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Neuroimaging in borderline personality disorder

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Abstract

Neuroimaging has become one of the most important methods in the investigation of the neurobiological underpinnings of borderline personality disorder. Structural and functional imaging studies have revealed dysfunction in different brain regions which seem to contribute to borderline symptomatology. This review presents relevant studies using different methodologies: volumetry of limbic and prefrontal regions, investigations of brain metabolism under resting conditions, studies of serotonergic neurotransmission, and challenge studies using emotional, stressful, and sensory stimuli. Dysfunction in a frontolimbic network is suggested to mediate much, if not all of the borderline symptomatology.

Keywords: Neuroimaging; Borderline personality disorder; Prefrontal cortex; Amygdala

1. Introduction

The past few years have seen a rapidly growing body of research in the field of neurobiological correlates of borderline personality disorder (BPD) (Lieb et al., 2004; Schmahl et al., 2002; Skodol et al., 2002). In addition to research on the genetic basis of the disorder (Jang et al., 1996; Torgersen et al., 2000), psychopharmacological treatment (Soloff, 2000), and neuroendocrinology (Rinne et al., 2002), progress in neuroimaging has been fruitful in the elucidation of the underlying neurobiology of this severe and chronic disorder.

Affective dysregulation has been suggested to represent the core of borderline symptomatology and to underlie most if not all of the characteristic features of the disorder, such as instable self image, disturbed interpersonal relationships, and self-injurious behavior. Animal studies as well as investigations in healthy human subjects suggest that limbic as well as prefrontal regions play a decisive role in emotion regulation (Davidson and Irwin, 1999). Thus, it can be hypothesized that frontolimbic dysfunction underlies affective dysregulation as well as other closely connected symptoms of BPD. Consequently, structural as well as functional neuroimaging investigations have focussed on alterations in these brain regions.

This review on neuroimaging in BPD is arranged according to the different imaging methods used. It will start with studies using volumetrics and spectroscopy of different brain regions, such as hippocampus, amygdala, and prefrontal regions. An overview of functional neuroimaging will begin with studies of brain metabolism under resting conditions using FDG-PET. Imaging of the serotonergic neurotransmission system using serotonergic agents will then be reviewed, followed by challenge studies that investigate reactivity of brain areas to stimuli such as emotional pictures, stressful memories, or sensory challenges with the aid of PET or

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functional MRI. Finally, conclusions from the literature reviewed will be drawn and an outlook on future studies will be given.

2. Volumetrics and spectroscopy

Neuroimaging research in the field of BPD began in the early 1980s with the use of computed tomography (CT). Similar to research on brain alterations in schizophrenic patients, whole brain volumes and ventricle sizes were investigated. In contrast to findings in schizophrenia, studies in BPD did not show ventricular enlargement (Schulz et al., 1983; Snyder et al., 1983), or changes in ventricle–brain ratio (Lucas et al., 1989) in patients with BPD. With the advent of Magnetic Resonance Imaging, Lyoo reported a marginally significant reduction of overall frontal lobe volumes in BPD (Lyoo, 1998), although this finding has been criticized for technical reasons such as low spatial resolution and lack of correction for head tilt.

BPD has been suggested to be part of a trauma-related psychiatric spectrum of psychiatric disorders (Bremner, 2002), with posttraumatic stress disorder (PTSD) as the core of the spectrum, but also including BPD, depression and dissociative disorders. A major neurobiological finding of the last decade is a reduction in hippocampal volume as assessed by MR-based volumetry in combat-related (Bremner et al., 1995; Gilbertson et al., 2002; Gurvits et al., 1996) as well as abuse-related PTSD (Bremner et al., 1997; Bremner et al., 2003; Stein et al., 1997). There is an ongoing debate as to whether this volume reduction is due to an elevated activity of stress-associated neurobiological systems, such as the HPA axis or is genetically determined (Gilbertson et al., 2002). In contrast to the finding of reduced hippocampal volume, all published studies investigating amygdala volumes in patients with PTSD did not find any significant amygdala volume difference compared to controls (Bonne et al., 2001; Bremner et al., 1997; De Bellis et al., 1999; Gilbertson et al., 2002; Gurvits et al., 1996).

