Borderline personality disorder: Hypothalamus pituitary adrenal axis and findings from neuroimaging studies

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Summary Borderline personality disorder (BPD) is a complex and serious mental disorder that is commonly seen psychiatric practice. Although stress, especially early life stress, seems to be associated with the development of the disorder, there has been far less research on the function of the hypothalamic-pituitary-adrenal (HPA) axis in BPD, compared to other psychiatric disorders, such as major depressive disorder and post-traumatic stress disorder. Stress has been suggested to exert damaging effects on the brain, particularly the hippocampus; therefore, neuroimaging studies yield important insight into the neurobiology of BPD. This article reviews research on the HPA axis and neuroimaging studies in BPD and aims to integrate these findings.

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1. Borderline personality disorder: psychopathology and clinical features

Borderline personality disorder (BPD) is a complex and serious mental disorder, which is characterized by intense and rapidly changing mood states as well as by impulsivity, self-injurious behaviors, fear of abandonment, unstable relationships and unstable self-image (First et al., 1997; Saß et al., 2003). Suicidal behavior is also highly prevalent in BPD patients and seems to be related to affective instability and depressive mood states (Soloff et al., 2000a; Yen et al., 2004). BPD is estimated to occur in approximately 2% of the general population, 10% of psychiatric outpatients and up to 20% of psychiatric inpatients. BPD is predominantly found in women (75%). In most cases, maladaptive behavior is already evident in childhood and youth (Stone, 1993; Soloff et al., 2000a; Skodol et al., 2002; Saß et al., 2003). Patients with BPD often suffer from comorbid axis I disorders, with mood disorders (96.3%) and anxiety disorders (88.4%) being the most prominent ones. Substance use disorders (64.1%) and eating disorders (53.0%) are also highly prevalent in BPD (Zanarini et al., 1998). Interestingly, "complex comorbidity", i.e. multiple and shifting comorbid axis I disorders, was found to have strong predictive power for the borderline diagnosis, and it seems that a pattern of complex axis I comorbidity itself might be a useful marker for the borderline diagnosis (Zanarini et al., 1998).

Patients with BPD frequently report early, multiple, and chronic adverse or even traumatic experiences, such as repeated sexual or physical abuse or emotional or physical neglect (Herman et al., 1989; Ogata et al., 1990; Zanarini et al., 1997; Golier et al., 2003; McLean and Gallop, 2003). It has been suggested that early life stress might be an important risk factor in the development of BPD (Ogata et al., 1990; Johnson et al., 1999; Driessen et al., 2002; McLean and Gallop, 2003), although this may not be the case in all BPD patients (Grossman et al., 2003). However, early life stress/traumatization is not a specific risk factor for BPD. Traumatization is discussed to be a risk factor for many psychiatric, psychosomatic, and physical complaints (Gild, 1993; Goldberg et al., 1999; Heim and Nemeroff, 2001; Goodwin and Stein, 2004; Heim et al., 2006). It has been shown that women with a history of childhood sexual or physical abuse are more likely to exhibit symptoms of anxiety and depression or even full DSM IV axis I and II mental disorders, e.g. major depressive disorder (MDD) or post-traumatic stress disorder (PTSD), than women without such adverse early life experiences (Owens and Nemeroff, 1991; McCauley et al., 1997; Heim and Nemeroff, 1999; Johnson et al., 1999; Kendall et al., 2000a,b). PTSD and major depressive disorder (MDD) are also notably common in BPD, and the absence of these disorders as well as the absence of childhood sexual abuse and an adult rape history enhance the chance of early remission in BPD (Zanarini et al., 1998, 2006; Hidalgo and Davidson, 2000; McGlashan et al., 2000). Unfortunately, prospective or longitudinal studies investigating the impact of early traumatization in BPD are still missing. However, Zanarini et al. (2006) retrospectively examined which factors contributed to the long-time course of BPD and found that the absence of childhood sexual abuse was associated with earlier remission, suggesting early trauma to contribute to the severity of the disorder.

In sum, borderline personality disorder is a complex and heterogeneous mental disorder with a wide spectrum of symptoms and comorbid disorders. Especially mood and anxiety disorders, including PTSD, seem to play an important role in characterizing clinical features and treatment outcome (Zanarini et al., 2006). Stress, especially early life stress, seems to be associated with the development of the disorder. Furthermore, current stressors as well as interpersonal conflicts are frequently observed in BPD and may contribute to its maintenance. It is important to differentiate among different types of stress, such as early trauma as a risk factor of BPD vs. acute stress, such as daily hassles and life events. Due to the enormous influence of early life stress on several biological systems, such as the hypothalamic-pituitary-adrenal axis, the serotonergic system and the brain, findings that are related to any of these partially overlapping biological systems will be presented. We assume that physiological changes, possibly related to adverse early life experience, lead to problems with stress resilience and emotion regulation in later life, and that BPD can be understood as a prototypic example of such complex difficulties.

2. Hypothalamic-pituitary-adrenal (HPA) axis

Due to the fact that early life stress and traumatization are major risk factors for the development and persistence of mental disorders, many studies have investigated the functioning of the hypothalamic-pituitary-adrenal (HPA) axis, which is a major coordinator of the regulation of the stress response. Upon stress exposure, corticotropin-releasing factor (CRF) is released from the hypothalamus and is transported to the anterior pituitary where it stimulates the release of adrenocorticotropic (ACTH), which in turn stimulates the synthesis and secretion of glucocorticoids from the adrenal cortex. The neuroendocrine stress response is counter-regulated by circulating glucocorticoids via negative feedback mechanisms targeting the pituitary, hypothalamus, and hippocampus. This negative feedback loop is essential for the regulation of the HPA axis and, therefore, for the regulation of the stress response (Plotzky et al., 1998; Carrasco and Van de Kar, 2003). Preclinical and clinical studies suggest that early life stress induces a hyper-reactivity of the central CRF system.
(Heim and Nemeroff, 2001) and also changes the functioning of the glucocorticoid receptors (GR) (McGowan et al., 2009), with long lasting effects on the stress regulation.

