

# Borderline personality disorder, trauma, and the hypothalamus–pituitary–adrenal axis

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**Abstract:** Borderline personality disorder (BPD) is a complex psychiatric illness for which treatment poses a significant challenge due to limited effective pharmacologic treatments, and under-resourced psychological interventions. BPD is one of the most stigmatized conditions in psychiatry today, but can be understood as a modifiable, neurodevelopmental disorder that arises from maladaptive responses to trauma and stress. Stress susceptibility and reactivity in BPD is thought to mediate both the development and maintenance of BPD symptomatology, with trauma exposure considered an early life risk factor of development, and acute stress moderating symptom trajectory. An altered stress response has been characterized in BPD at the structural, neural, and neurobiological level, and is believed to underlie the maladaptive behavioral and cognitive symptomatology presented in BPD. The endocrine hypothalamus–pituitary–adrenal (HPA) axis represents a key stress response system, and growing evidence suggests it is dysfunctional in the BPD patient population. This theoretical review examines BPD in the context of a neurodevelopmental stress-related disorder, providing an overview of measurements of stress with a focus on HPA-axis measurement. Potential confounding factors associated with measurement of the HPA system are discussed, including sex and sex hormones, genetic factors, and the influence of sample collection methods. HPA-axis dysfunction in BPD largely mirrors findings demonstrated in post-traumatic stress disorder and may represent a valuable neuroendocrine target for diagnostic or treatment response biomarkers, or for which novel treatments can be investigated.

**Keywords:** borderline personality disorder, hypothalamus–pituitary–adrenal axis, trauma, stress

## Introduction

Borderline personality disorder (BPD) is a common psychiatric illness for which treatment poses a significant challenge due to limited effective pharmacological treatments and under-resourced psychological interventions.<sup>1,2</sup> It represents a serious public health condition in which recurrent suicidal ideation is reported in 69–80% of patients, and suicide rates are estimated to be up to 10%.<sup>3</sup> BPD is broadly characterized by

pervasive patterns of emotional lability, disturbed cognition (such as derealization, depersonalization or hallucinations), identity disturbances, impulsivity and interpersonal difficulties.<sup>4</sup>

Although these symptoms must persist and cause marked distress and/or functional impairment within a variety of contexts for a DSM-5 diagnosis, symptoms often

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fluctuate markedly, particularly in periods of stress. BPD is one of the most stigmatized conditions in psychiatry today,<sup>2,5</sup> but can be understood as a developmental disorder that arises from the maladaptive neurodevelopmental response to trauma and stress.<sup>6,7</sup> Using this framework allows for progress toward a better etiological understanding of BPD, and may provide novel treatment avenues in this complex, yet modifiable condition. This theoretical review will examine BPD in the context of a neurodevelopmental stress-related disorder and provides an overview of the neurodevelopment of the biological stress response, outlining measurements of stress, with a focus on hypothalamus–pituitary–adrenal (HPA) axis measurement and associated confounding factors.

## Rethinking BPD as a neurodevelopmental stress-related disorder

Stress susceptibility and reactivity in BPD is thought to mediate both the development and maintenance of BPD symptomatology, with heightened stress and trauma exposure considered an early life risk factor for developing BPD, and acute stress moderating symptom trajectory. Early life stress is widely accepted as an environmental contributing factor to the onset of BPD, with 30–90% of diagnosed individuals presenting with a history of stressful or traumatic experiences.<sup>8,9</sup> This wide range is likely due to heterogeneity of sample size, classifications used to define the experience of types of abuse<sup>10</sup> and potentially varying operational definitions of trauma, with some studies using narrow trauma definitions that may include only overt trauma (ie, sexual abuse and severe neglect) but exclude an invalidating environment that can result in social attachment issues.<sup>11</sup> Reinelt et al demonstrated that negative mother–child interactions, including both rejection and over-protection, mediate the longitudinal transmission of BPD symptoms from mother to adolescent.<sup>12</sup> The biological stress response, activated by the spectrum of traumas, can promote a vulnerability toward a dysregulated stress response, and stress-related diseases. Inappropriate behavioral stress responses are clinically well characterized in BPD, with impulsivity, emotion dysregulation and problems with emotion perception and dissociation being core features of BPD symptomatology.<sup>13,14</sup> These are often considered to be maladaptive coping mechanisms, or avoidance strategies which may develop in the context of previously experienced trauma, particularly in early life.<sup>15</sup>

Such altered stress responses have also been well documented in BPD at the structural, neurological, and neurobiological level which is believed to underly the maladaptive behavioral and cognitive outcomes presented in BPD.<sup>16</sup>