The first investigation of MRI-based volume of hippocampus and amygdala (Driessen et al., 2000) found 16% smaller volumes of the hippocampus and 8% smaller volumes of the amygdala in women with BPD compared to healthy controls. Tebartz van Elst et al. (2003) found an even more pronounced volume difference between patients with BPD and controls with 20.5% smaller hippocampal and 24% smaller amygdala volume. In addition, they found a highly significant volume-reduction of the left orbitofrontal cortex and of the right anterior cingulate cortex. Our own investigation revealed a reduction of 13% for hippocampus and 21% for amygdala (Schmahl et al., 2003a). A fourth study (Brambilla et al., 2004) also found volume reduction of hippocampus and amygdala, however these reductions did not reach significance. The authors also explored structural brain changes in BPD in relation to childhood abuse. Compared to 20 healthy controls, the ten unmedicated (abuse: $n = 6$, no abuse: $n = 4$) BPD patients, male and female, had significantly smaller right and left hippocampal volumes and significantly increased right and left putamen volumes. There were still significant differences in hippocampal volume when BPD patients with history of childhood abuse were compared to healthy controls. This significance disappeared when comparing healthy controls to BPD patients without childhood abuse. No significant differences between groups were found for caudate, amygdala, temporal lobes, dorsolateral prefrontal cortex and total brain volumes. The authors conclude that early traumatic experiences may play a role in hippocampal atrophy.

Taken together, these findings suggest that, in contrast to PTSD, not only hippocampus but also amygdala volumes seem to be reduced in patients with BPD. In a study using voxel-based morphometry, grey matter volume loss was found in the left amygdala without differences in grey or white matter volume or density anywhere else in the brain (Ruesch et al., 2003).

A different approach to assess neuronal dysfunction is Magnetic Resonance Spectroscopy, which measures concentration of neurochemical metabolites such as *N*-acetylaspartate (NAA), choline, or lactate in specified brain regions. Tebartz van Elst et al. (2001) found a significant 19% reduction of NAA concentration in the dorsolateral prefrontal cortex in patients with BPD compared to controls, suggesting neuropathology in this area of the brain. More studies are needed in this area to draw definite conclusions about disturbed brain metabolism in BPD.

3. Brain metabolism under resting conditions assessed with FDG-PET

[^{18}F]Deoxyglucose positron emission tomography (FDG-PET) can be used to assess baseline brain metabolism under resting conditions. The first study using FDG-PET in BPD was conducted by Goyer and coworkers (1994). Their investigation comprised 17 patients with DSM III-R personality disorders, six of which (four women and two men) were clinically diagnosed with BPD. However, the average score on the diagnostic interview for borderlines (DIB; Zanarini et al., 1989) in the BPD group was only 3.7, which is only about half of the usual cut-off score of 7. Thus, the results have to be interpreted with caution. In the group of six BPD patients, the authors found decreased metabolism in upper bilateral prefrontal cortex as well as increased metabolism in lower left and right prefrontal areas. Since the spatial resolution of the analysis is

low and no Brodmann areas are presented, it appears difficult to specify which parts of prefrontal cortex are dysfunctional, e.g. if the regions shown to have elevated and decreased metabolism comprise parts of anterior cingulate cortex (ACC). A second functional brain imaging study employing FDG-PET was conducted in a series of 10 patients (eight women and two men) with BPD and a DIB score of 7 or higher (De la Fuente et al., 1997). This investigation revealed decreased metabolism in premotor areas and dorsolateral prefrontal cortex, parts of the ACC (BA 25), as well as thalamic, caudate and lenticular nuclei, in BPD patients as compared to controls. Soloff et al. (2003), in a series of 13 impulsive BPD subjects, found decreased metabolism only in the medial orbital frontal cortex bilaterally (BA 9, 10 and 11).

We studied brain metabolism at baseline in 12 medication-free female patients with BPD without current substance abuse or major depression and 12 healthy female controls by FDG-PET and statistical parametric mapping (Juengling et al., 2003). This study revealed glucose metabolism to be significantly increased in patients with BPD compared to controls in the anterior cingulate, the superior frontal gyrus bilaterally, the right inferior frontal gyrus and the opercular part of the right precentral gyrus. Decreased metabolism was found in the left cuneus as well as in the left hippocampus. We could not replicate the findings of De la Fuente and Soloff who found prefrontal hypometabolism. Divergent findings may be due to differences in gender homogeneity as well as the inclusion of different subtypes of BPD (impulsive versus anxious borderline patients).

4. Imaging of the serotonergic system

Impulsive aggression is part of the BPD phenotype and yet little is known about its neurobiology. Reduced serotonergic activity has been associated with impulsive aggression in metabolite and pharmacologic challenge studies, e.g. hormone responses to fenfluramine that increases serotonergic activity were shown to be abnormal in personality disordered patients with impulsive aggression (Coccaro et al., 1989). However, the neuroanatomical locus of this serotonergic dysfunction is still unclear. Preclinical and human studies suggest that the orbital frontal cortex and anterior cingulate cortex play an inhibitory role in the regulation of aggression. FDG-PET in conjunction with serotonergic agents such as fenfluramine or *meta*-chlorophenylpiperazine (*m*-CPP) can be used to assess the function of the serotonergic system and localize brain areas of serotonergic dysfunction.