2.1. Basal measurements

In major depressive disorder and PTSD, basal measurement of cortisol release has been investigated repeatedly. Frequently used assessment approaches are the collection of blood or saliva throughout the day to measure a day-profile of cortisol release or to collect 24-h urine and measure the entire cortisol release of the day. Most — but not all — studies suggest that cortisol release is enhanced among patients with MDD but is reduced among patients with PTSD (Musselmann et al., 1998; Yehuda, 2000; Holsboer, 2001). However, only a few studies so far have investigated basal cortisol release in patients with BPD. One of these studies (Southwick et al., 2003) compared 37 male combat veterans with PTSD comorbid with BPD vs. 18 combat veterans with PTSD in terms of their 24-h urine cortisol excretion. The group with both disorders had lower mean urinary cortisol levels than combat veterans with PTSD alone. Unfortunately, no healthy control group was recruited, which makes it difficult to interpret the cortisol data. Furthermore, the study did not control for affective disorders. Another study compared overnight urinary cortisol levels among BPD patients with a high number of PTSD symptoms vs. BPD patients with a low number of PTSD symptoms vs. healthy controls (Wingenfeld et al., 2007a). No differences between women with BPD and a high number of PTSD symptoms and control participants were found, whereas BPD patients with few PTSD symptoms had significantly higher cortisol release than healthy controls and BPD patients with a high number of PTSD symptoms (see Fig. 1). Consistent with these group comparisons, the amount of PTSD symptoms was negatively associated with cortisol release. On the other hand, depressive symptoms, measured by the Beck depression inventory, were positively associated with 12-h urinary cortisol. Overall, the study revealed evidence for HPA axis hyperactivity in BPD, but these alterations seem to be mediated by trauma-related symptoms and depressive psychopathology. There is also another study that provided evidence for an enhanced cortisol release in BPD (Lieb et al., 2004a). Cortisol was measured in saliva collected at several time points over the day on 2 consecutive days. In addition to a higher cortisol level over the day, the cortisol response to awakening was also exaggerated. In this study, patients suffering from current major depressive disorder were excluded and therefore, enhanced cortisol release in BPD seems unlikely to be a mere artefact of depression. In sum, studies on basal HPA axis activity, i.e. cortisol and ACTH, are needed, and such studies will need to examine or control for the influence of comorbid disorders, such as MDD and PTSD.

2.2. Feedback regulation

The dexamethasone suppression test (DST) is widely used to investigate the functioning of HPA axis feedback sensitivity (Carroll, 1982, 1984). When administering 1—2 mg dexamethasone (DEX), a synthetic glucocorticoid, in the evening when cortisol levels are low, a nearly complete suppression of cortisol release is observed on the following morning. Normally, morning cortisol levels are high due to the circadian rhythm of the HPA axis hormone release. It is important to note that dexamethasone cannot pass the blood—brain barrier and, therefore, the DST measures HPA axis feedback sensitivity only at the pituitary level (Pariante et al., 2002). Most studies in major depression have reported a reduced feedback regulation (Plotsky et al., 1998), possibly due to altered glucocorticoid receptor functioning (Pariante and Miller, 2001). Furthermore, decreased levels of glucocorticoid receptor mRNA has been found in suicide victims with a history of childhood abuse (McGowan et al., 2009).

In BPD, the standard DST (1 mg DEX) has been used repeatedly, yielding inconclusive results. Many of these studies have found high rates of non-suppressors: e.g. 73% (Baxter et al., 1984), 62% (Carroll et al., 1981), 54% (Konatxakis et al., 1987), 62% (Beeber et al., 1984), 54% (Sternbach et al., 1983). However, most of these results suggested an association of reduced feedback inhibition with affective dysregulation or even with comorbid MDD. It has been emphasized that in many of these studies, no sufficient diagnostic procedure was applied so that the data are difficult to interpret (Lahmeyer et al., 1989). Interestingly, in a sample of BPD patients who were well diagnosed in terms of axis I disorders, it has been shown that BPD patients with comorbid MDD had the highest cortisol levels after dexamethasone (1.5 mg), compared to those without comorbid MDD and BPD patients with PTSD or both (Rinne et al., 2002a). However, BPD patients with comorbid PTSD had the lowest cortisol release after dexamethasone, but the sample size of this subgroup was rather small. Accordingly, in BPD patients without comorbid MDD, low rates of DST non-suppressors have been reported (Lahmeyer et al., 1988). For example, De la Fuente and Mendlewicz (1996) found only 25% in patients with BPD compared to 65% in patients with MDD. Another study reported 26% non-suppressors in BPD patients with major depressive disorder compared to 11% in the BPD group without comorbid MDD (Korzekwa et al., 1991). However, normal DST results have also been found in BPD patients with a history of childhood abuse (McGowan et al., 2009).

Figure 1 Mean (SE) over night urinary cortisol release in BPD patients with high (N = 9) and low (N = 12) number of PTSD symptoms compared to healthy controls (N = 24) (F_{df:2,42} = 4.62, p = 0.021). From: Wingenfeld et al. (2007a), Copyright © 2006 Elsevier Masson SAS All rights reserved.
despite high levels of depressive symptoms (Soloff et al., 1982). In sum, the 1 mg DST in BPD has resulted in contradictory results and it still remains unclear whether the alterations are specific to BPD or are related to comorbid axis I symptoms, such as depression.

Apart from the study by Rinne et al. (2002a), only comorbid depression was taken into account when discussing DST results in BPD. In PTSD — in contrast to MDD — enhanced feedback sensitivity has been found when using a lower dose of DEX (Yehuda, 2000). Therefore, it might be inadequate to use only the standard dose when investigating HPA axis feedback sensitivity in BPD. Grossman et al. (1997) used the low dose (0.5 mg) DST, as proposed by Yehuda et al. (1993), and found enhanced cortisol suppression in four patients with BPD. PTSD was not found to have an influence on cortisol suppression, but the sample was very small. In another study with patients suffering from different personality disorders (of whom 42% had BPD), the same research group showed that higher suppression of cortisol after 0.5 mg DEX was associated with PTSD, while depression had no significant effect on cortisol suppression (Grossman et al., 2003). Unfortunately, no control group of healthy participants was examined in this study. Lange et al. (2005b) did not find differences in HPA axis feedback regulation between BPD patients and controls, but when subdividing the BPD group into subgroups with and without comorbid PTSD, reduced cortisol suppression after 0.5 mg DEX was observed only in those without PTSD. Another study also found reduced rather than enhanced cortisol suppression after 0.5 mg of dexamethasone in BPD patients, compared to healthy controls (Lieb et al., 2004a). In this study, none of the patients had comorbid major depressive disorder, but PTSD was not assessed, which is a major limitation of the study. When comparing BPD patients with low and high numbers of PTSD symptoms, respectively, Wingenfeld et al. (2007b) found reduced feedback sensitivity in BPD patients with few PTSD symptoms, while the BPD group with many PTSD symptoms did not differ from controls (Fig. 2). Furthermore, a positive association between percentage of cortisol suppression and PTSD symptoms as well as a negative association between percentage of cortisol suppression and depressive symptoms was observed. This pattern of findings suggests that trauma-related and depressive symptoms might interact with regard to their effects on HPA axis regulation.

