Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 07, 2024

The HPA-Plasticity Feedback Loop, Interactions Between Neuroplasticity, Borderline Personality Disorder, and the HPA-Axis: A Systematic Review

Yash Srivastav[1], Kapil Raghuwanshi[2], Jaya Singh[3], Anil Kumar[4], Vikram Kumar[5], G Vijaya Kumar[6], Sona A[7], Kamalesh Mistry[8], Arati Rai[*9]

[1]Assistant Professor, Department of Pharmacy, Azad Institute of Pharmacy and Research, Lucknow, Uttar Pradesh, India
[2]Assistant Professor, Department of Biochemistry, Chhindwara Institute of Medical Sciences, Chhindwara, Madhya Pradesh, India
[3]Assistant Professor, Department of Pharmacology, Tahira Institute of Medical Sciences, Gorakhpur, Uttar Pradesh, India
[4]Head & Assistant Professor, Department of Chemistry (PG), Sahibganj College Sahibganj, Jharkhand, India
[5]Assistant Professor, Faculty of Pharmaceutical Sciences, Baba Mastnath University, Rohtak, Haryana, India
[6]Professor, Department of Pharmacy Practice & Pharmacology, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, Andhra Pradesh, India
[7]Associate Professor, Department of Biotechnology, SAS SNDP Yogam College Konni, Pathanamthitta, Kerala, India
[8]HOD, Department of Pharmacognosy, Rai University, Ahmedabad, Saroda, Dholka,Gujarat, India
[*9]Principal, Department of Pharmacy, Saroj College of Pharmacy, Ahimamau, Lucknow, Uttar Pradesh, India
*Corresponding Author: Arati Rai, Principal, Department of Pharmacy, Saroj College of Pharmacy, Ahimamau, Lucknow, Uttar Pradesh, India

Article submitted on: 25/06/2024 **Article revised on: 03/07/2024** **Article accepted on 10/07/2024**

ABSTRACT:

Borderline personality disorder is characterized by heightened sensitivity to rejection, unstable interpersonal relationships, self-image, emotions, and behaviors. 1-2% of the population is associated with higher rates of comorbid psychiatric pathology and significant rates of suicide (10%). Recent studies have suggested that high levels of cortisol in individuals with borderline personality disorder result in altered glucocorticoid receptors, significant cortical reduction, and reduction of brain-derived neurotrophic factor, an essential protein in neuronal development, plasticity, and health. Urine samples of individuals with borderline personality disorder have displayed higher cortisol levels relative to healthy controls. Cortisol has significant metabolic

and mental changes and can significantly alter the neuronal structure, linked to multiple psychiatric disorders, greater levels of stress, and other BPD-like symptoms. Though preliminary evidence suggests connections between the three subjects, the relationship between neuroplasticity, glucocorticoids, and BPD has yet to be thoroughly analyzed. This literature review examines the connections between BPD, glucocorticoids, and neuroplasticity to present a correlation-based HPA-Plasticity Feedback Loop.

KEYWORDS:

Borderline personality disorder, HPA-Axis, neuroplasticity, BPD, psychopathology, BDNF, glucocorticoids

1. INTRODUCTION

1.1 Background

Personality disorders are characterized by inflexible or maladaptive thoughts and behaviors (Regier et al., 2013). Borderline personality disorder (BPD) is characterized by a heightened sensitivity to rejection, leading to unstable interpersonal relationships, self-image, emotions, and behaviors (Chapman et al., 2023; Kulacaoglu & Kose, 2018). BPD affects 1-2% of the population and around 20% of psychiatric inpatients (Chapman et al., 2023; Ellison et al., 2018). Within the population, there is an alarming correlation between comorbid psychiatric pathologies and suicide.

Individuals with BPD exhibit comorbid pathology of anxiety disorders (88%), substance abuse disorders (64%), eating disorders (53%), attention deficit hyperactivity disorder (ADHD) (10% to 30%), depression (71%-83%), and bipolar disorder (15%) (Chapman et al., 2023; Yoshimatsu

& Palmer, 2014). Between 65% to 85% of BPD patients have reported engaging in non-suicidal self-injury (NSSI) to the wrist and arms, and up to 10% of individuals with borderline personality disorder will die by suicide (Oumaya et al., 2008).

BPD's etiology is believed to be, like many psychopathologies, multifaceted, presenting contributions from environmental and heritable factors. In this literature review, we will focus on several biological processes that suggest vulnerability and correlation with BPD, look at the mechanisms that may contribute to biological vulnerability and pathology, and how such vulnerabilities contribute to the development and worsening of the condition.

Given the severity of BPD on the lives of many individuals and its high mortality rate, clinicians and researchers must make efforts to understand further the underlying causes, interactions, and mechanisms of the pathology to improve the lives of individuals with BPD. Heritability has been suggested to be approximately 40% in BPD. At the same time, alternations in amygdala development, gut microbiome, and exposure to childhood trauma - a critical period in time for brain development - such as abuse and neglect have, too, been commonly reported in the BPD population (Amad, 2014; Di Benedetto et al., 2022). Individuals with BPD face several challenges in their daily lives, including maintaining stable relationships, employment, and social isolation. Individuals with BPD have been associated with self-destructive behaviors, emotional dysregulation, unemployment, and impulsivity, each of which may further strain relationships (Amad, 2014; Kealy et al., 2021).

1.2 Glucocorticoid Background

Glucocorticoids, a class of steroid hormones involved in the stress response, have, at high levels, been implicated in disrupting neuroplasticity and resulting in BPD-like symptoms (Carvalho

Fernando et al., 2013; Filippone et al., 2019). Cortisol is the primary glucocorticoid in humans (Suri & Vaidya, 2013). These hormones are essential in regulating the body's response to stress, modulating various physiological processes such as immune function, metabolism, and cognition. Impairment and dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, the primary neuroendocrine system responsible for controlling glucocorticoid release, has been observed in individuals with BPD, as well for a range of other pathology (Carvalho Fernando et al., 2013; Thau et al., 2023). Elevated cortisol levels and hyperactivity have been reported as a response to stress in BPD patients. Cortisol hyperactivity puts patients at risk of toxicity, which may impair brain development (Carvalho Fernando et al., 2013; Coutinho et al., 2017; Musazzi & Marrocco, 2016). This dysregulation may contribute to the emotional and behavioral symptoms observed in individuals with BPD, contributing to the underlying neurobiology and mechanisms of the disorder.

1.3. Neuroplasticity

Neuroplasticity is an inclusive term that refers to the brain's ability to modify its functionality through structural changes to connectivity in response to different environmental stimuli such as learning and experience. Healthy brain development relies on the brain's plasticity to form memories, learn, and recover from injuries (Baroncelli et al., 2011; Puderbaugh & Emmady, 2023). In recent years, impaired neuroplasticity has been increasingly researched as a contributing factor to psychopathologies (Sengpiel, 2018). Current literature is far from fully understanding neuroplasticity's role in BPD, though preliminary data reveals several connections.

