental circumstances or exposures that contribute to similarity between twins, and is usually found to be of minor importance in personality.[20] Non-shared environment is what makes the twins different, and will be discussed elsewhere in this work.

While the model of genetic interactions in personality development may seem complex, the case of BPD might be even more so. Distel *et al.* showed that although BPD features are genetic in origin and influenced by the same genes in different ages, they are only partly transmitted to offspring because they require combinations with other genes in order to develop BPD, and these combinations may not be shared by parents and their children.[21]

A number of neurotransmitters and systems have been suggested to play a role in BPD etiology, including serotonin, glutamate and the hypothalamic-pituitary axis (HPA).[10,11,15,22,23] Of these, serotonin (5-HT) is the one whose involvement is more extensively documented. The exact dysfunction is nevertheless still elusive, with polymorphisms of a number of genes responsible for different steps in 5-HT metabolism and signaling cascade being found in BPD patients.

One of them is the serotonin transporter (5-HTT) gene. The 5-HTT gene-linked polymorphic region (5-HTTLPR) is one of the most commonly used polymorphic markers, with a short (s) allele associated with reduced transcriptional efficiency when compared to the long (l) variant. This leads to a decline in 5-HT reuptake in the presynaptic neuron and may be involved in emotional dysregulation.[24]

Ni *et al.* tested the association between variants of the 5-HTT gene and BPD in 89 Caucasian BPD patients and 269 Caucasian healthy controls. The group used the 5-HTTLPR and another marker, the intron 2 variable number of tandem repeats (VNTR). It is speculated that VNTR may play a role as a transcriptional enhancer of the 5-HTT gene with particular importance in brain development and synaptic plasticity, and the 10-repeat acts as a weaker enhancer than the 12-repeat.[15,25] They reported a higher frequency of the 10-repeat VNTR haplotype, a lower frequency of the 12-repeat and a higher genotype frequency with 10-repeat in BPD patients when compared to healthy

controls.[15] While they did not find a strong association between 5-HTTLPR and BPD, their results supported a possible combined effect of VNTR and 5-HTTLPR in 5-HT gene expression.[15] In 2008, Pascual *et al.* failed to replicate this finding, but it is pertinent to mention that, although the controls had no history of psychiatric illness, they were not screened to exclude BPD.[26] In 2011, Blom *et al.* studied the relationship between the two 5-HTTLPR alleles and personality disorder traits, and they also did not find a significant association between 5-HTTLPR and BPD.[27]

Another study found an association between the short (s) allele and BPD and antisocial personality disorder (APD) traits. With the results of Ni *et al.* in mind, the authors theorized that the 5-HTTLPR s-allele may be responsible for a broader endophenotype for impulsive, self-damaging and other-damaging behaviors, common to both borderline and antisocial personality disorders.[28]

The proposal that 5-HTTLPR does not play an independent role in BPD etiology but may be involved in gene-gene interactions is supported by Tadic and associates. The group studied the role of 5-HTT and catechol-O-methyl transferase (COMT) in BPD etiology, using 5-HTTLPR and a COMT functional single-nucleotide polymorphism (SNP Val158Met). The results revealed no significant difference in s/l genotype distribution between BPD patients and controls, but there was a significant gene-gene interaction between the short allele for 5-HTTLPR and COMT Met158, increasing susceptibility for BPD.[29]

While these studies were conducted using adult samples, Hankin *et al.* tested if the association of 5-HTTLPR and BPD traits could also be found in youth. The results indicated that children and adolescents carrying one or two copies of the s-allele of 5-HTTLPR displayed higher levels of BPD traits. Moreover, discriminant validity analyses

revealed that 5-HTTLPR was linked specifically with BPD traits but not with depressive symptoms, often found overlapping with BPD traits.[30]

Other genes presumably involved in BPD etiology include the 5-HT receptor (5-HTR), monoamine oxidase (MAO), tryptophan hydroxylase (TPH) and the already mentioned COMT genes. COMT and MAO are enzymes involved in dopamine and noradrenergic metabolism, and TPH is involved in serotonin synthesis.[6,29]