Overall, most studies suggest that BPD is characterized by a somewhat reduced HPA axis feedback sensitivity, similar to the pattern found among patients with depression. However, comorbid PTSD seems to influence results in the DST in the other direction, towards enhanced feedback sensitivity, which is in line with PTSD research.

### 2.3. Challenge tests and stress provocation

To evaluate dysfunctions of the HPA axis, there are several standardized challenge test to stimulate the axis on different levels, e.g. by intravenous injection of exogenous ACTH or CRF, thus allowing for the assessment of adrenal or pituitary output. While these methods are widely used in many mental disorders, less research has been done in BPD. However, Rinne et al. (2002a) used the combined DEX/CRF test, which is thought to be the most sensitive measure of HPA axis activity, namely glucocorticoid receptor (GR) mediated feedback inhibition (Watson et al., 2006). In that test, HPA axis activity is completely suppressed by dexamethasone treatment before exogenous CRF is given the following day. In healthy subjects cortisol secretion is still suppressed after CRF due to the dexamethasone treatment. In depressed patients as well as in persons with childhood trauma, an escape from suppression has been found with elevated ACTH and cortisol after CRF administration (Ising et al., 2005; Watson et al., 2006; Heim et al., 2008a). An exaggerated ACTH and cortisol response in the DEX/CRH test has also been found in BPD patients, but only among those who reported childhood abuse (Rinne et al., 2002a). Furthermore, comorbid PTSD attenuated the ACTH response. The results have been interpreted in terms of an exaggerated central CRF release in patients with early abuse experiences (Heim et al., 2008b).

A more naturalistic method to stimulate HPA axis is the exposure to stressful situations. A widely used paradigm in this context is the Trier Social Stress Test (TSST), which consists of a public speech in front of an audience and a mental arithmetic task (Kirschbaum et al., 1993). For women with a history of early abuse experiences, an enhanced ACTH response to the stressor has been found (Heim et al., 2000). In line with the results from the DEX/CRF test, an overactive HPA axis, presumably due to CRF hypersecretion, has been proposed. Simeon et al. (2007) performed the TSST in a sample of BPD patients, which included five patients with high and eight with low dissociation, vs. 11 healthy controls. Despite the small sample size, the study provided evidence for a greater peak cortisol response to stress in BPD patients with high dissociation. Notably, dissociation is known to be strongly associated with childhood abuse. Another study investigated the cortisol response after an interpersonal discussion between BPD patients and their mothers (Walter et al., 2008). Compared to healthy controls, the patients had higher cortisol levels, particularly after the stressor. However, the effect seems to be weak, and the study suffered from a very small sample size.
In sum, there is some evidence for an altered, exaggerated stress response in BPD, but the available studies only provide preliminary results. In fact, compared to other disorders, very few studies have investigated HPA axis disturbances using methods that go beyond basal measures and assessments of feedback regulation.

To conclude, studies investigating HPA axis functioning in BPD have provided compelling evidence for the impact of comorbid PTSD and depression on HPA axis feedback regulation in BPD. One might hypothesize that there are at least two subgroups of BPD patients with different endocrine patterns: one predominantly characterized by trauma-associated symptoms with unaltered to enhanced feedback sensitivity and normal to reduced cortisol release, and another subgroup with mood disturbances as core symptoms and HPA axis dysfunction in form of enhanced cortisol release and reduced feedback sensitivity (Fig. 3). One major difficulty in BPD research is to investigate patients without other comorbid disorders. Of course, high comorbidity is known to be a typical aspect of BPD (Zanarini et al., 1998), and therefore it would be artificial to exclude those patients from research studies. Based on the pattern of evidence, then, we do not believe that BPD is best construed as a homogenous diagnostic entity. When diagnosing BPD according to DSM-IV, patients have to fulfill five out of nine criteria, which indicates how heterogeneous this group of patients might be. On the other hand, emotional instability seems to be the core symptom of BPD, which underlies many of the other BPD symptoms. One might critically argue that findings on HPA axis functioning replicate only well known results from PTSD and depression research, or one might ask whether there is a distinct BPD pattern of HPA axis alterations. However, results on HPA axis functioning reflect insights gained from clinical work with these patients: that BPD is simply a very heterogeneous and complex disorder. Thus, psychobiological research might contribute to the debate of whether BPD should be regarded primarily as an affective or a trauma-related disorder. Both PTSD and major depressive disorder are characterized by a central CRF overdrive, but with different HPA-related alterations at the periphery. We assume that early life stress results in a sensitization of the central nervous system, i.e. CRF, while proceeding physiological changes may depend on later life circumstance, such as further major stressors or trauma as well as the individuals’ resources and also genetic factors. Further studies should not only investigate endocrine correlates using more sophisticated approaches, and control for influencing factors, such as early trauma, comorbid depression, PTSD as well as the amount of dissociation, but there is also a need to investigate whether subgroups of BPD patients require different forms of treatment, including pharmacological and psychotherapeutic approaches. Rinne et al. (2002b) for example could show that fluvoxamine treatment reduces hyper-responsiveness of the HPA axis in BPD patients, especially in those with childhood abuse. Interestingly, the magnitude of the reduction was not dependent on the presence of comorbid PTSD and depression. This kind of research approach holds promise to integrate endocrine and clinical approaches of BPD.

3. Findings from neuroimaging studies

Stress has been suggested to have damaging effects on the brain, particularly on the hippocampus, which is rich in glucocorticoid receptors (GR). The hippocampus plays an important role in learning and memory, especially declarative memory. Given findings of deficits in verbal declarative memory performance in patients with PTSD (Golier et al., 2002; Bremner et al., 2004a; Jelinek et al., 2006), related brain structures have been investigated in these patients, and a decreased hippocampal volume that is consistent with such memory deficits has been documented repeatedly (Bremner et al., 1995, 2003; Villarreal et al., 2002). However, the underlying mechanisms are still a matter of intense debate (Sapolsky, 2002), and early life stress is considered to be an important factor that may contribute to the emergence of hippocampal abnormalities (Szyf et al., 2008; McGowan et al., 2009). As reported above, BPD has also been conceptualized as a stress-related disorder, and many patients show HPA dysfunctions. Consistent with such findings, enhanced cortisol has also been discussed as one possible reason for hippocampal dysfunction (Bremner, 1999). Interestingly, similar to PTSD, BPD patients have also been found to have memory deficits and, thus, imaging studies might contribute to a better understanding of some aspects of BPD.

