The Neurobiology of Borderline Personality Disorder

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KEYWORDS

• Borderline personality disorder • Alexithymia • Genetics • Emotion dysregulation • Impulsive aggression • Neuroimaging • Oxytocin • Opioids

KEY POINTS

- Evidence clearly suggests that borderline personality disorder (BPD) is substantially heritable and at least as heritable as other major psychiatric disorders.
- Brain imaging studies have suggested a dysregulation in top-down control of emotions and behavior in BPD; however, this model is also seen in other disorders, such as panic disorder.
- Abnormalities in the oxytocin and opioid systems may underlie the interpersonal dysfunction characteristic of BPD.
- An impairment in emotional interoception (a disconnect between heightened objectively measured emotional responses and blunted subjective appreciation of those responses) may be a core feature of BPD.

INTRODUCTION

The name borderline personality disorder (BPD) was coined at Mount Sinai in New York by Adolph Stern[1] and has its origins in a Freudian conceptualization of the mind, with BPD on the border between psychosis and neurosis. However, because

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neurosis is no longer used in the language of clinical psychiatry, this name can lead to confusion. Rapid advances in understanding neurobiological features of BPD have also led to the view that this psychoanalytically grounded name seems obsolete. The surge in neurobiological studies of BPD emerged from evidence that BPD is a heritable illness.

There have been several reviews of the neurobiology of BPD, including very well written reviews of pharmacology, brain imaging findings, and candidate genes association studies. A comprehensive review of all recent empirical findings in brain imaging, genetics, heritability, and novel therapeutics would be very long and difficult to read. Instead, this article reviews the most salient neurobiological information available about BPD and presents a theoretic model grounded in those findings for what lies at the heart of BPD.

The empirical literature supports a coherent construct underlying the BPD diagnosis. Early studies showed 3 factors underlying BPD as defined in *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5): disturbed relatedness (unstable relationships, identity disturbance, and chronic emptiness), behavioral dysregulation (impulsivity, suicidality, or self-mutilatory behavior), and affective dysregulation (affective instability, inappropriate anger, and efforts to avoid abandonment). However, subsequent analyses showed that these factors were highly correlated with each other (r = .90, .94, and .99) and these correlations suggest and underlying unifying construct.[2] The DSM-5 emphasizes a general characteristic of personality disorders and evidence suggests that this so-called g-factor maps particularly on to BPD.[3] What precisely that g-factor is has not been agreed on. Affective instability and, particularly, emotional reactivity in the context of interpersonal relationships, has been viewed as the essential core of BPD.[4] Although it is clearly a very central characteristic, this review focuses on a very specific and underappreciated characteristic of BPD that has only recently come under investigative scrutiny. This review explores several different models but posits that the core characteristic of BPD may be an impairment in emotional interoception or alexithymia.

The article begins with a review of the heritability and genetics of BPD, followed by biological models of BPD, including the neurobiology of affective instability, impaired interoception, opiate models of poor attachment, and structural brain imaging over the course of the development in BPD.

GENETICS, HERITABILITY, AND IMPLICATED GENES

Although family, twin, and adoption studies strongly and consistently suggest that BPD traits are heritable, the specific genetic underpinnings of BPD remain unknown.[5–7] Similar to most psychiatric disorders, BPD is believed to have a complex, multifactorial cause, resulting from the interaction of a genetic vulnerability with environmental factors.[8] The very limited understanding of the genetic architecture of BPD is a critical obstacle to advancing treatment and preventive efforts in BPD. Specifically, genetic research can help identify new treatment targets and develop preventive and disease-modifying treatments for BPD, which are not yet available.[9,10]

What follows is a brief overview of genetic studies of BPD and/or subclinical BPD traits, including most methodological approaches (eg, candidate gene association study, genome-wide association study [GWAS], gene-environment interactions, epigenetic modifications).