## Trauma and the neurodevelopment of the stress response

Contemporary views suggest a complex, epigenetic interaction between genes and environment over the lifespan ultimately governs the neurodevelopment of the stress response.<sup>17</sup> Biological adaptations to environmental cues begin at conception and are continually shaped by environmental and social exposures throughout life, with each “hit” serving as a general vulnerability factor that accelerates future stress reactivity. The brain interprets threats based on the current environment (sensory input), modulated by previous experiences (memory), and is dependent on genotype, trait-like responses, and the current reactivity or state of biological systems.<sup>18</sup>

Structurally, chronic stress has been shown to alter gray matter volume in brain regions central in stress responsivity; the amygdala becomes enlarged, and the hippocampus decreases, resulting in changes to fronto-limbic brain circuitry known to be involved in stress perception, emotion processing, and regulation.<sup>19</sup> Neuroimaging studies have demonstrated that individuals with BPD have volumetric reductions in the hippocampus, amygdala, and medial temporal lobes bilaterally,<sup>20</sup> brain regions central in stress regulation, and emotional regulation,<sup>16</sup> and compared to controls, show increased activation of the left amygdala and posterior cingulate cortex, and blunted prefrontal cortex activation, during the processing of negative emotional stimuli.<sup>21</sup>

As childhood represents a developmentally sensitive period in which the brain undergoes rapid development via myelination and synaptic production/pruning, trauma exposure that changes the underlying neurobiological developmental processes will be age-dependent.<sup>22</sup> Moreover, in addition to the timing of trauma being important, the type of stressor exposure has been shown to govern differential neurobiological brain changes, and resultant symptomatology. For example, using a “sensitivity by type and timing” model, Schalinski et al demonstrated that exposure to physical neglect at the age of five induced the most pronounced PTSD symptoms later in life, and observed a biphasic sensitivity pattern suggesting peak vulnerability is between the ages of 5–6 and 12–16 years.<sup>23</sup> Ultimately, accumulating

everyday experiences shift biological reactivity and neural pathways that underlie enduring patterns of physiological and emotional response. Such patterns of response are a core component that characterizes personality traits and states.<sup>24</sup> The development and maintenance of BPD symptomatology can be considered within this neurodevelopmental framework.

## Measuring stress reactivity

Organisms react to internal and external challenges by activating a coordinated set of brain–body responses collectively known as the stress response. In an acute stressful situation, the brain appraises and processes potential threats, and elicits neural networks that govern autonomic, neuroendocrine, and immune systems.<sup>25</sup> These homeostatic systems allow the organism to respond and adapt to threat using an integrated physiological, cognitive, and behavioral response. Tightly orchestrated feedback and compensatory mechanisms ensure each system returns to baseline after the stressor is removed, maintaining each system within appropriate biological ranges. Continued activity comes at a high energetic cost and the ability to return to baseline and maintain “allostasis” is thought to correspond with the organism’s “resilience”.<sup>26</sup> In large part, this ability determines our overall health. When the acute response is insufficient to resolve the perceived, or actual threat, or the regulatory and compensatory mechanisms are frail or faulty, the stress response becomes chronic. This results in “stress sensitive” metabolic, neuroendocrine, cardiovascular, immunological, and emotional responses becoming persistently active.<sup>27</sup>

As the stress response incorporates multiple integrated systems, at sociological, psychological, and physiological levels, measurement of stress biology in humans and psychopathology is inherently complex.<sup>28</sup> Patterns of these responses shape our future responses to stress, and ultimately may result in a cycle of maladaptive stress functioning. As a consequence of developing a maladaptive stress response, past exposure to trauma can confer a similar stress vulnerability into adulthood, increasing both the risk of exposure and sensitivity to further stressors, and responding inappropriately at the physiological and behavioral level.<sup>13</sup> Growing research suggests that in an adaptive response to early life trauma, activity of the stress endocrine system is overactive.<sup>29</sup> In order to ensure homeostasis, chronic negative feedback mechanisms work to attenuate the endocrine system. However, this results in chronic suppression, ultimately altering receptor levels,

brain structure, and homeostatic functioning.<sup>30</sup> This can drive changes in the individual’s ability to cope with future stressors and can result in an individual being more susceptible to developing stress-related disorders.<sup>30,31</sup> Although it is widely accepted that autonomic, metabolic, and immunological stress system changes due to allostasis are important in the context of trauma-related stress responses, and BPD, the HPA-axis of the endocrine axis is the most thoroughly investigated in the literature and is therefore the focus of the current review.

