ARTICLE

Is Epigenetic Stress the Link Between Childhood Maltreatment and Borderline Personality Disorder?

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Borderline personality disorder will affect approximately 18 million Americans in their lifetime (1). The 12-month prevalence of borderline personality disorder in the United States is 1.6% (2). Roy R. Grinker introduced borderline personality disorder to the academic community in the 1960s, with the first effort to define the syndrome, while Otto Kernberg wrote a series of papers introducing "borderline personality organization" and its treatment to the psychoanalytic community (3, 4). The *DSM-5* defines borderline personality disorder as "a pattern of instability in interpersonal relationships, self-image, and affects, and marked impulsivity" (5).

There are multiple studies that indicate that childhood maltreatment, specifically sexual abuse, is both commonly reported in and strongly associated with borderline personality disorder, with symptoms of the personality disorder, such as derealization or dysphoria, predictive of childhood abuse (6–8). Some speculate that this may just be bias in recall, dependent on the population sampled and its retrospective nature, or whether the child's difficult temperament led to some form of neglect (9). However, Johnson and colleagues (10) found that individuals with a history of childhood physical abuse, sexual abuse, or neglect were four times as likely to have a personality disorder in early adulthood compared with individuals who did not, even when difficult temperament, parental education, and mental health were controlled for. They further suggested that sexual abuse was "associated with elevated borderline [personality disorder] symptoms" (10). Childhood maltreatment, maladaptive parenting, and biological predisposition are all possible mechanisms that underlie the relationship between childhood maltreatment and borderline personality disorder (10). The present review aims to highlight the recent research on another possible explanation for an association between childhood maltreatment and borderline personality disorder: epigenetic modifications secondary to early-life stress.

THE HYPOTHALAMUS-PITUITARY-ADRENAL (HPA) AXIS AND STRESS RESPONSE

The HPA, consisting of the paraventricular nucleus (PVN) of the hypothalamus, the anterior lobe of the pituitary gland, and the adrenal gland, is the essential component of one's stress response. Stress activates the HPA. The principal regulator of the HPA, corticotropin-releasing factor, is released from the PVN and induces the downstream release of adrenocorticotropic hormone (ACTH) (11, 12). ACTH targets the adrenal cortex whereby it stimulates glucocorticoid synthesis and secretion. Glucocorticoids play a wide variety of physiologic roles. Most important to epigenetic stress is that glucocorticoids are a prominent regulator of HPA activation via negative feedback (13). Succinctly, stress induces the release of glucocorticoids, and high levels of circulating glucocorticoids then inhibit the axis upstream.

EPIGENETIC CHANGES

Epigenetics is the heritable modification of gene expression influenced by our environment. DNA methylation, histone modifications, and micro-RNA activity are mechanisms of silencing gene expression (14). Early-life stresses can cause DNA methylation, modifying gene expression, resulting in dysregulation of the HPA axis (15–17).

THE GLUCOCORTICOID RECEPTOR GENE *NR3C1*

Weaver and colleagues (18, 19) found that positive maternal care in rodents resulted in epigenetic modification—DNA methylation of certain CpG sites of exon 1_7 of the promoter of the glucocorticoid receptor gene *NR3C1*—inhibiting HPA activation, reducing stress, and, in a sense, programming their young's response to stress (18–21). Simply, quality care reduces stress in the young.

Whereas quality care leads to epigenetic modifications that reduce stress, glucocorticoid receptor gene *NR3C1* can also be a target of early-life stress because increased methylation of its promoter region in exon 1_F (the human homolog of the aforementioned rodent exon 1_7) has been documented in both patients with a history of childhood trauma and patients with borderline personality disorder (22–24).

THE RELATIONSHIP BETWEEN *NR3C1* METHYLATION AND BORDERLINE PERSONALITY DISORDER

In the first study to show an association between various types of childhood maltreatment and increased methylation of *NR3C1* in humans, Perroud and colleagues (22) recruited 101 patients from an intensive dialectical-behavior therapy center and found that sexual abuse significantly correlated with *NR3C1* methylation status when compared with non-sexually abused counterparts. The majority of the patients were females (94.06%) in their 30s, who were diagnosed with borderline personality disorder and suffered from comorbid major depressive disorder (73.26%), alcohol use disorder (61.3%), and substance use disorder (51.6%).

Childhood maltreatment was quantified using the Childhood Trauma Questionnaire (CTQ). The CTQ assesses five types of self-reported trauma: physical abuse, physical neglect, emotional abuse, emotional neglect, and sexual abuse. The scores are correlated to cut-off points to determine severity: none, low, moderate, and severe.

NR3C1 methylation status was determined by DNA extracted from leukocytes. Perroud et al examined exon 1_F because increased methylation in this location was 1) shown by Oberlander and colleagues (25) to be a possible link between prenatal maternal mood and an infant's modified HPA stress reactivity and 2) shown by McGowan and colleagues (26) to be associated with subsequent decreased hippocampal *NR3C1* gene expression in suicide victims with a history of childhood abuse. The *NR3C1* exon 1_F gene sequence also includes a nerve growth factor inducible protein A (NGFI-A) binding site that regulates gene transcription, but the CpG sites that have been extensively studied do not include this site (22). NGFI-A is highly expressed in young rodents that received quality maternal care (27).