Most earlier genetic studies in BPD are candidate-gene association studies.[5,6] Most have very small sample sizes and positive results have not been confirmed by meta-analyses.[6] Most of the candidate association studies have focused on genes within

the serotonergic, dopaminergic, and noradrenergic systems, which had been previously linked to BPD symptomatology. Only a few studies have examined other genes, such as those coding for the brain-derived neurotrophic factor; the vasopressin receptor 1A; and the sodium channel, voltage-gated, type IX, alpha subunit.[6]

As with other complex diseases, it is expected that the genetic vulnerability to BPD is the result of many individual risk variants, each with a very small effect on the risk of developing BPD. Because of the very small effect of each variant, very large samples are needed to identify risk variants using genome-wide approaches.[11] For example, in schizophrenia, successful GWASs have included tens of thousands of subjects.[12] In contrast, the only GWAS of the full BPD diagnosis to date included just fewer than 1000 BPD subjects.[13] Although no genetic variants reached genome-wide significance in this underpowered study, gene-based analysis yielded 2 significant genes: dihydropyrimidine dehydrogenase (DPYD) on chromosome 1 and Plakophilin-4 (PKP4) on chromosome 2. Moreover, the study also observed significant genetic overlap between BPD and bipolar disorder, major depressive disorder, and schizophrenia. There have also been 1 GWAS[14] and 1 genome-wide linkage study[15] of subclinical BPD traits, with significant results implicating the serine incorporator 5 (SERINC5) gene and chromosome 9, respectively.

Given the key role of trauma (objective or perceived) in traditional models of the genesis of BPD, it is surprising that there are very few studies examining gene-environment interactions in BPD subjects.[8] Most have small samples and have identified gene-environment interactions that have not been replicated. Research evidence has suggested that there is a gene–environment interaction in BPD, suggesting that those genetic factors that increase risk for BPD also increase risk for exposure to environmental stressors that may trigger BPD.[8] Although animal models of the interaction between genetic factors and early life experience can be very valuable, larger, longitudinal studies in humans are needed to elucidate the gene–environment interplay leading to BPD. Ideally, these studies will include large, prospective children cohorts.

Epigenetics is a relatively new field that opened a new avenue for exploring changes in gene expression caused by environmental conditions. Epigenetic modifications affect gene expression and include DNA methylation, histone remodeling, and noncoding RNA silencing.[16,17] Several studies have investigated patterns of epigenetic modifications in BPD.[18–28] Some of them have found DNA methylation abnormalities associated with BPD[18,24,27] and severity of childhood maltreatment.[19,21–25,28] One study suggests that methylation status can be modified through psychotherapy in BPD patients.[24]

In summary, despite the known heritability of BPD, no specific risk genes or molecular pathways have been identified to date.[5,6] It behooves the field to perform larger, better powered, genetic studies in BPD subjects. Advancing genetic research in BPD is a critical step toward the identification of new drug targets and the development of disease-modifying therapies against the core pathophysiological features of BPD, which are currently lacking. Moreover, other genetic research approaches, such as deep sequencing, induced pluripotent stem cells, and postmortem brain studies, which have not yet been used in BPD, may help uncover the neurobiological underpinnings of this disorder.

BIOLOGICAL MODELS

Alexithymia

The discovery of high levels of alexithymia in BPD emerged out of evidence that there is a disconnect between objectively measured emotional responses in BPD (which are

heightened) and the subjective appreciation of those responses (which is blunted). This is called an impairment in emotional interoception. This view, grounded in neurobiology, may come closer to the description of this disorder as a disorder of the self.

The authors' interest in this idea came from an early study we did measuring emotional responsiveness in BPD subjects using affective startle. The simple hypothesis was that BPD subjects would be hyperresponsive to unpleasant emotional probes. Affective startle is a very well-studied approach for measuring affective arousal and valence.[29] Individuals often have a characteristic eye blink response to a loud sound burst. Providing a prepulse or a warning that such a sound is about to occur at a particular time can influence the intensity of the blink. Providing that prepulse with an affective valence can influence the intensity of the blink. For example, if the prepulse is the showing of a word such as *murder*, the blink is amplified compared with a prepulse of a neutral valence, such as the word *table*. Similarly, a word with a positive valence, such as *cuddle*, will decrease the amplitude of the blink in response to the sound blast. The prepulse need not be a word and is, in fact, often an emotional picture. This objective way of measuring emotional response has been shown to be reliable and is thought to reflect amygdala activity.[30]