In this section, results from structural imaging studies will be presented, followed by a review of results of resting state condition and serotonergic functioning. The serotonergic system is one important neurotransmitter system in the context of BPD with close relationship to stress regulating systems. As problems in emotion regulation are a core difficulty in BPD, fMRI studies which investigated the neural correlates of emotion regulation are presented in the following section. How we deal or cope with our past is of highly relevance when confronted with actual interpersonal situations and conflicts, especially in personality disorders. Thus, data on autobiographical memories retrieval are summarized. Furthermore, in BPD neuropsychological disturbances have been discussed (O’Leary, 2000) and some studies investigated related neural correlates, which are presented at the end of this chapter.

3.1. Changes in brain structure: volumetric studies

Before the advent of DSM-III, BPD was sometimes construed under label of “borderline psychosis”, and consistent with this conceptualization, the first imaging studies investigated
whole brain volume and ventricle sizes via computed tomo-
ography, as had been done in schizophrenia research. How-
ever, findings did not indicate any similarities between
patients with schizophrenia and those with BPD (Snyder
et al., 1983; Lucas et al., 1989). One of the first structural
MRI studies in BPD provided evidence for a smaller frontal
lobe volume, compared to healthy controls (Lyoo et al.,
1998), but that study suffered from several methodological
problems. More recent studies focused on brain structures
that are involved in memory as well as in emotion and stress
regulation, such as the hippocampus and the amygdala,
consistent with the notion that BPD can be construed as a
stress- or trauma-related disorder. In an initial study by
Driessen et al. (2000) a reduced hippocampal volume as well
as a reduced volume of the amygdala was found. Particularly,
the result of hippocampal volume reduction has been repli-
cated in several studies (Schmahl et al., 2003b; Tebartz van
Elst et al., 2003; Brambilla et al., 2004; Irie et al., 2005; Zetzsche et al., 2007; Soloff et al., 2008), whereas a sig-
ificantly smaller amygdala has been found in only some

<table>
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<tr>
<th>Study</th>
<th>Method</th>
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<th>Other results</th>
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<tr>
<td>Lyoo et al. (1998)</td>
<td>MRT</td>
<td>25/25</td>
<td>Frontal lobe</td>
<td>No volume reduction of temporal lobes, lateral ventricles, and cerebral</td>
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<td>hemispheres</td>
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<td>Schmahl et al. (2003b)</td>
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<td>Tebartz van Elst et al. (2003)</td>
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<td>Brambilla et al. (2004)</td>
<td>MRT</td>
<td>10/20</td>
<td>ACC, orbitofrontal cortex hippocampus</td>
<td>No volume reduction of the amygldala, left ACC, caudate, temporal lobes,</td>
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<td>dorsolateral prefrontal cortex</td>
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<tr>
<td>Hazlett et al. (2005)</td>
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<td>50/50</td>
<td>ACC, posterior cingulate cortex</td>
<td>No volume reduction of whole cingulate, frontal lobe volume</td>
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<td>Irie et al. (2005)</td>
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<td>Chanen et al. (2008)</td>
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<td>Cingulate gyrus, hippocampus, amygdala parahippocampal gyrus</td>
<td>ACC volume was correlated with parasuicidal behavior, impulsivity, and fear of abandonment</td>
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<td>Whittle et al. (2009)</td>
<td>MRI</td>
<td>15/15</td>
<td>Left ACC</td>
<td>No difference between patients with and without PTSD</td>
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<td>Schmahl et al. (2009)</td>
<td>MRT</td>
<td>25/25</td>
<td>Hippocampus</td>
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BPD: borderline personality disorder; ACC: anterior cingulate cortex.
(Rusch et al., 2003; Schmahl et al., 2003b; Tebartz van Elst et al., 2003, 2007; Soloff et al., 2008) but not all studies (Brambilla et al., 2004; New et al., 2007; Zetzsche et al., 2006; Chanen et al., 2008). Taken together, these findings suggest two major conclusions: First, the results of hippocampal volume loss are in line with the idea that stress, and especially early life stress, may exert a damaging effect on the brain of these patients. However, it is still matter of debate whether a reduced hippocampal volume is a consequence of stress or is genetically determined, as suggested by the work of Gilbertson et al. (2002). Furthermore, in this context there are impressive similarities between BPD and PTSD patients, who also display a substantial hippocampal volume reduction (Bremner et al., 1999, 2003; Villarreal et al., 2002) as well as difficulties in declarative memory (Golier et al., 2002; Bremner et al., 2004a; Jelinek et al., 2006). Of note, many patients with BPD also suffer from PTSD and, thus, it is not yet clear whether these results are predominantly due to trauma-related aspects of the disorder. Second, a smaller amygdala might be interpreted in the context of emotional dysregulation in BPD. Interestingly, in PTSD, there is no evidence for a reduced volume of the amygdala (Bremner, 2002), and possibly these findings are more specific for BPD. Consequently, Tebartz van Elst et al. (2003) reported not only reduced volume of the amygdala but also the anterior cingulate cortex (ACC), which is significantly involved in the regulation of emotions and response inhibition. This finding was replicated in a sample of adolescents with first-presenting BPD (Whittle et al., 2009). Consistent with these results, lower gray matter concentration in the ACC has also been reported for BPD patients, compared to healthy controls (Hazlett et al., 2005; Minzenberg et al., 2008). At this point it must be emphasized that findings of structural brain changes, especially of the amygdala, are very heterogeneous, and our ability to draw firm conclusions is therefore still limited. However, supporting the hypothesis that structural brain changes are associated with BPD symptoms, ACC volume was found to be correlated with parasuicidal behavior, impulsivity, and fear of abandonment (Whittle et al., 2009). As discussed for structural changes of the hippocampus, genetic studies also indicate an association between structural changes of the amygdala and a gene polymorphism that is involved in serotonergic neurotransmission and is associated with anxiety, depression and suicidal behavior (Zetzsche et al., 2008). Of note, disturbances of the serotonergic system have been described not only for MDD, but also for BPD, showing close relationships with impulsive and aggressive behavior in these patients (Lieb et al., 2004b; Schmahl et al., 2002; Van Praag et al., 2004). Table 1 summarizes extant findings of structural brain imaging studies performed in BPD patients.