A study from Dammann *et al.* found that BPD patients had increased methylation levels for serotonin 2A receptor (5-HTR2A), glucocorticoid NR3C1 receptor, soluble COMT, MAO-A and MAO-B genes in peripheral blood samples. It is unknown, however, whether the same pattern of methylation in these genes is found in other tissues (e.g. brain).[10]

Other studies have failed to find an association between 5-HTR2A and BPD diagnosis[22,31], but Ni *et al.* found an association between 5-HTR2A and BPD personality traits.[22] While another variant of the 5-HT receptor, 5-HTR1B, has reportedly no association with BPD[23,31], the 5-HTR2C variant is presumably involved in gene-gene interactions with the TPH2, MAO-A and 5-HTT genes, resulting in an increased risk for BPD.[31]

Finally, in addition to the epistatic effect reported for the COMT gene, the Met158 polymorphism also has an independent association with BPD, which suggests a role of dopaminergic and/or noradrenergic neurotransmission dysfunction in the etiology of the disorder.[29]

In conclusion, although many genes seem to be involved in the development of borderline personality disorder, the exact mechanism is not yet known. As it appears, BPD arises as the outcome of a complex network of genetic interactions that do not

remain unchanged in the face of different environmental influences, as we will discuss in another section.

LIFE EXPERIENCES: THE ENVIRONMENTAL INFLUENCE IN BORDERLINE PERSONALITY DISORDER

Emotions are a fundamental part in attachment relations. If emotional disturbances are present, as is the case in BPD, they can exert an influence in relationships throughout life. Emotional and affective expression in adulthood may be shaped by early social experiences, with relationships with parents or caretakers serving as a model for future interpersonal exchanges.[5] For instance, good maternal care in childhood was associated with high self-esteem, decreased trait anxiety and decreased salivary cortisol in response to stress in a sample of college students.[32]

On the other hand, the environment outside the home is also important in personality development: a study from 2009 found a relationship between adolescent school climate and PD traits. Specifically, cluster B symptoms were less present in students of schools with higher learning focus.[33] The authors speculate that the demands and structure of such schools would suppress the impulsive and rule-breaking behaviors that are characteristic of cluster B PDs. Considering that BPD matures during adolescence[34], it is easy to believe that young people who are at risk for the disorder (for instance, because of emotional vulnerability) are more likely to express symptoms under conditions of low social cohesion or instability during this period.[3] Accordingly, when Wang *et al.* screened traits from cluster A and cluster B personality disorders in high school students, they found that students from remarried families or with a low subjective perception of social status had higher borderline scores.[4] This underlines the

importance of a well-defined role in the community, a good social support and a stable family environment in tempering individual susceptibility to BPD. A good network of role models or parental surrogates and supportive community institutions can provide the basis for the child to deal with the impact of adverse parent-child relationships and familial pathology.[16]

Another important factor in BPD etiology appears to be the exposure to serious life events (SLEs). In fact, life experiences seem to play an important part in the development of BPD, with unique environmental influences being responsible for 54,9% of the variance in borderline personality in a study of 2009.[21] Several SLEs have been related to BPD, such as abuse, parent loss or separation, family conflict or familial psychopathology, or having a complicated/unusual illness during childhood.[16,35,36] While studies have been discordant about the real effect of some of these events in BPD, a consensus seems to exist when it comes to factors like neglect, childhood abuse and trauma.[6,16,36,37] Moreover, the severity of abuse appears to correlate with the severity of BPD symptoms.[38]

How these environmental stressors exert their influence on behavior and personality traits is still a question, and a number of possible explanations have been proposed. Molina *et al.* speculate that some BPD traits, depending on the context, can be viewed as adaptive or at least as having the purpose of acting as such.[5] For example, as impulsive strategies can be useful if survival depends on a quick response (e.g. in war), some disruptive traits may have had a useful short-term function in helping patients managing environmental adversity or obtaining social aid. However, over time or in a context where the adverse element no longer exists, they prove themselves maladaptive.[5] Another study states that the cognitive mechanism of thought suppression, often used by victims of abuse to try to deal with unpleasant memories,

may actually exacerbate BPD traits and contribute to the development of symptoms.[39] On the other hand, a majority of studies consider that environmental stressors do not act alone in increasing the risk for BPD, and instead interact with the genome in producing this vulnerability. In the last few years this theory has been discussed and tested using specific genes and SLEs, as we review in the following section.