Glucocorticoids such as cortisol have been studied and determined to influence neuroplasticity, such as modulation of synapses, dendritic remodeling, and neurogenesis (McEwen & Akil, 2020). While glucocorticoids are vital to preserving neuroplasticity, chronic exposure to glucocorticoids has influenced the structure and function of neurons, resulting in toxicity and atrophy of cells (McEwen, 2015). Research has supported that high levels of cortisol result in reduced expression of the brain-derived neurotrophic factor (BDNF) (Santiago et al., 2020). Patients diagnosed with BPD are known to possess high levels of cortisol (Thomas, Gurvich, Hudaib, et al., 2019). Cortisol is correlated with high levels of stress (Eckert et al., 2017) and BPD-like symptoms, which may furthermore contribute to higher levels of cortisol (Lee et al., 2019). These connections between BPD, glucocorticoids, and neuroplasticity combine to present a promising correlation based on "HPA-Plasticity Feedback Loop Theory," in which BPD is influenced due in part to the relationship between cortisol levels and neuroplastic changes throughout individuals with BPD.

This review analyzed current scientific literature that supports the early connections between neuroplasticity, BPD, and glucocorticoids. The potential links between glucocorticoids and neuroplasticity in BPD were investigated, reviewing relevant studies examining these relationships and their implications for treatment and interventions, as well as for limitations in the current literature and potential future directions. Ultimately, a deeper understanding of these relationships may further the development of more effective treatments and interventions, helping to improve clinical outcomes for individuals living with this challenging pathology.

2. NEUROPLASTICITY AND BPD

2.1. Introduction to Neuroplasticity and BPD

Neuroplasticity refers to the brain's ability to adapt structurally and functionally through reorganization and the strengthening and weakening of neural networks (regarding synaptic strength, e.g., activity in the brain, dendric, molecular protein abundance, and changes in neural pathways and function) (Mateos-Aparicio & Rodríguez-Moreno, 2019). Research on neuroplasticity has grown into various subfields, primarily focusing on neuronal presentation and collateral sprouting, such as plasticity and functional reorganization: equipotentiality, vicariation, and diaschisis.

The subdivision of neuronal regeneration and collateral sprouting consists of divisions of neuroplasticity that consist of motivation, exercise, modulation via drugs, and other environmental factors that ultimately are learning-centric (Brzosko et al., 2019; Johnston, 2009; Maier et al., 2019). Neuronal regeneration and collateral sprouting include timing of action potentials and their effects on strengthening and weakening synaptic plasticity; spike-timing-dependent-plasticity (STDP), activity-dependent changes among networks of neurons; meta plasticity, the mechanisms that maintain homeostasis in a network over time; homeostatic plasticity, and the brains further genesis of neurons as an adult; adult neurogenesis (specifically in the hippocampus and olfactory bulbs) (Puderbaugh & Emmady, 2023).

Functional reorganization is a unique concept in neuroplasticity relating to damaged brain areas. The brain's capacity to compensate for functional loss via utilizing its other hemisphere, equipotentiality, and its capacity to overtake lost functions using unintended parts (networks) of the brain: Vicariation. A third, though separate branch of reorganization, includes diaschisis, in which damage to the brain results in loss of function on an interconnected pathway (Puderbaugh & Emmady, 2023).

Each of these processes explored in neuroplasticity sheds light on how the brain fundamentally functions, and networks, and the pieces come together as an essential tool for optimal maintenance and brain function, playing crucial roles in development, learning, memory, and recovery from brain damage. Studies have suggested that alterations in neuroplasticity may aid in the progression of psychiatric disorders, including BPD (Bozzatello et al., 2021). BPD is a complex psychiatric condition, its etiology ranging from a combination of neurobiological, genetic, environmental, and various other factors (Chapman et al., 2023). Emerging research has highlighted neuroplasticity as a possible neurobiological contributor to BPD and other psychiatric disorders (Amad et al., 2016).

2.2. Cortical Reduction and BPD

While research in neuroplasticity and BPD is up and coming, based on our understanding of neuroplasticity, the subject may be applied to cortical representation. Biological and neuroendocrine imaging studies have determined cortical volume reduction in multiple areas of the brain, especially the amygdala and hippocampus (Nunes et al., 2009). Aguilar-Ortiz et al. conducted a 76-women matched-control study using whole-brain, voxel-based morphometry (VBM). This technique examines the whole brain to detect small changes in volume measurements. The study measured, using VBM, that volume decreases in the dorsolateral prefrontal cortex, the right dorsolateral frontal cortex, and the ventromedial frontal cortex. However, it did not find the expected volume reductions in the amygdala and hippocampus—the patterns in volume reduction aligned with those of major depressive disorder (MDD). The connections between the amygdala and the medial frontal cortex have been hypothesized to have a relationship with BPD and MDD, as the pathway plays a role in emotional regulating and mood disorders (Aguilar-Ortiz et al., 2018; Price & Drevets, 2012).

2.3. Amygdala and BPD

Though the previous study discussed did not note findings of the amygdala's changes in volume, it is a significant structure in the limbic system that regulates many aspects of emotion and memory and has been supported by meta-analysis to play a role in BPD and is worth discussing (Morey et al., 2012; Nunes et al., 2009; Vatheuer et al., 2021). The amygdala plays an essential role in emotional and fear learning and feelings such as happiness, fear, anger, and anxiety; situations that challenge the sympathetic response are related to increased activity in the medial amygdala, and those with BPD tend to be hypersensitive to social threat, triggering "flight responses on behavioral, neuronal, autonomic, and hormonal levels" (Bertsch et al., 2020)." Neuroimaging studies have reported heightened amygdala activation in disorders such as BPD, posttraumatic stress disorder (PTSD), social phobia, and specific phobia (Shin & Liberzon, 2010). The amygdala has been noted to have different volume and activity variations in individuals with BPD. Findings from using imaging (VBM, fMRI) to detect volume reductions have shown an average of 8% reduction in volume in the amygdala compared to healthy controls (Cattane et al., 2017). Literature examining activity via threat circuits using a variety of hostile faces through video and photo-flashes has noted increased activity in the amygdala in participants with BPD (Bertsch et al., 2020; Coutinho et al., 2017; Morey et al., 2012). Changes in the strength and connectivity of neural pathways can lead to changes in the functioning of brain structures, as shown by post-mortem tissue samples with impairments (Schloesser et al., 2008); this decreased ability for the brain to adapt and change according to new stimuli may implicate abnormalities in synaptic and cellular plasticity and its relation to BPD. One study analyzed amygdala-prefrontal intrinsic connectivity with 48 BPD patients and 39 non-patient controls using resting-state functional magnetic resonance imaging (fMRI). The study

determined that individuals with BPD had altered connectivity states between the amygdala and prefrontal cortex (PFC), which may contribute to BPD's emotional dysregulation and impulsive behaviors (Morey et al., 2012). The potential change in volume, reactivity, and connectivity of an impaired amygdala in individuals with BPD further suggests a link between neuroplasticity and BPD.