Similar to findings from endocrine research, structural MRI studies also yielded mixed results. There might be several reasons for this. Reviewing structural brain abnormalities in PTSD research, Karl et al. (2006) found group differences to be moderated not only by MRI methodology, but also by symptom severity, medication, age and gender. For major depressive disorder, where hippocampal volume reduction is also a prominent finding (Videbech and Ravniklde, 2004) childhood trauma (Vythilingam et al., 2002) as well as illness duration (Sheline et al., 1999) seems to be associated with a smaller hippocampal size. Thus, a recent study examined whether comorbid PTSD is related to hippocampal volume loss in BDP (Schmahl et al., 2009). In line with previous findings, hippocampal volume was reduced in BPD patients, but patients with comorbid PTSD did not differ from those without PTSD. However, the investigated sample was relatively small, but to our knowledge this is the first aim to analyze subgroups of BPD patients with different comorbid disorders with structural MRI in one study. Future studies should further investigate which parameters influence morphological change and which mechanisms may underlie these alterations. Following the discussion of potential damaging effects of stress, i.e. cortisol on the brain (Bremner, 1999; Lee et al., 2002; Sapolsky, 2002; Herbert et al., 2006) endocrine methods should be combined with MRI research.

3.2. Functional imaging studies

3.2.1. Resting state conditions and serotonergic system

Studies of resting cerebral blood flow or metabolism are predominantly done via [18F]deoxyglucose positron emission tomography (FDG-PET). To date, there are only few studies that have used the PET technique in BPD research, and these have revealed ambiguous results. De La Fuente et al. (1997) presented the first FDG-PET study that included a well-defined BPD sample. They found a decreased metabolism in frontal brain areas, the ACC, thalamus and caudate and lenticular nuclei. A more limited area of decreased metabolism in the medial orbital frontal cortex was reported by Soloff et al. (2003a). In a previous investigation with a smaller sample, a decreased activation of prefrontal regions, the left superior temporal gyrus and the right insular was shown after administration of a placebo (Soloff et al., 2000b). Another study found a pattern of deactivation, including the right temporal pole, anterior fusiform gyrus, left precuneus as well as posterior cingulate cortex (Lange et al., 2005b). Interestingly, there was an association between metabolic activity and impaired memory function in that study. Contrary to findings of decreased brain metabolism in BPD, there is also evidence for an increased glucose metabolism in these patients, namely in the ACC, the superior frontal gyrus and the opercular part of the right precentral gyrus (Juengling et al., 2003). Glucose hypometabolism was found in that study, by contrast, in the hippocampus and the cuneus.

In sum, there is no consistent pattern of hypo- or hypermetabolism in resting state among BPD patients, which might be due to a relative lack of studies, differences in sample characteristics and methodology. Consistent with structural studies, the hippocampus and the ACC seem to be of importance in the pathology of BPD. For a better understanding of the neural correlates of BPD, more specific methods of functional imaging are needed, as described below.

Such a more specific approach is to challenge relevant neurotransmitter systems, for example the serotonergic system, which seems to play an important role in BPD patients (Schmahl et al., 2002). Most studies using this approach employ fenfluramine or meta-chlorophenylpiperazine (m-CPP) as serotonergic agent to investigate disturbances of the serotonergic system. Rinne et al. (2000) found a significantly lower cortisol and prolactine response after m-CPP challenge in BPD patients, compared to healthy controls.
Additionally, a strong association between prolactine response and child abuse experiences could be revealed in this study. The result of a diminished prolactine response after a serotonergic agonist was confirmed in other studies (Soloff et al., 2003a). One of the first PET studies in this field found a reduced metabolism in BPD patients after fenfluramine, compared to placebo, in medial and orbital regions of the right prefrontal cortex, left middle and superior temporal gyri, left parietal lobe, and left caudate body (Soloff et al., 2000b). In line with this study, no activation of orbitofrontal regions after m-CPP has been found for patients with impulsive aggression, most of whom were also suffering from BPD (New et al., 2002). Furthermore, these patients showed a deactivation in the ACC, but a more pronounced activation of the posterior cingulate cortex, compared to controls. In an investigation with BPD patients with impulsive aggression, the authors could further show that SSRI treatment normalized prefrontal cortex dysfunction (New et al., 2004). At this point, it must be noted that there is some evidence for gender effects (Soloff et al., 2003a, 2005), which might contribute to the divergent results.

Another method investigating the serotonergic system focuses on the synthesizing capacity of serotonin (5-HT). Leyton et al. (2001) used unidirectional trapping of the 5-HT precursor analog alpha-[11C]methyl-L-tryptophan (alpha-[11C]MTrp) when investigating BPD patients, measuring brain regional alpha-[11C]MTrp trapping via PET. They found that male BPD patients had significantly lower alpha-[11C]MTrp trapping in the medial frontal gyrus, ACC, superior temporal gyrus, and corpus striatum. In women with BPD, significantly lower alpha-[11C]MTrp trapping was seen in fewer regions. For both men and women, impulsivity scores...
were negatively correlated with alpha-[(11)C]MTrp trapping in the medial frontal gyrus, anterior cingulate gyrus, temporal gyrus, and striatum. In a more recent study, Koch et al. (2007) investigated the serotonin transporter availability in patients with BPD as a marker of the central serotonergic system using a highly selective serotonin ligand (ADAM (2-((dimethylamino)methyl)phenyl)thio)). They found a 43% higher brainstem and a 12% higher hypothalamus ADAM binding in patients, compared with control subjects, as well as an association with impulsivity. These results could reflect a higher number of serotonin transporters with an increased capacity of presynaptic serotonin reuptake or might be the consequence of an increased number of available binding sites, which is in line with the hypothesis of lower endogenous serotonin levels in BPD. As mentioned before, the hippocampus is one of the key regions in the context of brain dysfunction in BPD, and there are strong connections between limbic regions and the serotonergic system. Accordingly, using the 5HT1A receptor antagonist [(18)F]altanserin, a significantly increased hippocampal 5HT1A receptor binding was found in BPD subjects (Slooff et al., 2007). These results have been interpreted in the context of a compensatory upregulation of postsynaptic 5HT1A receptors or a functional increase in receptor responsiveness. Interestingly, it has been shown that stress results in a decrease in 5HT1A binding within the hippocampus (Bremner, 1999) and administration of a serotonin reuptake inhibitor results in an increase in dendritic branching within the hippocampus (Duman et al., 1997). The results of the functional imaging studies focusing on the resting state and the serotonergic system are summarized in Table 2.