## Endocrine stress system

The endocrine HPA axis initiates a series of neural and hormonal cascades that, in addition to other metabolic functions such as increasing blood sugar levels, and suppressing immune function, serves to regulate the organism’s response to stress.<sup>32</sup> Although HPA activity functionally regulates a broad spectrum of physiological processes, HPA activity has been demonstrated to dynamically increase with environmental and psychological stressors, and consequently the dynamics and functional output of the HPA-axis is why it is one of the most thoroughly investigated physiological systems in clinical psychology and psychiatry,<sup>33</sup> with changes to stress endocrine levels interpreted as an indicator of HPA-axis dysregulation due to chronic illness or stress (Lupien and Seguin 2013). Moreover, it is now appreciated that the addition of biological measures may improve the diagnostic accuracy of psychiatric patient populations, and the HPA-axis has been suggested as a potential target in stress-related disorders.<sup>34</sup>

The HPA-axis, so-called due to the involvement of the hypothalamus, the pituitary, and the adrenals, integrates the central nervous system and peripheral tissues.<sup>35</sup> Neurons in the paraventricular nucleus of the hypothalamus release both corticotropin-releasing hormone and arginine vasopressin into the hypophysial portal vein, stimulating the anterior pituitary gland to produce and secrete adrenocorticotrophic hormone (ACTH) into the general circulation. ACTH in the circulation stimulates the zona fasciculata and zona reticularis of the adrenal gland to synthesize and release glucocorticoids. Glucocorticoids hormone (cortisol primarily in humans) is the end-product effector hormone of the HPA-axis neuroendocrine system, and binds two receptors highly expressed throughout the brain, the glucocorticoid receptor and mineralocorticoid receptor.<sup>36</sup> The hormone-receptor complex can act as transcriptional regulators, in addition to having fast acting, non-genomic activity which can modulate neurotransmitter activity, in what is referred to as

“adaptive plasticity”.<sup>37</sup> Both receptors work in synergy to adjust the HPA-axis and regulate their own release via negative feedback via the central nervous system.<sup>38</sup> This homeostatic mechanism is critical to ensure appropriate functioning of the endocrine response.

## Measures of HPA activity

The reactivity and sensitivity of the HPA-axis, and the ability to return HPA activity to baseline levels, can be assessed using several different measures including observational imaging, neurobiological techniques, and experimental pharmacological and psychological methods.

### Imaging

Neuroanatomical correlates of the stress response can be measured using structural and functional imaging approaches, which largely focuses on fronto-limbic structures critical for processes involved in stress regulation, including stress perception, emotion processing, and regulation (for review see<sup>39</sup>).

### Observational methods

End-point product of the HPA-axis, cortisol, can be assayed using an array of substrates which are simple, and relatively non-invasive, including blood (plasma, serum), saliva, and urine samples.<sup>40</sup> As a lipophilic molecule, majority of circulating cortisol is bound to carrier proteins (cortisol binding globulin (CBG)), with only a small fraction existing in a soluble, unbound form that is bioactive. Salivary cortisol escapes such binding proteins and enters the salivary glands and saliva and is therefore “bioavailable”.<sup>41</sup> Although the concentration of unbound, bioactive cortisol concentration in plasma or serum accurately reflects the levels observed in saliva, total cortisol levels can vary according to the levels of available CBG in blood. CBG concentrations can fluctuate according to estrogen levels, with CBG increasing in states of estrogen excess, eg, pregnancy and estrogen-containing oral contraceptives (OCP), which results in higher concentrations of total cortisol.<sup>42</sup> This emphasizes the importance of establishing reproductive phase, and menstrual cycle phase in females when investigating HPA activity, and the importance of including sex as a factor when analyzing HPA activity, further discussed below. In human, the secretion of cortisol from the adrenal glands generally follows a circadian rhythm that first increases profoundly after awakening, termed the cortisol awakening response (CAR), followed by a diurnal decline thereafter. The night-time

nadir reading occurring around midnight is the lowest cortisol concentration reading. Cortisol measurement can be taken at specific time-points during the diurnal cycle or across time-points to characterize a diurnal cortisol slope in individuals.

Cortisol is also excreted in urine in an unbound, bioavailable form and is therefore unaffected by fluctuations in CBG levels<sup>41</sup> and represents a longer representation of cortisol output. Additionally, hair sampling provides another chronic reading of cortisol levels.<sup>43</sup> As hair grows at an average rate of 1 cm/month, the 1 cm segment closest to the scalp is thought to represent cortisol levels during the most recent past month, with each following cm representing the month prior.<sup>44</sup> This measure is not influenced by the circadian rhythm of the HPA-axis, nor by acute stress, and is therefore thought to represent a retrospective index of long-term cortisol secretion.<sup>43,45</sup> However, seasonal variation, storage length, and hair characteristics such as hair care routines and hair dye, have all been documented to influence cortisol assessment and are considered as potential confounders.<sup>46</sup>