There was a positive correlation between the severity of childhood maltreatment (amount and frequency) and *NR3C1* methylation (22). The CpG sites studied by Perroud and colleagues and McGowan and colleagues had increased methylation in those with childhood sexual abuse (22, 26). Perroud and colleagues suggested that increased methylation occurred in specific areas located near recognition elements for NGFI-A, since the NGFI-A binding site is upstream of the CpG sites studied, but the significance remains unknown (22, 25, 26).

For each type of maltreatment, there was significant association with increased methylation. Participants with childhood sexual abuse had increased methylation compared with counterparts who did not; the more severe the abuse, the higher the methylation status (22). There was also highly significant association between methylation status and emotional abuse (22). This is important to note because the literature tends to gravitate toward examination of sexual abuse; emotional abuse is an equally important factor and can be just as predictive (22).

Perroud and colleagues were unable to correlate the degree of methylation to borderline personality disorder severity (22). Additionally, McGowan and colleagues used postmortem hippocampal samples of suicide victims, while Perroud and colleagues used peripheral blood (22, 26). Thus, the results by Perroud and colleagues cannot be readily applied to genetic expression in the brain.

Martin-Blanco and colleagues (23) aimed to correlate methylation status with borderline personality disorder severity. They recruited 281 patients with borderline personality disorder from specialized inpatient units that treat the disorder and examined 1) the genomic DNA extracted from their peripheral leukocytes, 2) their history of previous hospitalizations, 3) their self-injurious behaviors, and 4) their self-reported childhood trauma via the CTQ. They examined the same eight CpG sites (22, 25, 26). Similar to the study by Perroud and colleagues, the participants were predominantly female (85%), with a mean age of 29 years (23). The authors found that there was a "significant positive correlation" between *NR3C1* methylation status and childhood physical abuse (23). There was significant association between methylation of specific sites—CpG 1, 2, and 3—and physical abuse and emotional neglect ($p=0.08$); methylation of CpG 6 correlated to emotional abuse (23). Additionally, the authors noted a significant association between methylation and clinical severity as measured by the Revised Diagnostic Interview for Borderlines, self-injurious behaviors, and past hospitalizations (23).

Radtke and colleagues (24) examined 46 participants, mainly adolescents and young adults, recruited via advertisement and compensated monetarily, and found a statistically significant correlation between methylation of a CpG site (cg17860381) within exon 1_F in lymphocytes, childhood maltreatment, and symptoms of borderline personality disorder. Their statistical analysis indicated that childhood maltreatment and cg17860381 methylation were both significant predictors for the symptoms of the disorder and its intensity; however, they did not detail the specific symptoms (24).

THE SEROTONIN 3A RECEPTOR 5-HT_{3A}R

The serotonin 3A receptor (5-HT_{3A}R) has a role in cortical circuit formation, HPA function, and regulation of acute stress-induced HPA activity, and it factors into anxiety, fear, anxiety-related behaviors, and cognition and regulates corticotropin-releasing hormone in the central amygdala (28, 29). Considering its multifaceted nature, 5-HT_{3A}R has piqued the interest of researchers.

Perroud and colleagues (30) also studied 5-HT_{3A}R and, specifically, the single-nucleotide polymorphism (SNP) rs1062613, leading to a C to T polymorphism, which has been implicated in bipolar disorder (31). The methylation of multiple CpG sites in the glucocorticoid response element region (CpG3II, CpG2III, CpG5III) has been associated with childhood maltreatment, especially physical abuse, while methylation in other sites (CpG2III, CpG4III) is increased in patients with a history of suicide attempt, previous hospitalization, and substance dependence (30). These findings suggest that there are multiple receptors affected by epigenetic modification in response to environmental stressors, such as physical abuse, and may contribute to high-risk behaviors.

Furthermore, these epigenetic modifications may be additive, since those with the resultant CC genotype from the rs1062613 SNP demonstrated the highest level of methylation at CpG2III in the presence of childhood maltreatment (32). This additive effect decreases 5-HT_{3A}R expression, which functions in emotional processing during stress.

CONCLUSIONS

There has been a shift in ongoing borderline personality disorder research from identifying "vulnerability genes" to identifying genes that can be influenced by the environment and contribute to adult psychopathology (33). While further epigenetics and genetic research awaits, the studies reviewed here can help us to understand how early-life traumatic stress produces molecular changes that correlate with adult personality pathology.

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KEY POINTS/CLINICAL PEARLS

- In a community-based longitudinal study of 639 youths and their mothers between 1975 and 1993 that also controlled for difficult temperament, parental education, and mental health, individuals with a history of childhood physical abuse, sexual abuse, or neglect were four times more likely to have a personality disorder in early adulthood compared with individuals who did not have such history.
- Epigenetics, consisting of DNA methylation, histone modifications, and micro-RNA activity, is a mechanism of gene expression influenced by the environment.
- Glucocorticoid receptor gene *NR3C1* is a target of early-life stress because increased methylation of its promoter region in exon 1_F has been documented in both patients with a history of childhood trauma and patients with borderline personality disorder.
- In one study, patients who had suffered from childhood maltreatment, especially physical abuse, had high rates of DNA methylation of specific CpG sites in the glucocorticoid response element region of the 5-HT_{3A}R, which may be associated with the frequency of suicide attempts and hospitalizations.

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