MODULATION AND SYNERGY: HOW GENES AND ENVIRONMENT CAN RELATE IN BORDERLINE PERSONALITY DISORDER

There are three possible ways genes and environment can influence the susceptibility to psychopathology: by way of additive effects of both genetic and environmental factors, with genes controlling the sensitivity to the environment, or with genes controlling the exposure to the environment.[40]

In the additive model, the individual's vulnerability to a disorder is the sum of genetic and environmental influences. One example is the vulnerability threshold model, in which the risk for psychopathology (as defined by inherited susceptibility) increases with increased exposure to certain environmental aggressors.[6,41] If an individual is already vulnerable for a condition because of genetic factors, even a small environmental insult may be sufficient for its development.[41]

If the sensibility to the environment depends on the genetic background, we can assume that the environment wields an effect on gene expression, with specific "susceptibility genes" for a disorder being expressed under certain conditions or in response to certain life events.[1,41] The diathesis-stress model, which postulates that environmental stressors ("stress") contribute to BPD symptoms and traits only in the context of emotional and behavioral vulnerability ("diathesis"), fits in this

description.[19,39] This model implies that a specific situation may have a bigger or smaller impact on the individual depending on his or her genotype.[17]

Finally, if genetic background and life experiences are somehow correlated, this means that life experiences are determined by genetic endowment. In other words, an individual creates his or her own life experiences according to his genetic context and predisposition.[17] For instance, a child who shares a predisposition to negative affectivity with his or her parents is also more likely to be nurtured in a hostile and abusive family setting. This can either be due to their shared background or because the child's genetic tendency to disinhibition elicits an aggressive response by his or her parents.[37]

Recent research has tried to clarify this relationship. It has been suggested that epigenetic mechanisms (e.g. methylation of gene promoters) are involved in determining resistance to stress and personality traits.[1] It is interesting to observe that monozygotic twins share similar degrees of DNA methylation in an early age, but differ significantly later in life[42], and we can speculate that this discrepancy is due to non-shared experiences.

In line with the epigenetic proposition, Perroud *et al.* found an increased methylation of the glucocorticoid NR3C1 receptor gene promoter in BPD patients exposed to abuse or neglect during childhood. The degree of promoter methylation was also significantly correlated with severity or repetitions of abuse.[18] Curiously, both this work and another by Dammann *et al.*[10] found an increased level of NR3C1 methylation in BPD patients with no history of abuse. These findings are in line with the hypothesis of a relationship between childhood abuse and BPD being mediated by common genetic and environmental factors, as described by Bornovalova and associates.[37]

Grosjean *et al.* suggested that NMDA neurotransmission may also be implicated in the neurobiological consequences of environmental stressors. The NMDA pathway,

particularly important in brain development and neuroplasticity, is activated by stress hormones and can have a neurotoxic effect on brain cells. Neuronal damage may vary according to the intensity, duration and type of stress, and NMDA-induced neuroplasticity might be a key factor in susceptibility to traumatic events, as it modifies the neurotransmission threshold level concerning the physiological response to stress.[11]

A study from Tadic *et al.*, already mentioned in this article, found that the short allele of the 5-HTTLPR, in addition to being involved in an interaction with the COMT gene, also appears to have a moderating effect on other susceptibility factors for BPD like SLEs.[29] There is also some indirect evidence supporting this effect of 5-HTTLPR: one study found an association between the s/s genotype and the development of emotional problems after experiencing bullying[43], and another found an additive effect of the s-allele and emotional abuse in distress intolerance.[44] As we saw, emotional dysregulation is one of the features of BPD[19], and distress intolerance has been associated with this disorder in the past.[45]

Wilson *et al.* also found that the A allele of the TPH1 gene, besides being more prevalent in BPD patients, significantly moderated the association between childhood abuse and BPD as an adult, with more severe abuse rendering a higher risk for the disorder.[38] Furthermore, the increasing severity of the abuse also influenced the severity of the disorder, as indicated by the number of DSM-IV criteria met for BPD.