Hazlett and colleagues[31] (including the current authors, Goodman and New) studied individuals with BPD compared with age-matched and sex-matched healthy controls using affective startle in response to negative and neutral words. As predicted, both the BPD and healthy control groups showed an increased startle response to negative compared with neutral words; however, the BPD group showed a heightened enhancement of startle response on average to negative words specifically compared with healthy controls. What was entirely unexpected was that when subjects were asked to report on how the words made them feel, the BPD subjects reported a more neutral response to the negative words than did the controls.

Since that initial study, Hazlett and colleagues[32] (including the current authors, Goodman and New) have gone on to find the same pattern of results in affective response comparing BPD subjects to healthy controls and to a clinical control group of schizotypal subjects using functional MRI blood oxygenation level-dependent (BOLD) response instead of affective startle. Subjects were shown pictures with positive, negative, and neutral valence. Again, BPD subjects showed a heightened objectively measured emotional response in the mean amygdala BOLD response to negative images and to positive images. Yet, BPD subjects showed a blunted (or more neutral) rating of their own responses to those emotional images and this was particularly pronounced in the negative valence. Other studies of responses to emotional probes in BPD have shown the same heightened emotional responses with blunted (or at least not heightened) subjective ratings.[32] These observations led New and colleagues[33] to measure a clinically observed psychological attribute called alexithymia or, examining the Greek etymology, difficulty reading emotions. Using the Toronto Alexithymia Scale, subjects with BPD had extremely high levels of alexithymia compared with healthy controls and, indeed, the effect size was very large. The difficulties for identifying and describing their own feelings were pronounced.

In Mannheim, Germany, Dr Christian Schmahl conducted a body of work on pain responses in BPD, which is related to the work on emotional responses. As in emotional responses, a similar disconnect between objectively measured and subjectively assessed is seen in relation to pain in BPD.[34] Schmahl and colleagues[35] did an elegant study that showed that BPD subjects have a heightened pain threshold, tolerating higher levels of pain than controls, while retaining an intact capacity for subtle sensory discrimination tasks using laser-evoked potentials (LEPs). This methodology

permits assessment of very rapid response near the somatosensory cortex that precedes cortical response to stimuli. That study showed that, although pain thresholds were higher in subjects with BPD than in controls, the rapid LEP response, reflecting the immediate and preconscious neural signature of the sensory experience of pain, was normal or heightened in BPD. These data support a higher pain threshold (the experience of pain is diminished) although the evidence suggests that the neural signature of pain is intact. This is another instance of the discrepancy between objectively measured experience and subjective appraisal of that experience in BPD.

Further evidence of the impaired ability of patients to perceive or process their own emotional and even physical experiences emerged from a study of heartbeat-evoked potentials (HEPs), which are used as an indicator of the cortical processing of bodily signals from the cardiovascular system. Generally, there is a neural imprimatur of heart beats in the anterior insula. Subjects with BPD have been shown to have significantly reduced mean HEP amplitudes compared with healthy controls; subjects with BPD in remission have intermediate HEP.[36] Furthermore, HEP amplitudes were negatively correlated with emotional dysregulation.

This neurobiologically grounded model of impaired emotional interoception is particularly compelling for BPD because, as work progressed in laboratories studying this disorder, very effective evidence-based psychotherapies were being developed for BPD. These include, most famously, dialectical behavioral therapy, as well as mentalization-based therapy; transference-focused therapy; Systems Training for Emotional Predictability and Problem Solving; schema therapy; and, most recently, good psychiatric management for BPD.[37] What lies at the heart of these therapies is that they are focused, often time-limited, and emphasize practical approaches to present day problems.[38] What is central to teaching mentalization skills? Clinicians seem to have recognized that BPD patients are imperfect at knowing their own emotional experiences and so the treatments that have been most effective in this disorder are not those that focus on past experiences but rather those that teach patients to reflect on their own present emotions and how they come across to others. It is, therefore, a lovely synergy that is rare in psychiatric research that there is a convergence on the development of clinical treatments with understanding that has developed in the laboratory, each strengthening the importance of the other.