### Experimental methods

Reactivity of the HPA-axis can be measured using pharmacological challenges and through exposure to laboratory-induced stressors. The overnight low-dose dexamethasone suppression test provides a pharmacological approach to challenge the HPA-axis which has extensively been used clinically to measure the response of the adrenal glands to ACTH. Dexamethasone, a potent glucocorticoid ( $\times 30$  higher potency than cortisol) is administered to patients at 11 pm, with cortisol levels being measured before drug administration, and the following morning. Dexamethasone, in the same way, cortisol negatively feedbacks and attenuates further activity, lowers the amount of ACTH released by the pituitary gland. This in turn lowers the amount of cortisol output by the adrenal glands in healthy individuals.<sup>47</sup> In patients with Cushing’s syndrome, a clinical case of hypercortisolism, morning cortisol levels will remain at high levels. This biological paradigm is also used in sub-clinical studies to assess the stress response in psychological and psychiatric studies.<sup>48</sup> Psychologically induced stress reliably generates a physiological stress response in individuals and many developed standardized psychosocial protocols are in use today including the Trier social stress test (TSST), a protocol for the induction of moderate to intense psychosocial stress under laboratory conditions.<sup>49</sup> The TSST involves a 3-min anticipatory period, a 5-min public-speaking task,

and a 5-min mental arithmetic task, all in front of an evaluative panel of “experts”, which reliably induces a 2–4-fold elevation in cortisol above baseline within 30 mins.<sup>49</sup> Meta-analysis of psychological stress protocols suggests that the TSST is the most useful and appropriate standardized protocol for studies of stress hormone reactivity.<sup>50</sup> Physical stressors such the cold pressure test whereby participants submerge their hand in ice water for as long as can be tolerated (typically up to 1–2 mins) also induces a reliable stress response also used to assess the reactivity of the stress response.<sup>51</sup>

## BPD and HPA-axis activity

Considering the growing interest of stress reactivity in BPD, multiple studies assessing HPA activity and end-product cortisol have been conducted. Growing evidence supports a maladaptive or altered HPA function which may contribute to the pathophysiology of BPD by influencing both acute stress reactivity, and the neurodevelopment of traits known to be dysfunctional in BPD, such as emotion regulation, cognitive processing, and impulsivity. Inconsistencies regarding the strength and direction of HPA function in BPD exists, largely due to methodological differences, but patterns are emerging.

Using the standardized psychosocial challenge (TSST), Aleknavičiute et al<sup>52</sup> explored salivary cortisol levels in females diagnosed with BPD in comparison with cluster C personality disorder diagnosis, and healthy controls and demonstrated that although both clinical patient groups reported similar levels of subjective mood disturbances, BPD individuals demonstrated statistically reduced levels of cortisol levels compared to both groups for baseline measures and for HPA-axis activity. Similarly, Deckers et al<sup>53</sup> and Duesenberg et al<sup>54</sup> showed reduced cortisol reactivity/blunted cortisol responses in cohorts of BPD patients compared to control groups subsequent to the TSST challenge. In contrast, a recent finding reported by Inoue et al demonstrated increased cortisol reactivity in female BPD patients after the TSST challenge, as opposed to male patients who showed significantly decreased cortisol levels.

HPA endocrine responses to a pharmacological dexamethasone challenge have also been considerably reported within the BPD literature. Fernando et al<sup>55</sup> compared BPD patients with major depressive disorder and non-psychiatric controls, dosing with 0.5 mg dexamethasone and found that both BPD and major depressive disorder (MDD) exhibited increased cortisol levels (reduced suppression) compared to

controls. Positive correlations were also found between childhood trauma, severity of BPD symptoms, and cortisol output.<sup>55</sup> Carrasco et al, using a dose of 0.25 mg dexamethasone demonstrated opposing findings reporting enhanced suppression (reduced cortisol output). Additionally, Lang et al<sup>56</sup> found no differences in relative suppression after administering 0.5 mg dexamethasone between BPD patients compared to controls. However, they did find that patient with co-morbid post-traumatic stress disorder (PTSD) showed significantly increased suppression compared to those without.<sup>56</sup>

Observational studies investigating endogenous basal or baseline cortisol levels demonstrate considerable variability with increased, decreased, and n/s differences when comparing BPD patients to non-psychiatric healthy controls, particularly when singular time-points only were assessed. For example, Carrasco et al,<sup>57</sup> Mazer et al,<sup>58</sup> and Inoue et al<sup>59</sup> (female cohort only) showed attenuated cortisol levels in comparison to non-psychiatric controls, whereas Fernando et al<sup>55</sup> reported increased cortisol levels in BPD patients, while Paris et al showed no significant differences. Furthermore, chronic or continuous cortisol levels, largely defined by 24-hr urinary cortisol output<sup>55</sup> and multi-sampling morning assessment<sup>60</sup> have shown increased basal cortisol levels, whereas chronic output assessed by hair analysis has shown no significant differences between BPD patients and controls.<sup>61</sup>