In sum (imaging) studies investigating the serotonergic system have provided compelling evidence for a serotonergic dysfunction in patients with BPD. Prefrontal brain regions as well as limbic structures seem to play an important role in this context. Of note, in major depressive disorder, dysfunctions of the serotonergic system have been reported repeatedly, including reduced 5HT1A receptor binding in the medial prefrontal cortex, amygdala and hippocampus (Savitz et al., 2009). Of course, the serotonergic system is not the only neurotransmitter system that might be involved in BPD, but it is closely associated with other systems, e.g. the HPA axis, which is regulated via the hypothalamus and hippocampus, in which serotonergic dysfunction has been shown. There is also evidence that serotonin mediates the effects of stress on hippocampal glucocorticoid receptor expression (Smythe et al., 1994; Laplante et al., 2002). Preclinical and clinical studies strongly suggest early life stress to be associated with alterations in glucocorticoid receptor functioning (Liu et al., 1997; McGowan et al., 2009). One might hypothesize that stress-related alteration of HPA axis regulation in concert with diminished serotonergic functioning may contribute to change in brain structure and metabolism in BPD, e.g. the hippocampus.

3.2.2. Response to emotional stimuli
Given that BPD is characterized by difficulties in regulating affective responses, the question arises whether these are related to dysfunctions in brain regions involved in the processing of emotions. One widely used method in emotion research is to expose subjects to emotional stimuli (e.g. emotional pictures) and to measure the reactivity of emotional responses and/or related physiological parameters. The first study using fMRI in BPD patients was done by Herpertz et al. (2001a). They compared BPD patients with healthy controls in terms of their neural responses to emotional pictures. The main result was an increased responsiveness of the amygdala in BPD patients to negatively valenced pictures. It must be mentioned that the sample was very small (six subjects per group). Thus, the statistical approach was weak; only fixed-effect analyses were performed. Another study with a larger sample presented emotional faces and replicated the result of a (predominantly left-sided) hyperactive amygdala by Donegan et al. (2003). Post hoc analyses showed that a greater level of left amygdala activation was found for neutral, sad and fearful faces, but not for happy faces. However, excluding one outlier in the control group, the amygdala was found to be overactive to happy faces in BPD patients, too. No effect of comorbid depression and PTSD could be shown in this study. Minzenberg et al. (2007) also presented pictures of faces with neutral, fearful and angry expressions. Region of interest analyses (ROI) were done with the amygdala and the ACC defined as ROI. In addition to an increased activation of the amygdala, a decreased activation of the ACC was found in response to fearful stimuli but not to angry faces. Moreover, in a most recent study Koenigsberg et al. (2009) showed exaggerated activity of the amygdala in BPD patients when viewing negative social pictures as well as in further brain regions, i.e. fusiform gyrus, primary visual areas, and superior temporal gyrus. However, the amygdala activation was only seen after a statistical correction procedure, while differences in other regions were more obvious. Thus, not only does the amygdala seem to be involved in emotional dysfunction of BPD patients, but a neural network including further limbic structures, e.g. the ACC, also seems to play an important role. Another study presenting emotional pictures that are known to stimulate autobiographical memory found an increased activity of orbitofrontal and insular regions, left ACC, medial prefrontal cortex as well as parietal and parahippocampal areas (Schnell et al., 2007). This study also indicated that BPD patients lack a differential activation pattern in the amygdala, the orbitofrontal and cingulate regions for the different types of pictures, as displayed by the control group. In Table 3, the studies discussed above are summarized.

Taken together, these results provide some evidence for a dysfunction of the amygdala, suggesting a strong involvement of that region in the emotional disturbances of these patients. Methodological problems in the presented fMRI studies, such as small sample sizes or unsatisfactory statistical approaches complicate interpretations and contribute to the heterogeneity in the pattern of results. The finding of a hyperactive amygdala is in line with the observation that BPD patients with high impulsivity are characterized by a strong intensity of affective responses (Herpertz et al., 1997), and that negative emotions such as anger are not only stronger, but also more prolonged in these patients (Jacob et al., 2008). However, research on psychophysiology also revealed contrary results (see below). One study, for example (Ebner-Priemer et al., 2005) found an exaggerated startle response (a marker of amygdala reactivity) in BPD, but also showed that dissociation is an important influencing factor. As reported above, dissociation has also been shown to
influence the endocrine stress response (Simeon et al., 2007). While stress and dissociation seem to be positively correlated (Stiglmayr et al., 2008), the startle response was diminished in subjects with high dissociation (Ebner-Priemer et al., 2005). The relation between stress regulation, dissociation and its neural correlates should be investigated in future fMRI studies, examining the hypothesis whether dissociation may slow down stress-related brain activations, while peripherally the organism is still under pressure.

### 3.2.3. Autobiographical memory

As BPD is also conceptualized as a stress- or trauma-related disorder, neural correlates of autobiographical memory are of compelling interest to understand the psychopathology of this condition. Most brain imaging studies in BPD have focused on major negative autobiographical memories. In two PET studies, memories of abandonment and traumatic events, respectively, were analyzed (Schmahl et al., 2003a, 2004). While the participants listened to scripts describing neutral and personal abandonment events, BPD patients showed increases in blood flow in bilateral dorsolateral prefrontal cortex regions (middle frontal gyrus) as well as the right cuneus, relative to a psychiatric control group. Furthermore, abandonment memories were associated with greater decreases in right anterior cingulate in BPD patients (Schmahl et al., 2003a). When exposed to individual traumatic scripts, abused women with BPD had increases in blood flow in right dorsolateral prefrontal cortex compared to abused women without BPD. Further, the BPD group failed to activate the anterior cingulate gyrus and the orbitofrontal cortex (Schmahl et al., 2004).

Using fMRI Beblo et al. (2006) compared autobiographical memories of unresolved vs. resolved life events in BPD relative to controls. In this study, individual cue words were used to stimulate autobiographical memory. Patients showed increased bilateral activation of the frontal cortex, including

<table>
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<th>Study</th>
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<td><strong>Response to emotional stimuli</strong></td>
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<tr>
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<td>Amygdala (negative vs. neutral slides)</td>
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<td>fMRT</td>
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<td>Amygdala (left) to neutral, sad, fearful (and happy) faces</td>
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<td>Schnell et al. (2007)</td>
<td>fMRT</td>
<td>14/14</td>
<td>Orbitofrontal and medial prefrontal cortex, insula, left ACC, parietal and parahippocampal areas</td>
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<td>Minzenberg et al. (2007)</td>
<td>fMRT</td>
<td>12/12</td>
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<td><strong>Autobiographical memory</strong></td>
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<td>Schmahl et al. (2003a)</td>
<td>PET</td>
<td>10/10</td>
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<td>Schmahl et al. (2004)</td>
<td>PET</td>
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<td>Buchheim et al. (2008)</td>
<td>fMRI</td>
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<td>Orbitofrontal cortex, insula, temporal lobe, amygdala</td>
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<td><strong>Cognitive function</strong></td>
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<td>Wingenfeld et al. (2009a)</td>
<td>fMRI</td>
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<td>ACC, frontal cortex</td>
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Table 3: Functional imaging in borderline personality disorder: response to emotional stimuli, autobiographical memory and cognitive function.
parts of the insula, and of the orbitofrontal cortex, as well as
temporal activation, including the amygdala. These findings
suggest altered brain functioning during the retrieval of
negative autobiographical events in BPD. Interestingly, there
is evidence that comorbid PTSD is a relevant confounding
variable (Driessen et al., 2004).