Emotion Dysregulation in Borderline Personality Disorder

Affective instability or disturbance is a feature found across multiple diagnoses,[39] including posttraumatic stress disorder, substance abuse, eating disorders, and BPD.[40] It is associated with considerable morbidity, including suicidality, aggression, and disrupted relationships.[41] Affective dysregulation is a primary feature of BPD, along with disturbed cognition, impulsivity, and intense unstable relationships.[42] The observed dysregulated affect includes hypersensitivity and hyperreactivity to emotional triggers[41]; rapid increases in depressed, anxious, and irritable affect; and impairments in emotion regulatory control.[43,44] The dysregulation of affect in BPD is quite different from the mood dysregulation seen in depression or bipolar disorder in which the mood disturbance is sustained for days, weeks, or months, and is relatively autonomous from environmental triggers. Here, the published evidence supporting abnormalities in emotion regulation in BPD is reviewed (behavioral, neuroimaging, and physiological studies).

From a behavioral standpoint, the emotional hyperreactivity in BPD may be more apparent for individually salient, or significant, emotional stimuli than a blanket hyperresponsiveness to all emotional stimuli.[45] BPD patients display greater mood variability in response to daily stress and may be particularly sensitive to affective triggers involving social rejection and abandonment, resulting in excessive emotional

reactions.[46] Additionally, they experience greater negative affect and do not develop appropriate and adaptive emotion regulation strategies, engaging instead in maladaptive ways of coping. Some of these coping mechanisms include nonsuicidal self-injurious behaviors,[47] rumination,[48] thought suppression,[49] and impulsive suicidal behaviors.[50] They have low emotional awareness[51] and distress tolerance,[52] which likely contributes to the dysfunction exhibited in BPD (**Fig. 1**).

As previously noted, some physiologic measures, such as the affective startle modulation (ASM), have provided useful nonverbal metrics of affective valence, independently of arousal, which is useful in BPD. Hazlett and colleagues[31] (including the current authors, Goodman and New) showed that BPD subjects had exaggerated ASM during imagery of BPD-salient scripts describing rejection and abandonment but not during generally unpleasant scripts.[31] Recent data suggest that other factors, such as substance abuse or dissociative experiences, may modulate the ASM in BPD. A recent study that examined BPD subjects with and without a history of substance-use disorders (SUDs) showed lower startle modulation in the BPD-SUD group, suggesting that comorbid SUD may dampen the pattern of exaggerated ASM to unpleasant stimuli in BPD.[53] Other studies evaluating the effect of dissociative experiences in ASM in BPD found that greater dissociative symptoms reduced startle response magnitudes during imagery of idiographic aversive scripts in BPD subjects.[54] Dissociative experiences involve detachment from the overwhelming emotional aspects of trauma. According to the corticolimbic disconnection model,[55] dissociation is a mechanism that dampens affective reactivity to avoid emotional overstimulation. This model further suggests that during dissociation the medial prefrontal cortex inhibits processing of external emotional stimuli in the amygdala, thus attenuating emotional responses to these stimuli.[56] This concept is supported by a BPD study showing that subjects experiencing no dissociative symptoms showed larger startle response amplitude compared with subjects with high dissociative experiences.[57]

There is robust evidence from behavioral, neuroimaging, and physiologic studies that BPD patients are characterized by poor emotion regulation, hyperarousal state, and hyperreactivity to negative stimuli. Future lines of research should explore the biological basis of emotion dysregulation, as well as prevention; earlier treatment; and, especially, expansion of the therapeutic dimension.