The influence of HPA activity on cognition including memory retrieval has also been explored in BPD, as cognitive dysfunction has been described as a core feature of BPD symptomatology.<sup>62</sup> Largely consistent results in healthy individuals report the administration of cortisol (hydrocortisone) or psychosocial challenges impairs memory retrieval and executive function. However, improved memory retrieval after hydrocortisone administration has been described in BPD patients when compared to healthy controls.<sup>63</sup> Yet, the same authors also demonstrated that when challenged with the TSST psychosocial stressor, in contrast to the pharmacological intervention, BPD patients demonstrated an attenuated response of the HPA-axis and no improvement of memory retrieval when compared to controls,<sup>54</sup> adding complexity to the picture and highlighting that different stressor modalities may impart differential stress responses, in different populations. Furthermore, it has also been shown that subsequent to a psychosocial stressor, cognitive empathy is reduced in BPD compared to healthy controls.<sup>64</sup> The authors suggest that reduced emotional empathy after stress may exacerbate interpersonal conflicts, a core symptom characteristic in BPD.<sup>64</sup>

These variable findings may be attributable to the complex, heterogeneous nature of BPD diagnosis and symptom trajectory. However, sample characteristics, and employment of differential observational and experimental methods including singular or continuous/chronic readings (eg, 24-hr output) and various types of stressor administered, further complicate the picture. Known confounding variables when assessing HPA activity should be considered including sex differences and co-morbidities, sample collection and timing, experimental paradigm employed, and moderators such as trauma type and timing and genetic profile.

## Confounding variables when assessing HPA activity in BPD

### Influence of sex and sex hormones

Clear sex differences in HPA activity and cortisol response to stress in healthy individuals have been demonstrated,<sup>65</sup> and therefore is important to account for when investigating cortisol reactivity in the BPD population. The HPA stress response in females is characterized by a larger, more sustained secretion of ACTH and cortisol, suggesting enhanced activity and reduced negative feedback.<sup>66,67</sup> Although the mechanisms are yet to be completely elucidated, testosterone has been shown to largely have an inhibitory effect,<sup>67</sup> while estradiol appears to enhance HPA activity.<sup>67</sup> Accordingly, the association between menstrual cycle phase and endogenous cortisol levels have been demonstrated in reproductive women; in the luteal phase of the menstrual cycle females have a similar cortisol response to men, whereas in the follicular phase, and menopause, they show an reduced cortisol production.<sup>68</sup> High levels of CBG due to oral contraceptive use results in high total cortisol levels, but unbound cortisol levels largely remain the same, regardless of CBG levels.<sup>42</sup> Interestingly, following psychosocial TSST exposure, Inoue et al stratified a BPD population into males and females and found that while salivary cortisol levels were significantly decreased in female patients, they were significantly increased in male patients compared with controls. This supports sex differences in HPA activity may moderate differential stress responses between the sexes in BPD patients, and emphasize the importance of taking gender and sex into consideration.<sup>59</sup>

### Influence of sample collection methods

As cortisol follows a circadian rhythm of secretion with low values upon first wakening, peak values observed 30 mins

after awakening, and follows a steady decline throughout the rest of the day, it is imperative that the timing of sample collection is consideration. This morning “peak” can be measured using a minimum of three separate sampling times (time of wakening, 30 mins after waking, 45 mins after waking), and is known as the CAR.<sup>69</sup> Although there are studies employing a “minimal protocol” analyzing one time point only,<sup>70</sup> this has potential implications for the reliability of measurement. It has been recommended that four measures at 2 consecutive week days are required to reliably measure the CAR response as a trait measure. Furthermore, for cross-sectional studies, it is recommended that up to 6 consecutive days of samples are to be collected for accurate assessment.<sup>71</sup> As phasic and tonic levels of cortisol may be differentially affected in stress-related disorders, measuring acute cortisol reactivity, alongside long-term cortisol measures may provide a clearer picture of dysfunction. Plasma, serum, and saliva can serve as biological matrices.