2.4. Hippocampus and BPD

As previously discussed, the hippocampus has been a topic of interest over the last two decades regarding volume, activity, and plasticity in psychiatric pathology. The hippocampus is a brain region involved in learning, memory, and stress regulation. It has exhibited reduced volume by up to 16% (Cattane et al., 2017) and altered connectivity among various other parts of the brain in individuals with BPD (Orth et al., 2020). One study from March 2022 discusses the role of neuroplasticity in MDD, suggesting that the hippocampus is a highly plastic region of the brain, as it is essential for learning and memory (Tartt et al., 2022). High levels of interleukin-1 beta (IL-1β) were noted to impair neuroplasticity and negatively affect MDD. BPD has limited research on IL-1β, and while BPD and MDD are two distinct disorders, 96% of individuals with BPD meet the criteria for a mood disorder, 71%-83% of individuals exhibiting depression in their lifetime (Zimmerman et al., 2019), and there is significant genetic overlap and comorbidity between the two conditions (Lohoff, 2010). IL-1β both boosts the production of glutamate and inhibits the production of brain-derived neurotrophic factor (BDNF), an important promotor of neuroplasticity, which causes toxicity to neurons and the inhibition of neuronal growth, respectively (Krystal et al., 2009). Promoting toxicity in the brain may contribute to the lack of plasticity (development) of connections through the brain. It may be a contributing factor to BPD and other pathologies.

2.5. Molecular Markers

Studies investigating cellular and molecular markers of neural plasticity have also provided insights into altered neuroplasticity in BPD. Neurotrophic factors like BDNF have been shown to play a crucial role in the molecular and cellular processes that support brain plasticity, neuroprotection, and neurogenesis (Levy et al., 2018). A neurotrophic hypothesis suggests psychiatric pathology may be due in part to imparted neurotrophic support, suggested by the correlation of low levels of BDNF and high frequencies of mood disorders, underlying mechanisms being modulated by kinase activity resulting in changes in cyclic AMP levels and altered responses in element binding protein, which regulates the expression of BDNF (Krystal et al., 2009). In this review, this relationship may also be applied to BPD. Studies have found that individuals with BPD have reduced levels of BDNF, as mentioned in the previous section, which may contribute to the impaired neuroplasticity observed in this population (Di Benedetto et al., 2022).

Furthermore, studies have explored genetic causes of BPD, including polymorphic variants in HPA axis genes (Cattane et al., 2017) and DNA methylation patterns (Quevedo et al., 2022). A study by Di Benedetto et al. in 2022 found that the BDNF gene may serve as a biomarker for the effect of childhood trauma on BPD symptoms (Di Benedetto et al., 2022). Individuals diagnosed with BPD frequently exhibit elevated cortisol levels, indicative of a hyperactive hypothalamic-pituitary-adrenal (HPA) axis (Thomas, Gurvich, Hudaib, et al., 2019). BDNF, a vital protein involved in neuroplasticity and HPA axis activity, has been found to have a significant connection with the HPA axis's reactivity to stress. Research suggests that HPA axis activation may adversely affect BDNF expression, subsequently impacting neuroplasticity and leading to

detrimental mental health consequences and stress responses (Castillo-Navarrete et al., 2023; Fiocco et al., 2020; Kunugi et al., 2010).

3. GLUCOCORTICOID AND BORDERLINE PERSONALITY DISORDER

3.1. Introduction to Glucocorticoids

Glucocorticoids (GCs) are a steroid hormone produced by the adrenal glands as a stress response, playing an essential role in the body's immune system. Glucocorticoid receptors (GRs) belong to the nuclear receptor family of ligand-dependent transcription factors and regulate the expression of GC-responsive genes, essential for autoimmune, inflammatory, allergic, and lymphoproliferative diseases (Nicolaides et al., n.d.). The relationship between glucocorticoids and BPD has been steadily growing, as research has shown that individuals with BPD may have abnormalities in the functioning of glucocorticoid receptors, suggesting a biological basis for dysregulation of the stress response (López-Villatoro et al., 2022). In this review, we focus on a class of GCs, a steroid hormone, cortisol (also manufactured as hydrocortisone), which is a potent hormone released from the hypothalamus and modulates the regulation of the stress response, as well as other processes such as blood pressure, metabolic function, and the circadian rhythm (Kouhnavardi et al., 2023). However, for this review, the stress response will be the primary focus.

3.2. HPA axis and Cortisol

In response to stress, the hypothalamic-pituitary-adrenal (HPA) axis is activated. Initiated in the hypothalamus, corticotropin-releasing factor (CRF) and arginine vasopressin (AVP) are released from the paraventricular nucleus (PVN), resulting in the secretion of adrenocorticotropic

hormone (ACTH), which binds to receptors of the adrenal gland and stimulates the release of cortisol. The HPA is part of the neuroendocrine system and the body's natural response to stress. Prolonged hyperactivity of the HPA axis can lead to chronic stressors on the body and the brain, which may result in psychiatric disorders and other pathology.

Recently, a 2019 systematic review and meta-analysis by Thomas et al. found that individuals with BPD have higher baseline cortisol levels compared to non-psychiatric controls, suggesting the interplay of the HPA axis and mental illness (Thomas, Gurvich, Hudaib, et al., 2019). Another study by López-Villatoro et al. in 2022 suggested that abnormal functioning of glucocorticoid receptors at the cellular level may be found in individuals with BPD. The study's results highlighted the alterations of the HPA axis in individuals with BPD, showing a naturally lower expression of glucocorticoid receptors (López-Villatoro et al., 2022).

3.3. Neural Development and Youth

The dysregulation of the HPA axis has been linked to a variety of mental health conditions, including BPD (Thomas, Gurvich, & Kulkarni, 2019). Literature has identified that individuals with BPD have altered cortisol levels, further linking BPD with the HPA axis (Thomas, Gurvich, Hudaib, et al., 2019). Childhood trauma is a risk factor in the onset of BPD (Cattane et al., 2017). Studies have shown the relationship between exposure to chronic stress and dysregulation of the HPA axis, which is responsible for the production of glucocorticoids (Thomas, Gurvich, & Kulkarni, 2019). In 2017 Cattaneo et al. investigated the association of the HPA childhood trauma-associated vulnerability and developmental stress. It was found that among biological systems affected by childhood trauma, neuroplasticity, neurotransmission, the HPA axis, and endogenous opioid systems were affected. Regions like the hippocampus and the amygdala

exhibited changes partly due to prolonged chronic cortisol exposure, suggesting early-life adversity may biologically affect neuronal and personal development (Cattane et al., 2017).

