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Neurobiological Findings in Youth with Borderline Personality Disorder

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Abstract

This review summarizes recent neurobiological research into youth with borderline personality disorder (BPD) to better delineate the biological factors involved in the development of this disorder. Psychobiological studies when BPD first becomes manifest are of particular interest, because there are fewer confounding factors (e.g., duration of illness, drug abuse, medication, other therapeutic interventions) at this time. This article focuses on recent findings in the field of neuroimaging, neuropsychology, neuroendocrinology, genetics, and pain perception, and it aims to integrate these findings in a developmental psychopathology model of BPD. In studies of clinical samples of adults with BPD, structural imaging studies revealed abnormalities predominantly in the frontolimbic areas. Disturbances in emotional information processing—particularly involving negative stimuli—may mediate affective dysregulation as a core feature of BPD. Genetic studies could reveal that the stability of BPD traits in youth is largely influenced by a combination of genetic and non-shared environmental factors. Hyporesponsiveness to a laboratory stressor indicates an enduring alteration of the hypothalamic–pituitary–adrenal axis. Findings of a higher pain threshold indicate that pain processing is already disturbed during the early stages of BPD, which could contribute to the initiation or maintenance of self-injurious behavior. All biological factors, together with environmental risk factors, may contribute to the core symptoms of BPD: severe emotional and behavioral dysregulation. Further research should investigate the development of BPD in youth by using longitudinal designs to determine whether the neurobiological factors are a cause, an effect, or an epiphenomenon of BPD.

Keywords: borderline personality disorder; adolescents, developmental pathways; neurobiology; neuroimaging; genetics; pain perception; neuroendocrinology; neuropsychology

Introduction

Although neurobiological aspects of borderline personality disorder (BPD) in adulthood have been the subject of scientific interest during the last 15 years, few studies of BPD in youth using a basic neuroscience approach have been conducted so far. The delay of research activities involving BPD in this age group may be the result of a longstanding controversy surrounding the diagnosis of personality disorders in adolescents (1). However, recent evidence has clearly demonstrated that the diagnosis of BPD is as reliable and valid during adolescence as it is during adulthood (1,2). Thus, the proposed *International Classification of Diseases, 11th Revision,* and the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,* have recently confirmed the legitimacy of the diagnosis of BPD in adolescents (3,4).

Neurobiological studies of BPD in clinical samples of adolescents and young adults have focused mainly on structural morphological brain alterations and changes in the neuroendocrine system (5). Such psychobiological studies conducted when BPD first becomes manifest are of particular interest. At this stage of the process of BPD development, there are fewer confounding factors (e.g., duration of illness, drug abuse, medication, other therapeutic interventions) that can cause morphological changes or alterations in the stress response system, and this is particularly relevant for identifying biological vulnerabilities (6,7). This review summarizes findings from studies that have

included young people between 14 and 24 years of age.

Genetics

Only moderate influence has been attributed to genetics in the etiology of BPD (8). It has been suggested that genetic vulnerability is more likely to be linked to certain factors of temperament, such as negative emotionality, impulsivity, and introversion (8). In accordance with the psychobiological model of temperament and character developed by Cloninger (9), a temperamental constellation of high novelty seeking and high harm avoidance has been considered to be prototypical for BPD during adulthood (9). It has been suggested that this specific temperamental profile reflects an "approach–avoidance" conflict that may affect the affective instability feature of BPD (9). This BPD-specific temperamental pattern that comprises these opposing temperamental traits was recently found in a clinical sample of adolescents with BPD compared with clinical and healthy controls (10). This finding was in accordance with those obtained from samples of adults with BPD (11).

In particular, serotonergic and dopaminergic genes have been found to be associated with the temperamental dimensions of novelty seeking and harm avoidance (12). Genetic polymorphisms have also been found to be closely linked to different temperamental traits. Therefore, altered synthesis of the biogenic amines may contribute to the configuration of temperamental factors, which in turn could form the basis for specific reactions to stress and for the development of a psychopathological condition. The clinically apparent coincidence of externalizing symptoms and internalizing symptoms is characteristic of adolescents with BPD, and it may reflect the underlying temperamental factors of BPD (10). Recently, a neuroimaging study found a relationship between rightward hippocampal asymmetry and temperamental factors in adolescents with BPD traits, which emphasizes the importance of considering interactions between biological and temperamental factors (13).