### Influence of co-morbidity and heterogeneity

Comorbid Axis I symptoms including PTSD and MDD, both highly prevalent co-morbidities of BPD, have also shown altered HPA activity, although in opposing directions. Individuals with PTSD demonstrate an attenuated HPA output, while MDD patients have been reported to have increased cortisol levels, when compared to healthy controls.<sup>65,72</sup> Moreover, there is growing evidence for differential HPA-axis function between melancholic depression and atypical depressive subtypes with melancholic depression characterized by increased basal cortisol levels, while atypical depression is characterized by normal or decreased cortisol levels.<sup>73</sup> Consequently, changes in HPA-axis activity in BPD appear to be moderated by such comorbid symptomatology. Lang et al investigated HPA activity in BPD patients with and without comorbid PTSD compared to controls and demonstrated that although basal levels were not significantly different comparing the three groups, BPD patients with comorbid PTSD showed increased feedback sensitivity compared to BPD patients without co-morbid PTSD.<sup>74</sup> In diagnosed BPD patients, reduced feedback sensitivity was found in those patients who presented with a low number of PTSD symptoms, while findings in patients presenting with a high number of PTSD symptoms did not differ from those in controls.<sup>75</sup> The same authors showed that depressive symptoms were

positively correlated to cortisol levels.<sup>75</sup> Such results have led to the hypothesis that biologically distinct groups may exist in BPD based on their endocrine profile, with one patient group presenting with predominate trauma-associated PTSD symptomatology, with associated decreased cortisol levels and increased in HPA-axis suppression, and another presenting with predominate affective dysregulation and depressive symptoms, with associated decreased HPA-axis suppression, and increased cortisol output.<sup>76</sup>

BPD is consistently misdiagnosed as bipolar disorder due to many overlapping clinical features. It has also been suggested that BPD should be conceptualized as part of bipolar spectrum, at least with regards to overlapping etiologies.<sup>77</sup> However, on an endocrine level, recent meta-analysis reports that bipolar disorder is associated with higher levels of basal cortisol when compared to controls,<sup>78</sup> and a direct study comparing BPD and bipolar patients demonstrated differences with regards to neuroendocrine functioning, and differential stressor subtype moderators.<sup>58</sup> The authors showed that a positive correlation was observed between a history of sexual abuse and cortisol levels among patients with BPD, while a negative correlation was observed in patients with BD, suggesting a different inhibitory response for each disorder.<sup>58</sup>

Type of childhood adversity has also been studied in the context of HPA activity and BPD, with higher cortisol levels positively correlating with severity of sexual abuse in BPD patients, and lower cortisol levels being measured in BPD patients who present with a background of emotional and physical neglect.<sup>79</sup> In a study investigating the influence of adversity during different neurodevelopmental ages on cortisol stress response in later adolescence, it was demonstrated that hypersecretion of cortisol activity resulted from adversities before the age of 11, and hypo-secretion after the age of 11, emphasizing timing as an important factor in the development of the neuroendocrine axis.<sup>80</sup> This highlights the importance of considering type and timing of early life stress within the context of stress neurobiology in BPD, as different modalities and neurodevelopmental timing of such adversity could correspond to biologically unique subtypes.

## Genetics and epigenetics

Not all individuals exposed to stress will develop stress-related psychiatric disorders, and there is great variability in individual responses to stressors. Those with enhanced homeostatic resilience mechanisms can adapt successfully to stress without developing neurodevelopmental psychopathology. Stress-

related disorders have been hypothesized to arise due to the complex interaction between genes and the environment. Early life stressors can leave an epigenetic chemical mark on the brain that can “program” the developing brain and stress mechanisms and can regulate such susceptibility and resilience. “Epigenetics” refers to the “stable alterations in gene expression potential that arise during development and differentiation, and is under the influence of the environment”.<sup>81</sup> For example, epigenetic DNA methylation can inhibit transcription and reduce gene expression of targeted genes. In particular, genes involved in HPA-axis activity appear to be vulnerable to early life stress epigenetic modification.<sup>82</sup> For example, the 51 kDa FK506 binding protein (FKBP5) is a co-chaperone of heat shock protein 90 (hsp90) that regulates glucocorticoid receptor sensitivity. When bound to cortisol, the glucocorticoid receptor can efficiently translocate into the nucleus, which can alter the transcription of many diverse genes via genomic mechanisms. The FKBP5 suppresses glucocorticoid receptor activity by decreasing its affinity to cortisol, and consequently reduces nuclear translocation and working in a negative feedback manner, downregulates the HPA stress response. Increased levels of FKBP5 can therefore prolong the stress response and alter circulating cortisol levels.<sup>83</sup> A functional single nuclear polymorphism (SNP) has been identified in the FKBP5 gene (rs1360780) that is associated with higher FKBP5 protein levels, and glucocorticoid receptor sensitivity differences,<sup>84</sup> and has also been implicated in risk of psychiatric disorders.<sup>84,85</sup> Moreover, polymorphisms in the FKBP5 gene, including rs1360780, has been shown to interact with early life stress and moderates’ risk of the development of depression and PTSD in adulthood.<sup>86,87</sup> Despite the known gene × environment interactions in BPD, only very few studies have evaluated such interactions. Two recent studies have explored genetic variants in HPA-axis functioning in association with BPD diagnosis. Martin-Blanco et al analyzed 47 polymorphisms in the HPA-axis in BPD compared to non-psychiatric controls, and found that two FKBP5 SNPs (rs4713902 and rs9470079) showed a significant association with BPD diagnosis.<sup>88</sup> Additionally, both SNPs were more frequent in patients reporting child abuse, and emotional neglect. In another recent publication, five FKBP5 SNPs (rs3800373, rs9296158, rs737054, rs1360780, rs9470080) were genotyped to assess potential interactions between the polymorphisms and childhood trauma. All SNPs concurred significant association with BPD, with a significant main effect observed between SNP rs3800373 and a history of emotional abuse, although this did not remain significant after correcting for multiple testing.<sup>88</sup>