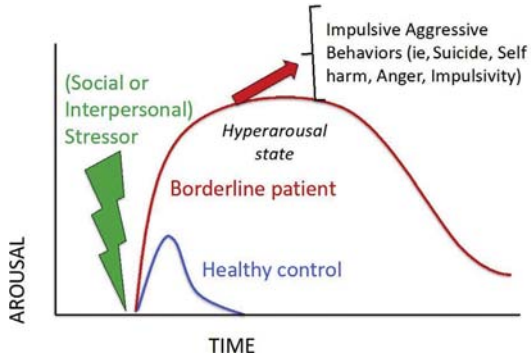

Fig. 1. Emotional dysregulation from a behavioral standpoint. When an individual with BPD encounters social or interpersonal stressors, they are unable to regulate their emotions and they enter a state of emotional hyperarousal, during which other state-potentiated vulnerabilities to impulsivity and aggression become overtly expressed, leading to impulsive, aggressive, and self-destructive behaviors.

BRAIN IMAGING

Functional neuroimaging has been the major tool used to study emotional processing in BPD. Affective instability in BPD has been associated with reduced top-down regulatory prefrontal cortex activity (orbitofrontal cortex, anterior cingulate cortex [ACC], and enhanced amygdala and insula activity while viewing emotional stimuli.[58–64] Additionally, some studies have suggested that patients with BPD have an impaired amygdala habituation, meaning that the amygdala is unable to decrease neural response when a negative stimulus is repeatedly presented.[32,44] Those studies found that amygdala activation increased in response to repeated negatively valenced pictures, whereas in healthy controls amygdala activation decreased. Failure to habituate correlates clinically with higher levels of trait anxiety,[65] aggression, and affective lability[32] (**Fig. 2**). BPD subjects, compared with controls, demonstrated enhanced coupling of the left amygdala with the dorsolateral prefrontal cortex and ventral striatum, suggesting a mechanism for abnormal top-down regulatory control.[66] Amygdala activity and habituation is a promising biomarker of treatment response, as shown by Goodman and colleagues[67] in a dialectical behavioral therapy trial.

Findings from structural MRI studies suggest that individuals with BPD, compared with healthy controls, have decreased volume in brain regions associated with emotion processing and regulation, which include the amygdala,[68–70] hippocampus,[68,69,71] orbitofrontal cortex,[72] and ACC.[61,72,73] A more recent meta-analysis showed that BPD subjects show "increased GM volume in bilateral supplementary motor area extending to right posterior cingulated cortex (PCC) and bilateral primary motor cortex, right middle frontal gyrus (MFG), and the bilateral precuneus extending to bilateral PCC. Decreased GM (Gray matter) was identified in bilateral middle temporal gyri, right inferior frontal gyrus extending to right insular, left hippocampus and left superior frontal gyrus extending to left medial orbitofrontal cortex," which encompasses frontolimbic circuits and the default mode network.[74]

Additional imaging methodologies used in BPD include diffusion tensor imaging (DTI), which permits visualization of white matter integrity. Although data on white

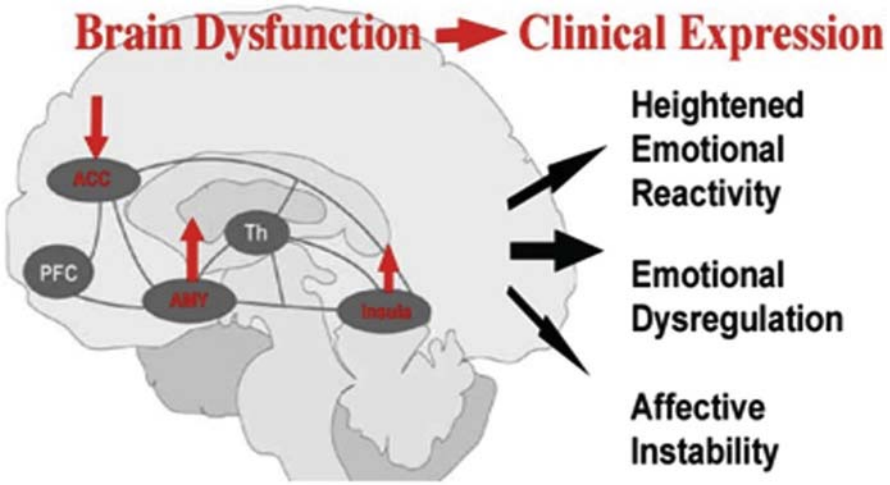

Fig. 2. This model posits that brain dysfunction is characterized by an underactive ACC and/or an over-reactive amygdala (AMY) and insula, and/or functional disconnectivity results in heightened emotional reactivity and difficulties regarding this affect, which is clinically expressed as affective instability. PFC, prefontal cortex; Th, thalamus.