A genetic study in adults with BPD provided evidence that both gene–environment interaction and gene–environment correlation contribute to the development of BPD (14). Another study found that the stability of borderline personality traits appears to be significantly influenced by a combination of genetic and environmental (non-shared) factors from mid to late adolescence (15). However, at a later age (24 years), the influences of shared environmental factors (e.g., socioeconomic status, parent–child relationships, peer-group relationships) were not significant. Thus, the stability of borderline symptoms over the study period appeared to be primarily influenced by a combination of genetic and non-shared environmental factors. This finding suggests that older adolescents play a more active role in selecting the environments and determining the social relationships that influence their behavior.

Studies of candidate genes in the serotonergic and dopaminergic systems have not yielded any convincing empirical or sufficiently reliable results (16). A single study of adolescents postulated that a specific gene polymorphism (i.e., the short allele of the serotonin transporter gene, 5-HTTLPR) was a risk factor for the development of BPD (17). In a nationally representative birth cohort of 1116 pairs of same-sex twins, a highly significant interaction was found between harsh treatment in the family environment and BPD-related characteristics measured at the age of 12 years (18). This association demonstrated environmental mediation and was stronger among children with a family history of psychiatric illness, thereby indicating that inherited and environmental risk factors make independent and interactive contributions to the etiology of BPD (18). This means that individuals with a "sensitive" genotype may be at greater risk of developing BPD in the presence of a predisposing environment. In addition, genes that influence BPD characteristics also increase the likelihood of being exposed to certain adverse life events (19).

Although a recent meta-analysis revealed an estimated heritability of approximately 40% on the basis of familial and twin studies, association studies demonstrated no significant relationship for the serotonin transporter gene, the tryptophan hydrolase 1 gene, or the serotonin 1 B receptor gene (20). Against the background of this discrepancy, the authors suggested that both positive and negative life events may interact with "plasticity" genes rather than the "vulnerability" genes that contribute to the pathogenesis of BPD (20).

Neuroimaging

Functional imaging studies have replicated the evidence of altered neural mechanisms of emotion processing, and morphological changes in adult patients with BPD have been found as well (21). In addition to the often replicated finding of hyperactivity of the limbic system, imaging studies showed simultaneous deactivation of prefrontal structures that are associated with the ability to control emotions, thus supporting the model of frontolimbic dysfunction in patients with BPD (22,23). This model suggests that a reduced cognitive ability to control (top-down regulation is reduced) in combination with pronounced limbic activation (bottom-up reactivity is increased) may

lead to an impaired ability to regulate emotions. It is assumed that this dysfunction is the basis for the imbalance between behavioral and affective regulation. Experimental studies with functional imaging methods in youth have not been published so far. However, only a few studies of brain morphology among youth with BPD exist.

Structural brain imaging

In adults with BPD, alterations in the frontal lobe, the anterior cingulate cortex, the amygdala, and the hippocampus have been repeatedly identified (21). A recently published meta-analysis provided information about the role of the insula in adults with BPD (24). The authors described a link between hyperarousal and negatively valenced emotional stimuli, which may be the result of heightened activity in the insular cortex. Alterations of the insula have not been identified in adolescents with BPD. Neuroanatomical changes in adult subjects with BPD are probably caused not only by neuroanatomical correlates of the disorder itself but also by confounding factors (e.g., long-term medication use, the chronicity of the disorder). However, the findings of a recent study suggest that modest volume reductions of the amygdala and hippocampus bilaterally among individuals BPD are not influenced by illness state or comorbid psychopathology (25). These changes have been repeatedly found in adults with BPD, but they have rarely been identified in adolescents with the disorder.

Nevertheless, examining adolescents with BPD provides a unique opportunity to identify cerebral alterations that represent neuroanatomical correlates of the disorder, because confounding factors are minimized during the early stages of BPD.