3.4. Theoretical Glucocorticoid Dysregulation in BPD

One theory within the field of glucocorticoid dysregulation in BPD suggests that childhood trauma and temperamental traits correlate with glucocorticoid dysregulation to increase the risk of developing BPD (Cattane et al., 2017). A second theory suggests that BPD is a neurodevelopmental stress-related disorder in which early life stressors can lead to HPA axis dysregulation and subsequent BPD symptoms (Thomas, Gurvich, & Kulkarni, 2019). On the contrary, López-Villatoro et al. also suggest that the alteration of glucocorticoid receptor expression in BPD patients is not related to posttraumatic stress, hypothesizing overprotection, parental neglect, or other traumatic experiences in a modified social (rather than biological) model may be related to the development of BPD (López-Villatoro et al., 2022). Each theory describes the complex relationship between biological and environmental factors in the development of BPD. There is evidence that medications such as mood stabilizers and antidepressants targeting the HPA axis, the stress response system, may be effective for treating BPD (Olabi & Hall, 2010).

4. GLUCOCORTICOIDS, NEUROPLASTICITY, AND BORDERLINE PERSONALITY DISORDER

4.1. Introduction

It is important to consider the relationship between the three possible inputs, neuroplasticity, the HPA axis and BPD, their mechanisms, as therapeutic strategies targeting one route may improve the others. The HPA-Plasticity feedback loop in this review is defined by BPD's relationship

with the HPA axis, which in most pathologies is correlated with elevated sympathetic activity and high levels of cortisol. High levels of cortisol result in neuroplastic changes, affecting important regions for mood regulation, and may even worsen the pathology.

4.2. Neuroplastic Changes and Role in the Stress Reponse

Alterations of the HPA axis impact neuroplasticity, as structural changes to the brain may result from elevated stress levels (Fenoglio et al., 2006). Epigenetic changes, changes in gene expression that are not caused by changes in the DNA sequences, have been accepted to significantly impact an individual's ability to cope with stress (Pittenger & Duman, 2008).

Because cortisol plays a role in metabolic and mental influence, it has been claimed to significantly influence neuronal structure and function. The resulting consequences include neurodegenerative changes in sensitive brain regions such as the hippocampus (Dziurkowska & Wesolowski, 2021).

4.3. How Hippocampal and Limbic Structure Volume Contribute to Dysregulation

The hippocampus has been discussed as a brain region involved in learning, memory, and stress regulation. Chronic stress can reduce the number of dendric spines and result in the death of hippocampal pyramidal cells. However, the hippocampus regulates the HPA axis by connecting to other limbic structures like the prefrontal cortex and amygdala (Herman et al., 2005).

Studies have supported altered HPA axis in individuals with BPD, observing greater levels of stress hormones such as basal cortisol and reduced feedback sensitivity (Kulacaoglu & Kose, 2018). Due to the widely understood stress of excess basal Cortisol and HPA axis malfunction on

neuronal structure, the dysregulation of the HPA axis within individuals with BPD may have implications for neuroplasticity's involvement.

Literature suggests that the hippocampus, among other limbic regions like the amygdala, plays a crucial role in negative feedback loops of the HPA axis. Damage may result in dysfunction and worsened emotional dysregulation due to the disynaptic inhibition of corticotropin-releasing factor cells in the PVN (an inhibitory pathway), as their inhibition is important in regulating the HPA axis (Cole et al., 2022). Multiple studies have suggested that hippocampal distress and dysregulation (maladaptive neuroplasticity) have been implicated in the onset and maintenance of psychiatric disorders (Cole et al., 2022; Herman, 2016; Jaggar et al., 2019; Phillips et al., 2006).

4.4. BDNF in BPD Patients exhibits levels of High Cortisol

BDNF regulates the growth of neurons and is one of the most studied neurotrophins in the brain, known as an important component in the development of the entire nervous system. BDNF, a promotor of neuroplasticity, plays an important role in regulating the HPA axis. Growing evidence suggests that changes in the expression of BDNF have been associated with a wide variety of psychiatric illnesses, and it has been hypothesized that the reduced peripheral gene expression of BDNF may be a key factor in psychiatric pathology (Cattaneo et al., 2016).

BDNF, the HPA axis, and BPD are related commonly via the exhibition of higher levels of cortisol in individuals with BPD. One study explored the overnight urinary cortisol levels and reported higher cortisol levels in BPD patients (Cattane et al., 2017). Early juvenile exposure to stress is a known factor that reduces the expression of BDNF, leading to neuronal degeneration,

a reduction in plasticity in individuals who had traumatic experiences early in life, specifically within a caregiving environment, and can result in a decrease of BDNF through increased methylation, resulting in a repression of BDNF (Elzinga et al., 2011). Early juveniles' exposure to stress may be partially explained by the link of the HPA axis that has been associated with BPD; those with the condition, among many others, display elevated levels of cortisol, suggesting the HPA axis' association with BPD.

Furthermore, a study evaluated cortisol and BDNF levels and dictated through a linear regression model that patients with a history of childhood trauma and high levels of recent stressors predicted lower BDNF expression ($p<0.001$) (Mondelli et al., 2011). This combination of evidence strongly indicates that BDNF expression is decreased by experiencing psychological stress as the expression of cortisol and neuroinflammatory cytokines increases (Castillo-Navarrete et al., 2023).

These findings suggest that psychosocial stressors during childhood and the onset of mental illness play a pivotal role in increasing cortisol and reducing BDNF levels, resulting in the neuronal abnormalities and dysregulation visited in section 4.3. These abnormalities may further contribute to mismanagement of the stress response, discussed in section 4.5.

4.5. Termination of the Stress Response

Linz et al. (2019) suggested that stress recovery is associated with higher levels of BDNF. In comparison, lower levels of BDNF are associated with higher cortisol stress activity, resulting in a correlation between low levels of BDNF and high levels of cortisol. It was found in this particular model that individuals with a healthy stress response (defined as a steep recovery following stress-induced cortisol release) displayed higher levels of BDNF, as the BDNF protein

in higher concentrations acted antagonistically to higher cortisol stress activity (Linz et al., 2019). This is an important note, as the ability to terminate a stress response and recover from a rise in cortisol is essential in "reducing vulnerability to stress-related disease" (Linz et al., 2019). In other words, the emotional stability may result from the antagonistic effects of BDNF on the stress response.

Animal models have displayed that regulation of the HPA axis via terminating the stress response is important to maintain resilience from chronic stress, this resilience being the result of hippocampal BDNF expression, suggesting BDNF is an important factor in stress regulation (Herman et al., 2003; Linz et al., 2019; Snyder et al., 2011).