matter integrity using DTI has been inconsistent, a study of adult BPD showed decreased axial diffusivity in the cingulum and inferior occipital and inferior longitudinal fasciculus.[75] Another study showed decreased fractional anisotropy (FA), a measure of white matter integrity, in the corpus callosum, corona radiata, and dorsal areas of the ACC in BPD.[76,77] Finally, another study showed decreased FA in the uncinated fasciculus in BPD subjects compared with controls,[78] as well as in the cingulum and fornix in BPD.[79] Studies in adolescent subjects with BPD show decreased FA in the Inferior Longitudinal Fasciculus using tractography,[80] as well as in the fornix and uncinate fasciculus.[81] Although no single region is definitively involved in BPD, abnormalities in central white matter structure and long tracts within the limbic system seem to be present in almost all DTI studies in BPD. This tends to support the fronto-limbic disconnectivity hypothesis by providing an anatomic substrate for abnormalities in the tracts connecting limbic areas to prefrontal cortex in BPD. These findings also underscore the possibility that abnormal maturation of white matter structures may play an important mechanistic role in BPD.

The newest imaging methodologies delineate topological organizations of brain networks. Such analyses use graph theory–based complex network analysis. Initial findings of this type of approach suggest abnormal topological properties and connectivity in BPD,[82] although this methodology is still considered exploratory.

NEUROPEPTIDE MODELS: OXYTOCIN AND OPIOIDS

Impulsivity and emotional dysregulation have been known as the core symptoms of BPD for decades. However, in 2010, Stanley and Siever[84] suggested that the main core factor of this disorder is interpersonal sensitivity,[4] which in turn triggers impulsivity and dysregulated affect.[41,83,84] It is proposed that this interpersonal dysfunction could be related to underlying neuropeptide dysregulation, including abnormalities in opioids, oxytocin, and vasopressin systems.[84] Here the evidence supporting the role of opioids and oxytocin in BPD is reviewed.

Opioids

Increasing evidence supports the dysregulation theory of BPD, which proposes low basal opioid levels and compensatory supersensitivity of μ-opioid receptors have an essential role in presentations of BPD. Some of the main symptoms of BPD, such as chronic dysphoria, lack of sense of wellbeing, and feeling empty inside, are manifestations of low basal opioid levels. Repetitive nonsuicidal self-injuries could be a result of an increase in opioid levels after such behaviors. Low levels of β-endorphin and met-enkephalin have been shown in the cerebrospinal fluid of individuals with cluster B personality disorder and history of self-injury.[85] On the other hand, naltrexone, an opioid antagonist, has been shown to reduce these nonsuicidal self-injury behaviors in BPD,[86] which may be a result of decreasing the rewarding effects of these behaviors by blocking opioid receptors.

Recent studies show that, similar to physical pain, intrapsychic pain, which is a main feature of BPD, is under the control of the opiate system and the same neural pathways are involved.[87] The endogenous opiate system, through μ-opioid receptors, has long been implicated in regulation of emotional and stress responses. Opioid dysfunction has been associated with attachment behavior deficits and anxiety-like responses in animal models.[88–90] In human beings, the opioid system is involved in normal and pathologic emotion regulation,[91,92] in addition to its more traditional role in modulating both the sensory and affective dimensions of pain.[93] While the notion that physical pain and emotional pain have common physiological

mechanisms is well known,[94] more recently, evidence suggests that common neural substrates regulate pain of social rejection and physical pain.[87,95,96]