The described studies used paradigms in which partici-
pants passively listen to scripts or are instructed to remem-
ber a specific event. The problem of the latter method is the
impossibility to control what the subjects actually do in the
scanner. Buchheim et al. (2008) chose another approach by
investigating neural correlates of attachment trauma. In
their study, the participants had to talk about pictures from
a standardized attachment test presenting monadic (one
person) or dyadic (two persons) situations. BPD patients
showed significantly stronger activation of the anterior mid-
cingulate cortex, which was more pronounced to the monadic
pictures. Compared to controls, BPD patients showed less
activation of the right parahippocampal gyrus, but stronger
activation of the right superior temporal sulcus. This pattern
was found predominantly to dyadic pictures, which is inter-
esting in the context of the interpersonal problems of BPD
patients.

In sum, studies on autobiographical memory provide
further evidence for a dysfunctional network of several brain
areas instead of disturbances of single structures. In addition
to a hyperactive amygdala, prefrontal areas as well as other
limbic structures, i.e. the ACC, seem to be involved. This
fronto-limbic network (Schmah and Bremner, 2006) plays a
crucial role not only in emotional responses but also in
emotional control, e.g. inhibition. However, it seems to be
important whether the participants are exposed to autobi-
ographical stimuli or scripts or, instead, whether they actively
retrieve autobiographical memories. Again, studies are miss-
ing that systematically investigate the influence of confound-
ing factors, such as dissociation and comorbid PTSD and
depression. Furthermore, studies should differentiate more
clearly between traumatic vs. stressful memories vs. those
memories that are related to special BPD symptoms, such as
abandonment.

3.2.4. Cognitive function
Response inhibition has been suggested to be one of the
principal mechanism of emotion regulation, and inhibitory
dysfunctions have been hypothesized to play an important
role in BPD patients (Domes et al., 2006; Fertuck et al.,
2006). Inhibition involves the suppression of specific beha-
vioral or mental acts and is an important component of self-
regulation (Daffner and Searl, 2008). A widely used method
for investigating inhibition of interference is the emotional
Stroop task. Reduced inhibition has been shown in several
clinical populations, especially when emotional stimuli are
specifically related to the core psychopathology (Williams
et al., 1996). Using the Stroop task, two imaging studies
investigated patients with PTSD, both suggesting dysfunc-
tions of brain networks including the anterior cingulate
cortex when processing emotionally relevant stimuli. In
one study, combat veterans with and without PTSD were
studied with the emotional counting Stroop task, including
combat-related, generally negative and generally neutral
words (Shin et al., 2001). Only the non-PTSD group exhibited
BOLD (blood oxygen level dependency) increases in the
anterior cingulate cortex, whereas the PTSD group failed
to activate this region. Another study investigated women
with early childhood sexual abuse with and without PTSD
(Bremner et al., 2004b). Again, in women with PTSD, reduced
activity in the anterior cingulate cortex was found in the
emotional Stroop task as well as greater increase in blood
flow in visual and parietal cortex in women without PTSD. In
one of our own studies investigating BPD patients, we used
the emotional Stroop task, too, and found an increased blood
flow in the ACC as well as in the frontal cortex in response
to negative stimuli, compared to neutral stimuli, only in the
control group (Wingenfeld et al., 2009b). In contrast, BPD
patients failed to show this activation suggesting a dysfunc-
tional brain network including the ACC and frontal brain
regions. These results are in line with the study of Silbersweig
et al. (2007), which found a decreased activation of frontal
brain regions and cingulate cortex in a go/no-go task, which is
also a paradigm to assess inhibitory function.

Findings from neuropsychological studies have not only
provided evidence for dysfunctions in inhibition and execu-
tive functions (Domes et al., 2006; Fertuck et al., 2006), but
also memory dysfunctions have been reported repeatedly
(Dinn et al., 2004). Accordingly, Mensebach et al. (2009)
compared BPD patients and healthy controls with respect
to neural correlates of their episodic and semantic memory
retrieval. Despite unaltered memory performance compared
to the control group, BPD patients showed increased activa-
tion in the posterior cingulate cortex as well as temporal
regions in the episodic memory task, and increased activation
in posterior and anterior cingulate cortex as well as in the
fusiform gyrus and postcentral gyrus in the semantic memory
task. Thus, it seems that BPD patients have to engage larger
brain regions to reach a level of performance that is compar-
able to healthy controls.

Up to now, there are too few studies investigating neural
correlates of cognitive functions in BPD to draw final con-
clusions. However, the presented studies together with those
investigations on autobiographical memory provide further
evidence for disturbances in brain regions involved in emo-
tion regulation. As dissociation has been shown to inhibit
emotional, amygdala-based learning (Ebner-Priemer et al.,
2009) it would be of great interest to evaluate the underlying
neuronal processes.

4. Summary and conclusions
The neurobiology of mental disorders such as major depres-
sion and PTSD as well as early life stress has been investi-
gated intensively. Although many patients with borderline
personality disorder also suffer from these disorders, and
BPD itself is characterized by many affective and trauma-
related symptoms, its psychobiological correlates are less
well understood.

Concerning the regulation of the HPA axis, current litera-
ture provides heterogeneous results with most studies
emphasizing rather enhanced basal and stimulated cortisol
release, suggesting a hyperactivity of the axis. Furthermore,
feedback regulation of the HPA axis has been shown to be
reduced. Thus, BPD shows a substantial overlap with affec-
tive disorders in these tests. However, comorbid PTSD seems
to have an important influence on the HPA axis in BPD.
This leads to the suggestion that the BPD population is
heterogeneous and that there are subgroups with different endocrine patterns, which are associated with the corresponding symptoms, i.e. affective or trauma-related symptoms. A reduced feedback sensitivity has been interpreted in the context of altered glucocorticoid receptor functioning, which has been impressively demonstrated for major depressive disorder (Pariante and Miller, 2001).