Interestingly, it has also been demonstrated that FKBP5 genotype can significantly moderate long-term effectiveness of exposure-based psychotherapy for PTSD, suggesting that such genetic factors not only moderate disease risk, but also the responsiveness to intervention.<sup>89</sup> The oxytocin gene, responsible for the transcription of the oxytocin hormone considered to be important for socioemotional functioning, has also been studied in relation to BPD risk in the context of gene  $\times$  environment interactions. The SNP rs53576 was demonstrated to interact with quality of family functioning in childhood to predict BPD symptomatology later in life; A-allele carriers had high levels of BPD symptoms under negative family conditions and low levels under positive conditions, whereas GG homozygotes had average levels of BPD symptoms regardless of their family environment.<sup>90</sup> Epigenetic modifications of HPA-axis genes including increased methylation at the promoter region of the glucocorticoid receptor (NR3C1) have also been associated with patients with diagnosed BPD,<sup>91</sup> people with childhood trauma,<sup>92</sup> and in subjects with BPD and a history of childhood trauma.<sup>93</sup> Additionally, BPD clinical severity has also been significantly positively correlated with methylation levels of the NR3C1 gene, conferring further support of the environmental and gene interactions involved in the onset of BPD symptomatology, providing a plausible mechanism by which early life trauma may lead to later life psychopathology.<sup>94</sup> Collectively, these results provide examples of how “susceptible” genes may moderate BPD development and underlying traits which may be expressed under certain environmental conditions.

## Meta-analyses of cortisol in BPD

In order to resolve the discrepancies between studies assessing cortisol levels and HPA activity, two recent meta-analyses have been recently published, statistically investigating HPA activity and cortisol levels in BPD (one published by the current authors<sup>95</sup>). Drews et al<sup>96</sup> conducted a broad and comprehensive quantitative review, comparing BPD to healthy controls, and to clinical controls of major depressive disorder and other personality disorders. Ten studies were included to statistically reveal significant blunting of HPA activity with regards to acute stress and recovery from psychosocial stress when comparing BPD to healthy controls ( $p=0.003$ ,  $I^2=31\%$ , BPD  $n=183$ , HC= $n=180$ ), although no statistical differences were observed when comparing BPD to clinical cohorts (MDD, PD). Cortisol readings subsequent to pharmacological challenges (in a total of four studies) did not differ

between BPD patients and controls ( $p=0.688$ ,  $I^2=87\%$ , BPD  $n=83$ , HC= $n=92$ ). Five studies comparing chronic, continuous readings of overnight mean urinary cortisol (multiple readings) and 24-hr urine output (collective reading), in BPD and controls, demonstrated statistically increased elevated cortisol outputs ( $p=0.003$ ,  $I^2=1\%$ , BPD  $n=90$ , HC= $n=110$ ).