Empirical evidence supporting the endogenous opiate dysregulation theory of BPD is increasing. Beta-endorphin, which is the endogenous opioid peptide released during stress,[97] has a common precursor with adrenocorticotropin hormone (corticotropin),[98] the main hormone of stress response. Beta-endorphins are responsible for relieving pain in stressful situations to help the individual to survive.[98] Interestingly, individuals with BPD show increased pain threshold following acute painful stressors,[99,100] whereas they show lower tolerance for chronic pain[101] and more frequently report use of prescribed opioid analgesics.[102] One of the most compelling empirical reports supporting a definitive abnormality in opiate activity in patients with BPD comes from a recent PET imaging study that used the μ-opiate ligand, [^{11}C]carfentanil, to examine binding in the cerebral cortex of BPD subjects during induction of a neutral and sad sustained emotional state.[103] In the neutral state, BPD subjects showed more μ-opioid binding in regions of the prefrontal cortex, in the reward center (accumbens), and in the amygdala; and μ-opiate binding in prefrontal cortex correlated negatively with neuroticism in BPD. During sadness-induction, BPD subjects showed greater μ-opioid receptor-mediated neurotransmission compared with controls. The investigators interpreted the greater baseline μ-opiate receptor availability as perhaps reflecting deficits in endogenous circulating opiates. The mood induction seems to suggest that BPD subjects enhance endogenous opiate availability more than controls, which is convincing as a compensatory response.

Genetic studies suggest that the μ-opioid receptor gene is associated with attachment abnormalities and BPD. Polymorphism in the μ-opioid receptor gene (OPRM1 77G) in primates is associated with higher levels of attachment during early infancy and greater persistence of separation distress.[88] A more recent study demonstrated the role of μ-receptor genes in moderating the effects of social rejection on depression,[104] which may explain the severe reaction of BPD to interpersonal rejections. These data, although quite preliminary, raise the possibility that genetic variability in the opioid receptors may affect affective stability, attachment, and coherence of self-concepts.

Oxytocin

Interpersonal dysfunction is another feature of BPD[4,105] that has been proposed to serve as the main core component of this disorder.[84] One of the main regulators of social relationships is oxytocin, which plays an essential role in affiliation behaviors, such as parental caring and romantic partnering.[106,107]

Dysregulation of oxytocin has been shown in BPD and may explain the interpersonal hypersensitivity in this disorder.[108] Women with BPD had significantly lower plasma levels of oxytocin compared with a control group,[109] especially when they had a disorganized attachment style.[110] Oxytocin levels were negatively correlated with a childhood history of trauma.[109] Moreover, individuals with BPD show a reduction in oxytocin plasma levels after social exclusion.[111] Oxytocin abnormalities in BPD clinically manifest in misreading of social cues, difficulties in establishment of trust, and capacity for attachment in BPD.[84] Increasing evidence shows that individuals with BPD have a profound bias in facial emotion recognition toward identifying negative emotions in others, particularly anger.[112] Individuals with BPD also show an avoidant reaction to angry faces, which is correlated with their childhood history of trauma and diminishes after administration of intranasal oxytocin.[113] Brain imaging evaluations show increased and prolonged activation of the amygdala[114] and anterior insula[62] in response to negative emotional stimuli. Clinical studies show women with BPD exhibit

more and faster initial fixation changes to the eyes of angry faces combined with increased amygdala activation in response to angry faces, which are normalized after intranasal oxytocin administration.[109]

Recently, it is shown that individuals with BPD also demonstrate a bias toward perceiving other people's faces as more untrustworthy compared with healthy volunteers.[115] Interestingly, intranasal administration of oxytocin has been shown to significantly enhance trustworthiness and attractiveness of male and female targets in healthy people.[116] However, oxytocin has a trust-lowering effect in individuals with BPD,[117,118] which is correlated with a history of childhood trauma.[118] In a study of nonverbal communications, oxytocin increased affiliative behaviors in healthy subjects but not individuals with BPD.[119] These findings suggest that oxytocin effects should be evaluated in the context of childhood experiences and attachment patterns and may have contradictory effects in BPD. It is suggested that oxytocin may promote prosociality when social cues are interpreted as safe; however, in unsafe interpretation of the environment, oxytocin may promote more defensive emotions and behaviors.[120]