4.6. The Association and the HPA-Plasticity Hypothesis

Section 4.3 discussed neuroplastic dysregulation and how an altered HPA axis is correlated with BPD, where greater levels of basal cortisol result in hippocampal distress and synaptic changes. Section 4.4 discussed how high levels of cortisol over neuronal development correlated with BPD due to low levels of BDNF, suggesting cortisol negatively affects plasticity on structures mentioned in 4.3. Section 4.5 ties together 4.3 and 4.4, suggesting emotional regulation (a key component of BPD) decreases as BDNF decreases, though higher expression of BDNF results in greater emotional regulation. These findings suggest that individuals with BPD who display high levels of stress have higher levels of cortisol, resulting in reduced cortical volume, low levels of BDNF expression, and a resulting lack of emotional regulation.

The importance of these correlations can be established when bi-directionally comparing each of the variables:

4.7. Hypothetical Variable Comparison:

- Impaired plasticity results in lower BDNF expression, lower emotional regulation during stress, and higher baseline cortisol levels.
- High-stress levels induced in youth result in higher baseline cortisol, reduced cortical volume and plasticity, reduction in BDNF, reduced emotional regulation, and higher levels of stress-induced cortisol.
- BPD patients have a high baseline cortisol level, encounter emotional dysregulation, increased stress-induced cortisol, impaired neuroplastic and cortisol volumes, have reduced BDNF and other supporting factors, sympathetic activation, and further repetition of the symptoms and cycle of the HPA-Plasticity Hypothesis.

5. LIMITATIONS

There is growing evidence of impaired neuroplasticity and its role in BPD. It is essential to note that the literature on the relationship between neuroplasticity and BPD is still actively developing, as genetic, environmental, and neurobiological stress have vast and varying factors. As a result, this review is correlative. Many of the findings discussed in section two are based on cross-sectional studies, relationships, correlations, and theoretical analysis. Both preliminary and longitudinal studies are necessary to establish a better understanding of BPD and its relationship with neuroplasticity and the HPA axis. However, in theorizing the HPA-Plasticity Hypothesis, interesting conclusions and further hypotheses may be formed, helping perpetuate the field of psychiatric pathology.

6. CONCLUSIONS

The growth of supporting evidence in the relationship between BPD and the HPA axis' influence on neuroplasticity offers insight into the etiology and progression of BPD. The HPA-Plasticity Hypothesis illustrates how chronic stress and altered HPA axis functioning may contribute to the ongoing neuroplastic changes in individuals with BPD, which is crucial to furthering our understanding of BPD and seeking new and novel treatment mechanisms. Understanding the relationship between BPD, the HPA axis, and plasticity allows clinicians and researchers to approach specific mechanism-focused treatment involved with BPD while investigating multiple systems and inputs to BPD, including those beyond the scope of this paper. Future research should further focus on an emphasis on the mechanisms that underly the HPA-Plasticity Loop among other psychiatric disorders while additionally investigating longitudinally the casual relationships of cortisol and BNDF and their effects on BPD. Clinical trials exploring interventions involving the HPA axis or enhancing neuroplasticity could provide valuable information on how these fields may be applied therapeutically. Seeking improvement for the quality of life in individuals with BPD, emphasis on individuality and the different mechanisms underlying the disorder would provide significant insight for literature.

7. APPENDIX:

Figure 1

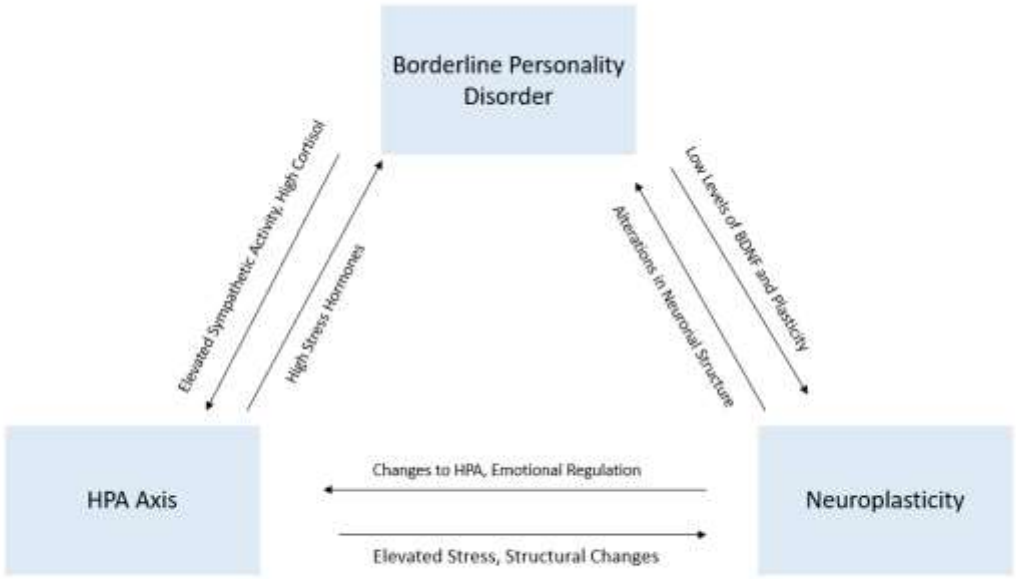

Figure 1 The relationship between the HPA axis, neuroplasticity, and BPD.

8. REFERENCES

Aguilar-Ortiz, S., Salgado-Pineda, P., Marco-Pallarés, J., Pascual, J. C., Vega, D., Soler, J., Brunel, C., Martin-Blanco, A., Soto, A., Ribas, J., Maristany, T., Sarró, S., Salvador, R., Rodríguez-Fornells, A., Pomarol-Clotet, E., & McKenna, P. J. (2018). Abnormalities in gray matter volume in patients with borderline personality disorder and their relation to lifetime depression: A VBM study. *PloS One*, *13*(2), e0191946. https://doi.org/10.1371/journal.pone.0191946

Amad, A. (2014). New developments in the genetics of borderline personality disorder. *European Psychiatry*, *29*(S3), 556–556. https://doi.org/10.1016/j.eurpsy.2014.09.362

Amad, A., Ramoz, N., Thomas, P., & Gorwood, P. (2016). The age-dependent plasticity highlights the conceptual interface between borderline personality disorder and PTSD. *European Archives of*

Psychiatry and Clinical Neuroscience, *266*(4), 373–375. https://doi.org/10.1007/s00406-015-0648-3

Baroncelli, L., Braschi, C., Spolidoro, M., Begenisic, T., Maffei, L., & Sale, A. (2011). Brain plasticity and disease: A matter of inhibition. *Neural Plasticity*, *2011*, 286073. https://doi.org/10.1155/2011/286073

Bertsch, K., Florange, J., & Herpertz, S. C. (2020). Understanding Brain Mechanisms of Reactive Aggression. *Current Psychiatry Reports*, *22*(12), 81. https://doi.org/10.1007/s11920-020-01208-6