Volumetric and morphometric studies

Several volumetric and morphometric studies have examined adolescents with BPD to identify brain alterations that occur during the early stages of the disorder. As compared with healthy controls, decreases in the gray matter volume of the right orbitofrontal cortex (7) and the left anterior cingulate cortex (26) as well as a shorter adhesio interthalamica have been found among individuals with BPD (27). Another study found a smaller volume of the left caudal superior temporal gyrus in individuals with BPD who had violent episodes as compared with those without violent episodes (28). Goodman and colleagues (29) detected a reduced gray matter volume in the anterior cingulate cortex of adolescents with BPD and comorbid major depressive disorder as compared with healthy adolescents. Brunner and colleagues (6) examined adolescents with BPD and compared them to both healthy controls and adolescents with other psychiatric diagnoses. Among individuals with BPD as compared with healthy controls, the researchers found decreased gray matter density in the dorsolateral prefrontal cortex bilaterally and in the left orbitofrontal cortex. In adolescents with other psychiatric disorders as compared with healthy control individuals, the researchers identified gray matter decreases in the right dorsolateral prefrontal cortex, which demonstrated that frontal alterations are not specific to BPD.

In contrast with the well-replicated finding of volumetric alterations in the amygdala and the hippocampus among adults with BPD (21), volume differences in adolescent patients with BPD were thought to be restricted to the aforementioned neuroanatomical structures (6,7,26,29). Only recently were differences in the hippocampus bilaterally and the right amygdala found in adolescents with BPD as compared with a clinical group and a healthy control group using a very sensitive method to assess subcortical structures (30). However, these differences were not specific for BPD. Investigating whether adolescents with BPD had alterations in cortical thickness—which together with the cortical surface area determines the volume of gray matter (31,32)—did not reveal any differences in the BPD group as compared with a clinical group and a healthy control group (30).

Structural brain differences have also been found to be associated with childhood maltreatment (33). Because a history of a broad range of adverse childhood experiences have been found in both adults (34) and youth with BPD (16), this raises the question of whether these early adverse life experiences may also be linked to the neuroanatomical changes seen in patients with BPD. So far, no imaging studies involving young patients with BPD have investigated the effect of prior exposure to early life stressors on brain anatomy.

Although the findings among children who have experienced childhood maltreatment were inconsistent with respect to differences in their prefrontal cortices, reduced corpus callosum volume was found in several studies (35). Adults who experienced childhood maltreatment had reduced gray matter volume in the prefrontal cortex, the anterior cingulate cortex, the hippocampus, and the cerebellum (36-38). These findings may correspond with similar neuroanatomical findings in adult patients with BPD. The discrepancies in the imaging findings between adults and younger people may be caused by variations in developmental timing, the age at the time of measurement, or the plasticity of the brain (39-41). A recent study of young adults with a history of

maltreatment revealed the potential for the decreased centrality of the brain regions involved in emotional regulation and internal emotional perception; this may contribute to the risk for the development of borderline pathology (42).

Diffusion tensor imaging studies

Two diffusion tensor imaging studies examined adolescents with BPD. Both research groups used a combination of tractography and tract-based spatial statistics. New and colleagues (43) found decreased fractional anisotropy in the inferior longitudinal fasciculus bilaterally, in the uncinate, and in the occipitofrontal fasciculus in patients with BPD as compared with healthy controls. Maier-Hein and colleagues (44) identified decreased fractional anisotropy in the fornices of patients with BPD as compared with clinical controls; they also found significant BPD-specific white-matter alterations in the long association bundles interconnecting the heteromodal association cortex and in the connections between the thalamus and hippocampus. Because parts of the heteromodal association cortex are also related to emotion recognition, it was concluded that deficits in both emotion regulation and recognition may simultaneously contribute to the disorder (44). These findings suggest that a large-scale network of emotion processing is disrupted, which goes beyond an isolated frontolimbic disconnectivity hypothesis.

Other radiological and nuclear medicine techniques

To the knowledge of the authors, no studies involving the use of computed tomography (CT), magnetic resonance spectroscopy (MRS), functional magnetic resonance imaging (fMRI), positron emission tomography (PET), or single-photon emission computed tomography (SPECT) have examined adolescents with BPD.