Oxytocin also is known to diminish the stress response. In clinical studies, administration of intranasal oxytocin increases positive communication and decreases cortisol levels after couple conflicts[121] and other types of social stressors in individuals with impaired emotion regulation abilities.[122] In BPD, oxytocin significantly reduces the stress-related dysphoria, as well as cortisol levels.[123] Neuroimaging studies consistently found that amygdala responses to emotional stimuli are reduced by oxytocin administration, which could be a result of reduced uncertainty about the predictive values of emotional stimuli.[124]

In 2015, Herpertz and Bertsch[108] suggested that, in addition to abnormal bottom-up generation of emotions, individuals with BPD suffer from an abnormal top-down emotional regulation. Functional neuroimaging studies have revealed prefrontal hypometabolism during regulatory control processes,[125] and reduced activity in the subgenual ACC and dorsolateral prefrontal cortex in BPD.[62] Interestingly, oxytocin significantly attenuates the increased neuronal activity in the medial prefrontal cortex and the ACC in social anxiety disorder,[126] which has an important role in emotion regulation.

Genetic studies investigated the role of the oxytocin receptor gene in the formation of BPD symptoms, which seems to have interactions with gender and childhood trauma. A study of more than 1000 low-income children demonstrate that girls with at least 1 A-allele of the SNP rs53576 and history of childhood maltreatment had more BPD presentations, whereas maltreated boys were more vulnerable to developing BPD symptoms when homozygous for the G/G allele.[127] A study of more than 1000 low-income children demonstrate that girls with at least 1 A-allele of the oxytocin receptor gene (OXTR) single nucleotide polymorphism (SNP) rs53576 and history of childhood maltreatment had higher rates of BPD, whereas maltreated boys were more vulnerable to developing BPD symptoms when homozygous for the G/G allele.[128] It seems that SNP rs53576 in the oxytocin receptor gene (OXTR) moderates the relationship between childhood experiences and BPD presentations.

SUMMARY

Although this review presents data from disparate approaches to studying the neurobiology of BPD, it begins to suggest a theoretic framework that can form a coherent theory of BPD. Evidence clearly suggests that BPD is substantially heritable and is at least as heritable as other major psychiatric disorders. Brain imaging studies have suggested a dysregulation in top-down control of emotions in BPD; however,

this model is also seen in other disorders, such as panic disorder. Thus the imaging may be of an upset brain. On the other hand, the structural and white matter abnormalities that are especially robust in adolescents suggest a developmental abnormality in neural circuitry underlying emotion regulation in BPD. The finding of impaired interoception is especially remarkable in BPD because it does seem to dovetail well with the focus on mentalization that underlies the evidence-based psychotherapies for this disorder and helps to explain the interpersonal difficulties in BPD. For example, if an individual with BPD is angry and manifests that in terms of their physiologic arousal but is unaware of that anger, then, when another person responds to the apparent anger, the individual is confused and hurt. This neurobiological model provides an explanation for the phenomenon that psychodynamic theory has described as projective identification. According to this model, in an interpersonal interaction, individuals with BPD may appear angry while being unaware of their feelings. The physiologic manifestations of anger then create anger in the person with whom they are interacting and the alexithymic BPD patients are not aware of their role in kindling anger in their interlocutor. This helps to explain why validation is so helpful; it is making explicit the perceived affect in the interaction about which the person with BPD may be unaware. The abnormalities in neuropeptides are somewhat contradictory in that some studies show improvement with oxytocin and others do not. Little is known about the opiate system in BPD but preliminary data suggest endogenous opiate deficits. This line of work is especially important and it holds the promise of a pharmacologic treatment of BPD, a tool that is unfortunately currently unavailable. Clearly further research into the neurobiology of BPD holds proximal promise of novel therapeutics and currently can help with psychoeducation of patients, family, and clinicians to enable more empathic contact with individuals with BPD.

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