Bozzatello, P., Garbarini, C., Rocca, P., & Bellino, S. (2021). Borderline Personality Disorder: Risk Factors and Early Detection. *Diagnostics (Basel, Switzerland)*, *11*(11), 2142. https://doi.org/10.3390/diagnostics11112142

Brzosko, Z., Mierau, S. B., & Paulsen, O. (2019). Neuromodulation of Spike-Timing-Dependent Plasticity: Past, Present, and Future. *Neuron*, *103*(4), 563–581. https://doi.org/10.1016/j.neuron.2019.05.041

Campbell, T. S., Donoghue, K. M., Ghosh, U., Nelson, C. M., & Roth, T. L. (2022). Early Life Stress Affects Bdnf Regulation: A Role for Exercise Interventions. *International Journal of Molecular Sciences*, *23*(19), 11729. https://doi.org/10.3390/ijms231911729

Carvalho Fernando, S., Beblo, T., Schlosser, N., Terfehr, K., Wolf, O. T., Otte, C., Löwe, B., Spitzer, C., Driessen, M., & Wingenfeld, K. (2013). Acute glucocorticoid effects on response inhibition in borderline personality disorder. *Psychoneuroendocrinology*, *38*(11), 2780–2788. https://doi.org/10.1016/j.psyneuen.2013.07.008

Castillo-Navarrete, J.-L., Guzmán-Castillo, A., Bustos, C., & Rojas, R. (2023). Peripheral brain-derived neurotrophic factor (BDNF) and salivary cortisol levels in college students with different levels of academic stress. Study protocol. *PLOS ONE*, *18*(2), e0282007. https://doi.org/10.1371/journal.pone.0282007

Cattane, N., Rossi, R., Lanfredi, M., & Cattaneo, A. (2017). Borderline personality disorder and childhood trauma: Exploring the affected biological systems and mechanisms. *BMC Psychiatry*, *17*(1), 221. https://doi.org/10.1186/s12888-017-1383-2

Cattaneo, A., Cattane, N., Begni, V., Pariante, C. M., & Riva, M. A. (2016). The human BDNF gene: Peripheral gene expression and protein levels as biomarkers for psychiatric disorders. *Translational Psychiatry*, *6*(11), e958–e958. https://doi.org/10.1038/tp.2016.214

Chapman, J., Jamil, R. T., & Fleisher, C. (2023). Borderline Personality Disorder. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK430883/

Cole, A. B., Montgomery, K., Bale, T. L., & Thompson, S. M. (2022). What the hippocampus tells the HPA axis: Hippocampal output attenuates acute stress responses via disynaptic inhibition of CRF+ PVN neurons. *Neurobiology of Stress*, *20*, 100473. https://doi.org/10.1016/j.ynstr.2022.100473

Coutinho, T. V., Reis, S. P. S., da Silva, A. G., Miranda, D. M., & Malloy-Diniz, L. F. (2017). Deficits in Response Inhibition in Patients with Attention-Deficit/Hyperactivity Disorder: The Impaired Self-Protection System Hypothesis. *Frontiers in Psychiatry*, *8*, 299. https://doi.org/10.3389/fpsyt.2017.00299

Di Benedetto, M. G., Scassellati, C., Cattane, N., Riva, M. A., & Cattaneo, A. (2022). Neurotrophic factors, childhood trauma, and psychiatric disorders: A systematic review of genetic, biochemical, cognitive and imaging studies to identify potential biomarkers. *Journal of Affective Disorders*, *308*, 76–88. https://doi.org/10.1016/j.jad.2022.03.071

Dziurkowska, E., & Wesolowski, M. (2021). Cortisol as a Biomarker of Mental Disorder Severity. *Journal of Clinical Medicine*, *10*(21), 5204. https://doi.org/10.3390/jcm10215204

Eckert, A., Karen, S., Beck, J., Brand, S., Hemmeter, U., Hatzinger, M., & Holsboer-Trachsler, E. (2017). The Link Between Sleep, Stress and BDNF. *European Psychiatry*, *41*(S1), S282–S282. https://doi.org/10.1016/j.eurpsy.2017.02.132

Ellison, W. D., Rosenstein, L. K., Morgan, T. A., & Zimmerman, M. (2018). Community and Clinical Epidemiology of Borderline Personality Disorder. *The Psychiatric Clinics of North America*, *41*(4), 561–573. https://doi.org/10.1016/j.psc.2018.07.008

Elzinga, B. M., Molendijk, M. L., Oude Voshaar, R. C., Bus, B. A. A., Prickaerts, J., Spinhoven, P., & Penninx, B. J. W. H. (2011). The impact of childhood abuse and recent stress on serum brain-derived neurotrophic factor and the moderating role of BDNF Val66Met. *Psychopharmacology*, *214*(1), 319–328. https://doi.org/10.1007/s00213-010-1961-1

Fenoglio, K. A., Chen, Y., & Baram, T. Z. (2006). Neuroplasticity of the hypothalamic–pituitary–adrenal (HPA) axis early in life requires recurrent recruitment of stress-regulating brain regions. *Frontiers in Neuroendocrinology*, *27*(1), 50–51. https://doi.org/10.1016/j.yfrne.2006.03.103

Filippone, M., Nardo, D., Bonadies, L., Salvadori, S., & Baraldi, E. (2019). Update on Postnatal Corticosteroids to Prevent or Treat Bronchopulmonary Dysplasia. *American Journal of Perinatology*, *36*(S 02), S58–S62. https://doi.org/10.1055/s-0039-1691802

Fiocco, A. J., D'Amico, D., de Beaumont, L., Poirier, J., & Lupien, S. (2020). Association between ***BDNF*** Polymorphism and Hypothalamic-Pituitary-Adrenal Activity in Later Adulthood. *Gerontology*, *66*(2), 131–137. https://doi.org/10.1159/000502143

Herman, J. P. (2016). *Limbic Pathways to Stress Control* (I. Liberzon & K. J. Ressler, Eds.; Vol. 1). Oxford University Press. https://doi.org/10.1093/med/9780190215422.003.0008

Herman, J. P., Figueiredo, H., Mueller, N. K., Ulrich-Lai, Y., Ostrander, M. M., Choi, D. C., & Cullinan, W. E. (2003). Central mechanisms of stress integration: Hierarchical circuitry controlling hypothalamo-pituitary-adrenocortical responsiveness. *Frontiers in Neuroendocrinology*, *24*(3), 151–180. https://doi.org/10.1016/j.yfrne.2003.07.001

Herman, J. P., Ostrander, M. M., Mueller, N. K., & Figueiredo, H. (2005). Limbic system mechanisms of stress regulation: Hypothalamo-pituitary-adrenocortical axis. *Progress in Neuro-*

Psychopharmacology & Biological Psychiatry, *29*(8), 1201–1213. https://doi.org/10.1016/j.pnpbp.2005.08.006