Neuropsychology

A recent review of neurocognitive profiles in adults with BPD reported inconsistent findings. There is an ongoing debate as to whether a general impairment or a selective deficit of neurocognitive function is related to BPD (45). Higher executive functions have been considered to be crucial determinants of self-regulation (46), and deficits in these areas have been linked to the phenomenology of increased impulsivity and to both self-destructive and aggressive behaviors, which are characteristic of patients with BPD. It has been argued that patients with BPD may particularly display deficits when performing tasks that require controlled information processing (cognitive flexibility); an impairment in "controlled cognitive processes" may underlie the impulsive and uncontrolled behavior associated with this disorder (47). Some studies of adult samples with BPD have replicated alterations in higher executive functions, which include cognitive flexibility and non-verbal functions such as visual memory performance and visuospatial abilities (48-53). The only meta-analysis in this research area suggested the possibility of widespread neuropsychological deficits in adult patients with BPD, particularly with regard to global dimensions of planning and visuospatial abilities (54). So far, there has only been one study of young school-aged children with borderline pathology that has suggested impaired cognitive flexibility early during the course of BPD (55).

With regard to alterations in emotional information processing, a meta-analysis (56) of studies of facial emotion processing found disturbances in emotion recognition and discrimination, which may contribute to interpersonal difficulties among patients with BPD (57). A further selective meta-analysis (58) determined that these individuals had difficulty recognizing specific negative emotions on faces; this corresponded partly with experimental studies in youth with BPD by focusing on possible alterations in emotional information processing (59-61). A prior study of adolescent patients with BPD demonstrated a stronger orientation toward negative emotional stimuli (i.e., the dot-probe paradigm) as compared with healthy control subjects (61). This finding could not be replicated in another study using the face morph task (59) in a sample of young people (15 to 24 years old) with BPD features in whom no evidence of a heightened sensitivity to emotional facial expressions was found. In another study, Jovev and colleagues (62) found an attentional bias toward fearful faces that reflected difficulty with disengaging attention from threatening information during preconscious stages of attention among youth with features of BPD. In the study by von Ceumern and colleagues (60), it was of particular interest that adolescent patients with BPD were not able to disengage their attention from negative facial expressions during attentional maintenance when in a negative mood. The increase in narrowing attention to negative emotional stimuli while in a negative mood may indicate that functional strategies to regulate emotions are absent (60). On the basis of this finding, the development of therapeutic strategies aimed at changing the focus of attention when in a negative mood may help to disrupt the vicious cycle of escalating negative emotions (60).

Further neuropsychological studies of BPD during adolescence found evidence of disturbances with regard to taking a social perspective (63-65).

Jennings and colleagues (63) found an impaired capacity to differentiate and integrate the perspective of self with the perspectives of others (i.e., the social perspective coordination model) among youth with BPD as compared with a group of patients with major depressive disorder. With respect to the theory of mind concept (i.e., "mentalizing"), Sharp and colleagues (64) found that adolescents with BPD features demonstrated an overinterpretive mental state reasoning rather than impairment in the theory of mind capacity per se. In line with this finding, a psychometric study of a population-based sample of adolescents demonstrated a prospective relationship between the avoidance of internal states and BPD features in a short-term follow-up investigation. A recent study of decision making and reward behavior revealed a preference for immediate gratification and a tendency to discount longer-term rewards among youth with BPD (66); this finding was not independent of the extent of the impulsivity trait. A study of social cognition involving the Cyberball paradigm revealed no differences between a group of youth with BPD and healthy controls with regard to emotional response and regulation, although the respondents reported a higher extent of negative emotions when they were confronted with this interpersonal rejection experiment (67).

Endocrinology

Clinically, adolescents with BPD seem to suffer from increased stress reactivity, which may be closely related to aggressive and auto-aggressive behavior (16). The idea of stress vulnerability in BPD led to the investigation of both the autonomic nervous system (ANS) and the hypothalamic–pituitary–adrenal axis.

Experimental studies involving the use of a laboratory stress paradigm (i.e., the Trier Social Stress Test) demonstrated an attenuated cortisol response to an acute psychosocial stressor in both adult patients (68) and in a group of adolescent patients engaged in repetitive self-injurious behavior; this group included a significant percentage of patients (43%) who fulfilled the diagnostic criteria for BPD (69). In addition, an imaging study found increased pituitary gland volumes in a group of adolescent patients and young adult patients with BPD who frequently engaged in self-injurious behaviors (70), which may indicate increased basal activity of the hypothalamic–pituitary–adrenal axis. Because the experience of early chronic stress has been linked to a pattern of hypothalamic–pituitary–adrenal axis hyperresponsiveness during early life, a switch to hyporesponsiveness of central cortisol release, peripheral cortisol release, or both may take place later in life (71).