As discussed, cortisol readings, particularly singular readings, are known to be moderated by many factors, including gender, biological matrix, time of sampling, and consequently high heterogeneity could be expected. Although Drews et al found no statistical difference of singular cortisol assessments between BPD and healthy controls ( $p=0.132$ , BPD  $n=698$ , HC= $n=832$ ), high heterogeneity between the studies was observed ( $I^2=94\%$ ), and potential publication bias was reported. Multiple samples taken from single studies (ie, morning and afternoon measurements from the same studies) also elicit concerns regarding statistical non-independence which can cause effect sizes to be correlated. Failing to account for such non-independence of data points can lead to erroneous conclusions.<sup>97</sup> Thomas et al<sup>95</sup> included 12 studies in their statistical analysis comparing BPD vs control singular cortisol time points, excluding those studies that had a prior subgrouping, and had predicted means based on modeling. The standardized mean difference of basal/baseline cortisol levels indicated significantly lower mean cortisol level for the BPD group when compared to non-psychiatric controls ( $p=0.014$ , BPD  $n=278$ , HC= $n=268$ ). Heterogeneity was moderate ( $I^2=53\%$ ), however no publication bias was observed. In addition, to further characterize the observed heterogeneity, subgroup analysis was conducted with consideration of biological matrix; subgroups were confined to blood samples, saliva samples, or other (which consisted of chronic readings of 24-hr urine output and longitudinal hair readings). Results reflected the larger pooled analysis, with both saliva and blood subgroups showing reduced levels of cortisol in BPD compared to non-psychiatric controls, with reduced heterogeneity (blood= $I^2=25.2\%$ , saliva= $I^2=43.3\%$ ). Interestingly, “other” sampling matrix including chronic 24 hrs urine and hair readings reported cortisol levels in the opposite direction (increased cortisol levels). While more studies may have confirmed a statistical increase, this mirrors Drew et al's findings who found higher statistical differences in continuous, or chronic levels of cortisol BPD. This may reflect differences in endogenous basal levels compared to longer, more chronic readings of



cortisol which consider the total temporal dynamics of cortisol levels over time.

Collectively, the results of the two recent meta-analyses support altered HPA function in diagnosed BPD patients, with lower levels of basal cortisol, blunted responses to psychosocial challenges, but with higher chronic cortisol readings. This could be hypothesized as although average endogenous basal levels are low in BPD, and the mounted stress response is blunted compared to non-psychiatric controls, there may be increased situations of perceived stress, or a hypervigilance toward potentially threatening events that results in constant activation of HPA activity and overall higher chronic readings. The results largely suggest BPD may parallel PTSD in overactive HPA feedback function, with reports of lowered basal/baseline levels compared to non-psychiatric controls, increased chronic readings, and increased reactivity after experimental stressors. This is interestingly considering the current debate to consider the use of the diagnostic category “complex posttraumatic stress disorder” (cPTSD) as detailed in the forthcoming ICD-11 classification system rather than the diagnostic classification of a personality disorder. cPTSD is characterized by the clinical features of PTSD plus additional symptom clusters of emotional dysregulation, negative self-cognitions, and interpersonal conflicts, thus resembling the clinical symptomatology observed in BPD.<sup>98</sup> Therefore, the diagnosis of the syndrome as a personality disorder continues to provoke controversy given the ubiquity of complex trauma in those diagnosed, and the distinct overlap with trauma-related diagnosis such as cPTSD and PTSD.<sup>99</sup> Alongside HPA dysfunction, BPD and PTSD present with additional similarities at the etiological, genetic, neurobiological, and clinical level, with similar rates of trauma and clinical features, dysfunction in fronto-limbic functionality, and FKBP5 genetic alterations. It has been proposed that the potential key difference of the two disorders is the timing of trauma exposure, which can differentially affect brain connectivity and therefore symptomatology; early life trauma more likely to lead to a diagnosis of BPD, while trauma exposure in adulthood increase the risk for PTSD.<sup>52</sup> Initial evidence suggests that hydrocortisone administered in the acute aftermath of trauma may promote enhanced synaptic plasticity and connectivity and prevent development of PTSD.<sup>100</sup> Although this research is still in its infancy, and the complexities surrounding manipulating a homeostatic system imperative for many functions of life appreciated, the suggestion of manipulating the neuroendocrine axis provides promise of future treatment possibilities in trauma-related disorders.

## Conclusion

Although the complexities of BPD result in significant therapeutic challenges, BPD can be considered as a modifiable, developmental disorder. Hypothesized to arise from maladaptive neurodevelopmental responses to stress, the stress response on a behavioral and physiological level has been reported as altered in diagnosed individuals. HPA-axis dysfunction in BPD largely mirrors findings demonstrated in PTSD, and may represent a valuable neuroendocrine target for treatment response biomarkers, or for which novel treatments can be investigated. The potential to modulate the stress response, or enhance stress resilience, in at risk populations based on neurobiological and genetic biomarkers of the stress endocrine system may prevent the onset of stress-induced psychiatric disorders, including BPD. A deeper understanding of the biological mechanisms implicated in trauma exposure and stress resilience and vulnerability, and how the biological endocrine system can influence both onset and symptom trajectory in BPD, will lead to critical advances in both basic science and clinical prevention and intervention. Using this framework may also help to decrease stigma and provide a much needed trauma-informed treatment approach for patients diagnosed with BPD.

## Disclosure

The authors report no conflicts of interest in this work.

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