Jaggar, M., Fanibunda, S. E., Ghosh, S., Duman, R. S., & Vaidya, V. A. (2019). The Neurotrophic Hypothesis of Depression Revisited: New Insights and Therapeutic Implications. In *Neurobiology of Depression* (pp. 43–62). Elsevier. https://doi.org/10.1016/B978-0-12-813333-0.00006-8

Johnston, M. V. (2009). Plasticity in the developing brain: Implications for rehabilitation. *Developmental Disabilities Research Reviews*, *15*(2), 94–101. https://doi.org/10.1002/ddrr.64

Kealy, D., Cox, D. W., & Rice, S. M. (2021). Borderline Personality Features and Impeded Personal Growth Initiative: The Importance of Dispositional Optimism. *International Journal of Mental Health and Addiction*, *19*(5), 1683–1689. https://doi.org/10.1007/s11469-020-00255-7

Kouhnavardi, S., Cabatic, M., Mañas-Padilla, M. C., Malabanan, M.-A., Smani, T., Cicvaric, A., Muñoz Aranzalez, E. A., Koenig, X., Urban, E., Lubec, G., Castilla-Ortega, E., & Monje, F. J. (2023). miRNA-132/212 Deficiency Disrupts Selective Corticosterone Modulation of Dorsal vs. Ventral Hippocampal Metaplasticity. *International Journal of Molecular Sciences*, *24*(11), 9565. https://doi.org/10.3390/ijms24119565

Krystal, J. H., Tolin, D. F., Sanacora, G., Castner, S. A., Williams, G. V., Aikins, D. E., Hoffman, R. E., & D'Souza, D. C. (2009). Neuroplasticity is a target for the pharmacotherapy of anxiety disorders, mood disorders, and schizophrenia. *Drug Discovery Today*, *14*(13–14), 690–697. https://doi.org/10.1016/j.drudis.2009.05.002

Kulacaoglu, F., & Kose, S. (2018). Borderline Personality Disorder (BPD): In the Midst of Vulnerability, Chaos, and Awe. *Brain Sciences*, *8*(11), 201. https://doi.org/10.3390/brainsci8110201

Kunugi, H., Hori, H., Adachi, N., & Numakawa, T. (2010). Interface between hypothalamic-pituitary-adrenal axis and brain-derived neurotrophic factor in depression: HPA, BDNF and depression.

Psychiatry and Clinical Neurosciences, *64*(5), 447–459. https://doi.org/10.1111/j.1440-1819.2010.02135.x

Lee, H. Y., Jamieson, J. P., Miu, A. S., Josephs, R. A., & Yeager, D. S. (2019). An Entity Theory of Intelligence Predicts Higher Cortisol Levels When High School Grades Are Declining. *Child Development*, *90*(6). https://doi.org/10.1111/cdev.13116

Levy, M. J. F., Boulle, F., Steinbusch, H. W., van den Hove, D. L. A., Kenis, G., & Lanfumey, L. (2018). Neurotrophic factors and neuroplasticity pathways in the pathophysiology and treatment of depression. *Psychopharmacology*, *235*(8), 2195–2220. https://doi.org/10.1007/s00213-018-4950-4

Linz, R., Puhlmann, L. M. C., Apostolakou, F., Mantzou, E., Papassotiriou, I., Chrousos, G. P., Engert, V., & Singer, T. (2019). Acute psychosocial stress increases serum BDNF levels: An antagonistic relation to Cortisol but no group differences after mental training. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *44*(10), 1797–1804. https://doi.org/10.1038/s41386-019-0391-y

Lohoff, F. W. (2010). Overview of the genetics of major depressive disorder. *Current Psychiatry Reports*, *12*(6), 539–546. https://doi.org/10.1007/s11920-010-0150-6

López-Villatoro, J. M., MacDowell, K. S., Diaz-Marsá, M., De La Torre-Luque, A., Prittwitz, C., Galvez-Merlin, A., Leza, J. C., & Carrasco, J. L. (2022). Reduced glucocorticoid receptor expression in blood mononuclear cells of patients with borderline personality disorder. *Frontiers in Psychiatry*, *13*, 951373. https://doi.org/10.3389/fpsyt.2022.951373

Maier, M., Ballester, B. R., & Verschure, P. F. M. J. (2019). Principles of Neurorehabilitation After Stroke Based on Motor Learning and Brain Plasticity Mechanisms. *Frontiers in Systems Neuroscience*, *13*, 74. https://doi.org/10.3389/fnsys.2019.00074

Mateos-Aparicio, P., & Rodríguez-Moreno, A. (2019). The Impact of Studying Brain Plasticity. *Frontiers in Cellular Neuroscience*, *13*, 66. https://doi.org/10.3389/fncel.2019.00066

McEwen, B. S. (2015). Preserving neuroplasticity: Role of glucocorticoids and neurotrophins via phosphorylation. *Proceedings of the National Academy of Sciences*, *112*(51), 15544–15545. https://doi.org/10.1073/pnas.1521416112

McEwen, B. S., & Akil, H. (2020). Revisiting the Stress Concept: Implications for Affective Disorders. *The Journal of Neuroscience*, *40*(1), 12–21. https://doi.org/10.1523/JNEUROSCI.0733-19.2019

Mondelli, V., Cattaneo, A., Murri, M. B., Di Forti, M., Handley, R., Hepgul, N., Miorelli, A., Navari, S., Papadopoulos, A. S., Aitchison, K. J., Morgan, C., Murray, R. M., Dazzan, P., & Pariante, C. M. (2011). Stress and inflammation reduce brain-derived neurotrophic factor expression in first-episode psychosis: A pathway to smaller hippocampal volume. *The Journal of Clinical Psychiatry*, *72*(12), 1677–1684. https://doi.org/10.4088/JCP.10m06745

Morey, R. A., Gold, A. L., LaBar, K. S., Beall, S. K., Brown, V. M., Haswell, C. C., Nasser, J. D., Wagner, H. R., McCarthy, G., & Mid-Atlantic MIRECC Workgroup. (2012). Amygdala volume changes in posttraumatic stress disorder in a large case-controlled veterans group. *Archives of General Psychiatry*, *69*(11), 1169–1178. https://doi.org/10.1001/archgenpsychiatry.2012.50

Musazzi, L., & Marrocco, J. (2016). The Many Faces of Stress: Implications for Neuropsychiatric Disorders. *Neural Plasticity*, *2016*, 8389737. https://doi.org/10.1155/2016/8389737

Nicolaides, N. C., George Chrousos, & Tomoshige, K. (n.d.). *Glucocorticoid*. Retrieved October 28, 2023, from https://www.ncbi.nlm.nih.gov/books/NBK279171/

Nunes, P. M., Wenzel, A., Borges, K. T., Porto, C. R., Caminha, R. M., & De Oliveira, I. R. (2009). Volumes of the Hippocampus and Amygdala in Patients With Borderline Personality Disorder: A Meta-Analysis. *Journal of Personality Disorders*, *23*(4), 333–345. https://doi.org/10.1521/pedi.2009.23.4.333