Other genes have also been reported interacting with environmental factors in the development of BPD features or traits. The short/short genotype for NOS1, a gene linked to the serotoninergic system[41], interacted with adverse family environment and SLEs increase impulsivity scores in males.[46] Also, the dopamine D4 receptor gene (DRD4) interacted with socioeconomic status in determining the expression of delay

discounting, a behavioral endophenotype of impulsive decision-making.[47] Finally, the correlation between SLEs and suicide, a behavior frequently seen in BPD patients, is reportedly mediated by genes involved in the HPA and in the 5-HT signaling system.[48,49]

With this in mind, we can state it is a commonly held view that genetic liability, early life stress and ongoing stress define individual responsiveness to life events and therefore the risk for BPD.[11] As discussed, when studying specific genes implicated in BPD etiology, variable patterns of expression can be found depending on the exposure to certain stressors or SLEs. When it comes to addressing the question of causality, however, the results to date are still uncertain.[16,41]

DISCUSSION

Reviewing the available research, we can establish that borderline personality disorder, in its etiology, encompasses a multitude of different factors. First we have the genetic inheritance of the individual, rendering him or her with a low or high susceptibility to psychopathology. Then, during childhood and adolescence, the potential triggers to a disruptive pattern of behavior and emotional dysregulation, such as traumatic events or abuse. The interface between the two can be one of interdependence, mutual regulation, or something of a slippery slope with the addition of multiple vulnerabilities. The behavior pattern of the BPD individual may be interpreted as a reaction to certain environmental stressors that, over time, has proven troublesome and maladaptive[5], but that nonetheless depend on genetic predisposition.[19]

As pointed by Torgersen, it is interesting to consider that both the genes and the environment are part of an inheritance from the parents to the offspring: the same set of

genes can be responsible for the emotional susceptibility of the individual and, if present in the parents as well, also for the invalidating environment that then creates a chaotic family dynamic. The mystery resides in the question of what is the cause and what is the consequence: either BPD emerges as a product of childhood maltreatment, or the maltreatment itself is the result of malfunctioning personality traits present both in the child and her parents. These traits correlate with poor parenting and, if genetically mediated, can explain the emotional liability present in the child.[17]

The relationship between BPD and traumatic personal experiences underlines the importance of psychotherapy in the approach of the patient, with emotional regulation strategies being helpful in maintaining functioning and reducing distress.[39] On the other hand, its social sensibility also points out the significance of sociotherapy.[3] As discussed, a well-structured social context can help the individual in coping with personal disadvantages and adverse environments, especially in the presence of an unstable family context.[16]

This work has a few limitations that should be addressed. First, the search conducted used terms contained in the abstracts and not MeSH terms. This is both a limitation and a strength, because if on one hand it may have precluded some articles without specific words in the abstract (but with the correct MeSH term) from the study, it also assured that studies regarding borderline personality traits and associated features, and not necessarily the disorder, could be included. Second, by limiting the initial search to works published in the year 2000 or after, there may have been important research that was not included merely because of the published date. Although there was an attempt to include such works on the second research stage (after reading the first 28 articles and identifying frequently quoted works), there is no guarantee as to whether there was any vital information lost in the process. A possible

strength should also be mentioned: because of the search for articles including "gene environment personality disorders" in the abstract and "gene environment personality" in the title, works regarding more than one PD could also be included. For this reason, I was able to retrieve important information about possible endophenotypes encompassing not only BPD but also other disorders.

Torgersen stated that the only safe way to infer about gene-environment interactions is by having experimental control over the environment.[17] Future investigations in this field should be performed using twin and family studies with large samples so as to increase statistical power, and preferably controlling for possible environmental confounding factors. Longitudinal studies are preferred to cross-sectional studies in order to safely state causality, and community samples are favored because of the known social sensitivity of BPD. Finally, clinical interviews are the ideal method to assess BPD scores, and special attention must be paid to potential informant biases regarding past events such as childhood abuse, neglect or trauma.

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