In the hippocampus, there is a high density of GR and, therefore, the hippocampus is not only an important mediator of the stress response, but also sensitive to the damaging effects of stress and glucocorticoids (Bremner, 1999). As shown for depressed patients (Videbech and Ravnkilde, 2004) and patients with PTSD, hippocampal volume has been found to be reduced in BPD. Whether these alterations have to be interpreted as a consequence of glucocorticoid exposure or have to be understood as a pre-existing risk factor is still a matter of debate (Sapolsky, 2001, 2002). Of note, the hippocampus plays an important role in learning and memory, and cortisol is known to impair memory retrieval in humans (Wolf, 2003). Although memory dysfunctions and HPA dysregulation are prominent in many mental disorders, these associations have attracted little scientific attention. In a sample of depressed patients, we recently investigated the influence of an acute cortisol treatment on autobiographical memory performance (Schlosser et al., 2009). In the placebo condition, depressed patients performed more poorly than controls. After hydrocortisone intake, healthy subjects reported significantly fewer specific memories on the autobiographical memory test compared to placebo treatment. In contrast, memory specificity of MDD patients was not affected by hydrocortisone treatment. These results are in line with the hypothesis of reduced central glucocorticoid sensitivity in these patients. Further studies should investigate whether BPD patients show similar peculiarities.

Another important finding from some but not all imaging studies is a relatively reduced volume of the amygdala, which sets BPD apart from other disorders, such as PTSD or major depressive disorder. On the other hand, functional imaging studies have provided some evidence for an increased activation of the amygdala when patients are exposed to emotional stimuli. Together with the finding of a reduced size and decreased activation of the ACC, a dysfunctional network of brain regions that are involved in the regulation of emotions and response inhibition might be proposed. The limbic system strongly influences the endocrine system and also has connections to higher brain areas, such as the frontal cortex. The role of comorbid disorders has not yet been examined intensively in these patients. One of its major functions is the regulation of emotions and stress; functions that are susceptible disturbed in BPD. As the emotional Stroop task is a widely used method for investigating response inhibition, we used an individual variant of this test in BPD patients and were able to show altered interference only in those patients with comorbid PTSD and to stimuli with personal relevance (Wingenfeld et al., 2009a). These results further emphasize the impact of comorbid disorders as well as the importance of stress-related memories.

It has been shown that patients with high impulsivity are characterized by a strong intensity of affective responses (Herpertz et al., 1997) and that negative emotions such as anger are not only stronger, but also more prolonged among these patients (Jacob et al., 2008). However, there is also evidence that these observations are not specific for BPD, but are also seen in other personality disorders and in depression (Koenigsberg et al., 2002; Renneberg et al., 2005). Several studies investigating physiological correlates of affective responses to emotional stimuli measured the startle response. Some (Ebner-Priemer et al., 2005) but not all (Herpertz et al., 1999, 2000, 2001b) of these psychophysiological investigations in BPD demonstrated an exaggerated startle response. However, an exaggerated startle response was interpreted in the context of an amygdala hyper-responsivity. Different methods may account for the conflicting results: while Ebner-Priemer et al. (2005) used an acoustic startle paradigm, Herpertz et al. used emotional pictures. Interestingly, only BPD patients with low dissociation were characterized by an enhanced startle reaction, which fits with the study of Simeon et al. (2007), who reported different stress responses for patients with and without dissociation. Furthermore, imaging studies suggest that frontal brain regions such as the orbitofrontal and dorsolateral prefrontal cortex seem to be involved, too. These frontal regions as well as parts of the limbic system are also associated with dysregulation of the serotonergic system in BPD patients. Symptoms of impulsivity, aggression and suicidal behavior seem to be strongly mediated by the serotonergic system and are prominent features in patients with BPD (Schmahl et al., 2002). Of note, there are strong interconnections between the serotonergic system, the stress response and the hippocampus (Bremner, 1999; Goodyer et al., 2009).

Based on this body of evidence, we hypothesize that BPD is characterized by a dysfunctional regulation of the HPA axis in concert with disturbances of the serotonergic system. Whereas the HPA axis seems to be characterized by a somewhat reduced feedback sensitivity and a mild hypercortisolism, the activity of the serotonergic system seems to be reduced (Schmahl et al., 2002). This leads to the assumption that the interaction between these systems, for example in terms of regulating the response to stress, seems to be disturbed. Early life stress, especially early traumatization, might be one important risk factor in this context. Other environmental factors such as unstable parental relationships as well as genetic factors but also individual and environmental resources will also be important. In BPD there are several alterations in brain regions that are involved in emotion regulation, response inhibition and autobiographical memory, especially the hippocampus, the ACC, the amygdala and prefrontal brain areas. Hormones or neurotransmitters from the HPA axis as well as serotonin play an important role in the regulation of these brain areas, and thus in emotion regulation and neuropsychological functions. A graphical depiction of this hypothetical model is presented in Fig. 4. Of note, the current literature has revealed many inconsistent findings and suggests BPD to be a heterogeneous disorder. Thus, future research has to support or refute this model by integrating different research fields, e.g. combining endocrine and imaging methods.

However, there are further biological aspects that have not been integrated in this review, such as genetics, the noradrenergic system, the opioid system and others. Due to the fact that BPD is a complex disorder in which several physiological systems are involved, future research should integrate these fields of research. Furthermore, several limitations of the reviewed studies have to be mentioned:
many studies only investigated small samples and did not control for comorbid diagnoses, medication dosage and other factors that might influence the results. Especially in endocrine research, effects of gender, consumption of oral contraceptive, menstrual cycle phase, age and other variables are important. In some studies, the statistical analyses were weak; for example, many fMRI studies only present results from fixed-effects analyses. Finally, only few investigations examine the course of physiological change in BPD. One study provides evidence for a relative stability of HPA-axis-related alteration when psychopathology did not change (Wingenfeld et al., 2007c). However, when investigating neural correlates of traumatic memories and of response to emotional stimuli, respectively, changes in brain activity could be revealed (Driessen et al., 2009; Schnell and Herpertz, 2007). Due to the lack of prospective studies, there is a need for further studies to separate physiological risk factors from those which are correlated with the disorder or with single symptoms in further studies.

Even though the summarized studies yielded heterogeneous results in some aspects, neuroimaging and endocrine studies have contributed to the understanding of the neurobiology of borderline personality disorder. A better understanding may lead to improvements in psychotherapeutic and psychopharmacological treatment of these patients.

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Conflict of interest

There are no conflicts of interest, financial or otherwise, to declare (all authors).

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Figure 4 Proposed model of the interaction between developmental factors of BPD, coexisting features/maintaining factors and selected biological alterations.


metabolic rate in prefrontal cortex in impulsive aggression. Psychopharmacology (Berl.) 176 (3—4), 451—458.