Olabi, B., & Hall, J. (2010). Borderline personality disorder: Current drug treatments and future prospects. *Therapeutic Advances in Chronic Disease*, *1*(2), 59–66. https://doi.org/10.1177/2040622310368455

Orth, L., Zweerings, J., Ibrahim, C. N., Neuner, I., & Sarkheil, P. (2020). Altered functional connectivity during evaluation of self-relevance in women with borderline personality disorder. *NeuroImage. Clinical*, *27*, 102324. https://doi.org/10.1016/j.nicl.2020.102324

Oumaya, M., Friedman, S., Pham, A., Abou Abdallah, T., Guelfi, J.-D., & Rouillon, F. (2008). [Borderline personality disorder, self-mutilation and suicide: Literature review]. *L'Encephale*, *34*(5), 452–458. https://doi.org/10.1016/j.encep.2007.10.007

Phillips, L. J., Mcgorry, P. D., Garner, B., Thompson, K. N., Pantelis, C., Wood, S. J., & Berger, G. (2006). Stress, the Hippocampus and the Hypothalamic-Pituitary-Adrenal Axis: Implications for the Development of Psychotic Disorders. *Australian & New Zealand Journal of Psychiatry*, *40*(9), 725–741. https://doi.org/10.1080/j.1440-1614.2006.01877.x

Pittenger, C., & Duman, R. S. (2008). Stress, Depression, and Neuroplasticity: A Convergence of Mechanisms. *Neuropsychopharmacology*, *33*(1), 88–109. https://doi.org/10.1038/sj.npp.1301574

Price, J. L., & Drevets, W. C. (2012). Neural circuits underlying the pathophysiology of mood disorders. *Trends in Cognitive Sciences*, *16*(1), 61–71. https://doi.org/10.1016/j.tics.2011.12.011

Puderbaugh, M., & Emmady, P. D. (2023). Neuroplasticity. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK557811/

Quevedo, Y., Booij, L., Herrera, L., Hernández, C., & Jiménez, J. P. (2022). Potential epigenetic mechanisms in psychotherapy: A pilot study on DNA methylation and mentalization change in borderline personality disorder. *Frontiers in Human Neuroscience*, *16*, 955005. https://doi.org/10.3389/fnhum.2022.955005

Regier, D. A., Kuhl, E. A., & Kupfer, D. J. (2013). The DSM-5: Classification and criteria changes. *World Psychiatry: Official Journal of the World Psychiatric Association (WPA)*, *12*(2), 92–98. https://doi.org/10.1002/wps.20050

Santiago, G. T. P., de Menezes Galvão, A. C., de Almeida, R. N., Mota-Rolim, S. A., Palhano-Fontes, F., Maia-de-Oliveira, J. P., de Araújo, D. B., Lobão-Soares, B., & Galvão-Coelho, N. L. (2020). Changes in Cortisol but Not in Brain-Derived Neurotrophic Factor Modulate the Association Between Sleep Disturbances and Major Depression. *Frontiers in Behavioral Neuroscience*, *14*, 44. https://doi.org/10.3389/fnbeh.2020.00044

Schloesser, R. J., Huang, J., Klein, P. S., & Manji, H. K. (2008). Cellular Plasticity Cascades in the Pathophysiology and Treatment of Bipolar Disorder. *Neuropsychopharmacology*, *33*(1), 110–133. https://doi.org/10.1038/sj.npp.1301575

Sengpiel, F. (2018). Overview: Neuroplasticity and synaptic function in neuropsychiatric disorders. *The Journal of Physiology*, *596*(14), 2745–2746. https://doi.org/10.1113/JP275940

Shin, L. M., & Liberzon, I. (2010). The neurocircuitry of fear, stress, and anxiety disorders. *Neuropsychopharmacology: Official Publication of the American College of Neuropsychopharmacology*, *35*(1), 169–191. https://doi.org/10.1038/npp.2009.83

Snyder, J. S., Soumier, A., Brewer, M., Pickel, J., & Cameron, H. A. (2011). Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. *Nature*, *476*(7361), 458–461. https://doi.org/10.1038/nature10287

Suri, D., & Vaidya, V. A. (2013). Glucocorticoid regulation of brain-derived neurotrophic factor: Relevance to hippocampal structural and functional plasticity. *Neuroscience*, *239*, 196–213. https://doi.org/10.1016/j.neuroscience.2012.08.065

Tartt, A. N., Mariani, M. B., Hen, R., Mann, J. J., & Boldrini, M. (2022). Dysregulation of adult hippocampal neuroplasticity in major depression: Pathogenesis and therapeutic implications. *Molecular Psychiatry*, *27*(6), 2689–2699. https://doi.org/10.1038/s41380-022-01520-y

Thau, L., Gandhi, J., & Sharma, S. (2023). Physiology, Cortisol. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK538239/

Thomas, N., Gurvich, C., Hudaib, A.-R., Gavrilidis, E., & Kulkarni, J. (2019). Systematic review and meta-analysis of basal cortisol levels in Borderline Personality Disorder compared to non-psychiatric controls. *Psychoneuroendocrinology*, *102*, 149–157. https://doi.org/10.1016/j.psyneuen.2018.12.009

Thomas, N., Gurvich, C., & Kulkarni, J. (2019). Borderline personality disorder, trauma, and the hypothalamus-pituitary-adrenal axis. *Neuropsychiatric Disease and Treatment*, *15*, 2601–2612. https://doi.org/10.2147/NDT.S198804

Vatheuer, C. C., Dzionsko, I., Maier, S., Näher, T., Van Zutphen, L., Sprenger, A., Jacob, G. A., Arntz, A., & Domes, G. (2021). Looking at the bigger picture: Cortical volume, thickness and surface area characteristics in borderline personality disorder with and without posttraumatic stress disorder. *Psychiatry Research: Neuroimaging*, *311*, 111283. https://doi.org/10.1016/j.pscychresns.2021.111283

Yang, T., Nie, Z., Shu, H., Kuang, Y., Chen, X., Cheng, J., Yu, S., & Liu, H. (2020). The Role of BDNF on Neural Plasticity in Depression. *Frontiers in Cellular Neuroscience*, *14*, 82. https://doi.org/10.3389/fncel.2020.00082

Yoshimatsu, K., & Palmer, B. (2014). Depression in patients with borderline personality disorder. *Harvard Review of Psychiatry*, *22*(5), 266–273. https://doi.org/10.1097/HRP.0000000000000045

Zimmerman, M., Balling, C., Dalrymple, K., & Chelminski, I. (2019). Screening for Borderline Personality Disorder in Psychiatric Outpatients With Major Depressive Disorder and Bipolar Disorder. *The Journal of Clinical Psychiatry*, *80*(1), 18m12257. https://doi.org/10.4088/JCP.18m12257