Studies of ANS reactivity among young people with BPD are not yet available. Studies of adults investigated ANS indicators such as skin conductance, heart rate, and the startle reflex; however, they revealed contradictory findings. Although the study by Herpertz and colleagues (22) involved no evidence of autonomic hyperarousal or enhanced startle reaction, the study by Ebner-Priemer and colleagues (72) discovered a significantly reduced startle response in a subgroup of patients with BPD and a high degree of dissociative symptoms. This finding supports the corticolimbic disconnection model of dissociation, which suggest that dissociation is related to the inhibited processing of stress in the limbic system and the concomitant dampened reactivity of the ANS (73).

Pain perception

Because frequent self-injurious behavior is highly associated with BPD, the question of whether altered pain perception contributes to the initiation or maintenance of these symptoms in patients with BPD was investigated (74). Significantly higher pain thresholds have been reported for both adult patients (75) and adolescent patients (76) with BPD. No differences from healthy subjects were found with regard to thermal detection thresholds or indices for alterations of somatosensory functioning. The extent of general psychopathology or dissociative symptoms did not correlate with pain sensitivity in the sample of adolescent patients with BPD (76). This finding supports the assumption that disturbed pain processing is not a consequence of a chronic course of illness but rather that it is already present when BPD becomes manifest. However, a strong tendency for pain thresholds to normalize was found in adult patients with BPD who had stopped their self-injurious behavior as compared with patients who still engaged in self-injurious behavior (77). These findings would argue against an enduring and hereditary alteration of pain perception. Reduced pain sensitivity may also be a consequence of chronic stress experience rather than an adaptive effect related to self-injurious behavior (76).

A functional imaging study of adult patients with BPD demonstrated evidence of the dysfunction of the affective–motivational component of pain perception, with intact sensory discrimination (78). No group differences were found with regard to intensity and quality; however, the deactivation of the anterior cingulate cortex and the amygdala was associated with simultaneous activation of the dorsolateral prefrontal cortex (78). The authors

concluded that reduced activity in these brain areas may reflect the neglect of painful stimuli in patients with BPD (78).

It has also been discussed that reduced pain sensitivity may be a side effect of an altered endogenous opioid system, because stress-induced analgesia (79) and changes in beta-endorphin and metekephalin levels in the cerebrospinal fluid could be found in adult patients with BPD (79). No studies of the endogenous opioid systems of youth with BPD have been conducted so far.

Conclusion

As a result of the lack of longitudinal studies, it remains unclear whether the reported neurobiological findings are a cause, an effect, or an epiphenomenon of BPD (16). Despite the lack of longitudinal studies, recent advances have been made in neurobiological research into youth with BPD, as outlined in the present article.

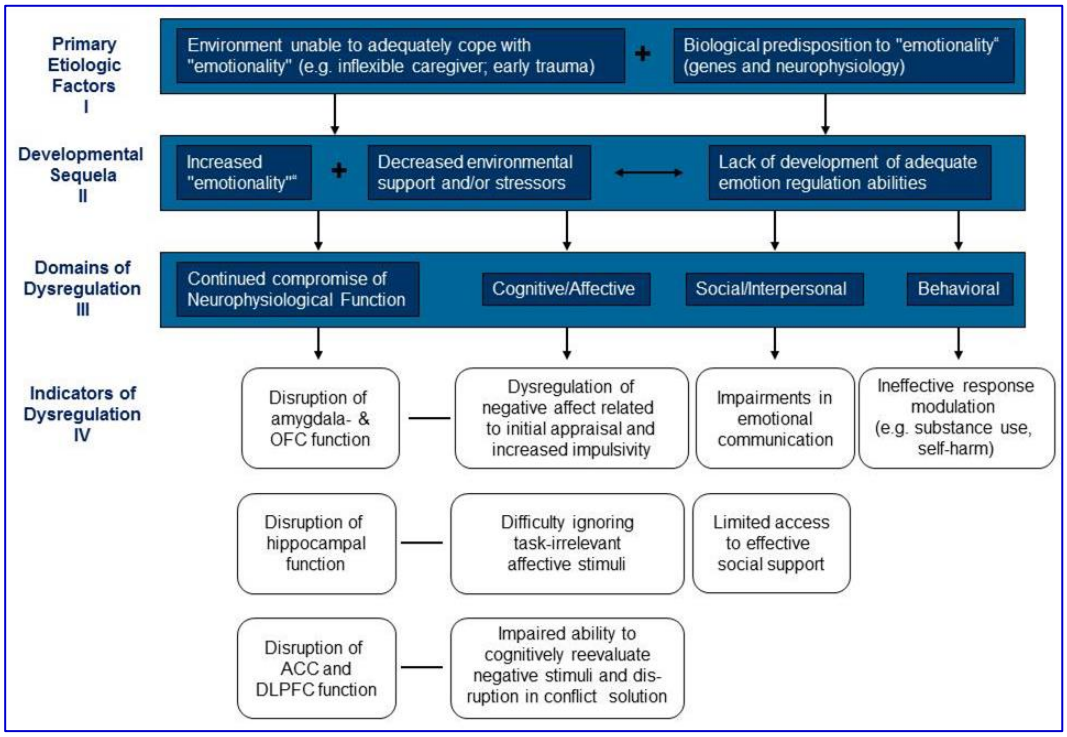

FIGURE 1. A developmental psychopathology model of borderline personality disorder. From Putnam KM, Silk KR: Emotion dysregulation and the development of borderline personality disorder. *Dev Psychopathol* 17:899-925, 2005

Note. OFC, orbitofrontal cortex; ACC, anterior cingulate cortex; DLPFC, dorsolateral prefrontal cortex

Nonetheless, empirical research addressing the development of BPD is still limited, and it seems rather early to create a comprehensive developmental model for the genesis of BPD in youth. The proposed biosocial model of the development of BPD, as outlined by Linehan and coworkers (80), has the potential to expand our current understanding of the etiology of the disorder, and it may stimulate future research and contribute to the deduction of treatment concepts. In this model, early vulnerability—including specific temperamental patterns—forms the basis of heightened impulsivity and emotional sensitivity, which will further lead to the core symptoms of extreme emotional, behavioral, and cognitive dysregulation when interacting with environmental risk factors such as abuse, neglect, or severe invalidation.

The findings of the current review are in partial accordance with the proposed model. The structural brain differences that especially involve the orbitofrontal and dorsolateral areas in adolescents and young adults with BPD may be related to heightened impulsivity as well as impaired cognitive control over the emotions. Studies of brain connectivity among adolescents with BPD have demonstrated alterations in brain networks that are important for both emotional regulation and emotional perception (44). Alterations in emotional information processing, especially when in a negative mood, may further contribute to the

characteristic interpersonal difficulties. Psychophysiological studies have reported the hyporeactivity of a specific biological stress response system (i.e., cortisol reactivity) that has been found to be related to increased adverse stress reactions in human experiments (81). However, studies of ANS reactivity have been inconclusive, and further studies are needed to delineate possible psychophysiological indices.

To summarize, BPD is a severe and often debilitating psychiatric disorder that can become manifest during adolescence. To enhance our understanding of this condition's development, increased research efforts in the field of neuroscience are urgently required. A better understanding of the developmental pathways of BPD may consequently provide essential suggestions for improving early detection and intervention for youth with BPD. Future biological studies should focus on the core features of BPD: affective dysregulation, dysfunctional self-concepts, and difficulties with social interaction domains. A combination of methods that includes new basic science approaches and the assessment of environmental interactions appears to be necessary to clarify the etiology of BPD. The field may benefit from recent studies of the impact of childhood adversity on the developing brain, especially by investigating the associated possible disturbances of the brain network architecture (42) and the biological stress response systems (19,82). The etiopathogenic model of BPD as outlined by Putnam and Silk (83) (Figure 1) illustrates the potential interactions among biological, psychological, and social factors in the genesis of BPD and identifies various areas and indicators for further investigation. To enhance our understanding of these areas and their interactions, an interdisciplinary approach that includes a wide range of clinical research as well as basic neuroscience research is mandatory.

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