In a study using fenfluramine challenge and FDG-PET, Siever et al. (1999) investigated six outpatients (four males and two females) meeting criteria for Impulsive Aggressive Disorder, four of whom also met criteria for BPD. Impulsive-aggressive patients showed significantly less activity after fenfluramine as compared to placebo in the ventral medial frontal region, right middle and left upper cingulate gyrus, left lateral orbital and right dorsolateral prefrontal cortex. Blunted metabolic response in these regions to fenfluramine, which enhances serotonergic activity by direct release of serotonin, antagonism of serotonergic reuptake, and possibly direct receptor effects (Coccaro et al., 1996), may be related to reduced serotonergic modulation of inhibitory regions important in controlling impulsive aggression. These findings were replicated in a study of five patients with BPD and eight healthy controls (Soloff et al., 2000), which found reduced metabolism in response to fenfluramine as compared to placebo in right medial and orbital prefrontal cortex, left middle and superior temporal gyri, left parietal lobe, and left caudate body. This investigation also revealed baseline differences following placebo in large areas of the prefrontal cortex, namely reduced metabolism in right anterior frontal lobe, Brodmann areas 10 and 11 bilaterally, and right insula in BPD patients as compared to controls.

Using positron emission tomography in response to *meta*-chlorophenylpiperazine *m*-CPP), which acts as an agonist at serotonin receptors, New et al. (2002) investigated 12 personality disordered subjects (seven men and five women) with impulsive aggression, eight of whom had BPD, and 12 normal controls. Unlike normal subjects, patients with impulsive aggression did not show activation specifically in the left anteromedial orbital cortex in response to *m*-CPP. The anterior cingulate, normally activated by *m*-CPP, was deactivated in patients; in contrast, the posterior cingulate gyrus was activated in patients and deactivated in controls. In this study, no baseline differences in response to placebo were found. In a second study of this group, 27 male and female patients with BPD and 23 controls were investigated (New et al., 2003). At baseline, BPD men with physical aggression had less activity across the frontal cortex and cingulate gyrus as compared to BPD men with verbal aggression and controls. Verbally and physically aggressive BPD men had decreased activity specifically. Following *m*-CPP challenge, BPD men, but not women, revealed reduced activity across the frontal cortex as well as left cingulate gyrus, as compared to controls. Recently, a normalization of prefrontal cortex dysfunction by SSRI treatment (Fluoxetine 20 mg/day) could be shown in impulsive-aggressive BPD patients (New et al., 2004). Overall, pharmacologic challenge studies with fenfluramine and *m*-CPP revealed serotonergic dysfunction in prefrontal cortex as well as ACC; however, there seem to be important differences between male and female impulsive-aggressive BPD

patients with men showing reduced prefrontal activity as a possible correlate of aggression.

Another method to assess serotonergic function in specific areas of the brain, is to use PET with the 5-HT precursor analogue α-[(11)C]methyl-L-tryptophan (α-[(11)C]MTrp). α-MTrp is taken up by 5-HT neurons, where it is trapped in the 5-HT synthesis precursor pool. The rate of trapping provides an index of 5-HT synthesis capacity (Chugani and Muzik, 2000). Leyton et al. (2001) measured brain regional α-[(11)C]MTrp trapping with positron emission tomography in 13 medication-free subjects with BPD (eight women and five men) and eleven healthy comparison subjects. Impulsivity was assessed by using a laboratory measure of behavioral disinhibition, go/no-go commission errors. Compared to healthy men, men with borderline personality disorder had significantly lower α-[(11)C]MTrp trapping in corticostriatal sites, including the medial frontal gyrus, anterior cingulate gyrus, superior temporal gyrus, and corpus striatum. In women with borderline personality disorder, significantly lower α-[(11)C]MTrp trapping was seen in fewer regions, but in both men and women negative correlations with impulsivity scores were identified in the medial frontal gyrus, anterior cingulate gyrus, temporal gyrus, and striatum. It can be concluded that low 5-HT synthesis capacity in corticostriatal pathways may contribute to the development of impulsive behaviors in persons with borderline personality disorder. However, it should be pointed out that serotonin is not the only neurotransmitter thought to be involved in BPD. Disturbances in other neurochemical systems (e.g., the opioid and the HPA axis system) may underlie parts of the BPD symptomatology besides impulsivity (Skodol et al., 2002). Neuroimaging studies using tracers and/or challenges from these systems will be valuable for a better understanding of the roles these systems play in BPD.

5. Functional imaging studies with emotional, stressful, and sensory challenges

BPD was suggested to be part of a spectrum of stress-associated disorders together with PTSD, depression and dissociative disorders (Bremner, 2002) and reactivity to stress and stressful reminders appear to underlie affective dysregulation characteristic of patients with BPD. One method to test this reactivity is to expose subjects to emotional challenges or to stressful memories. Challenge studies are using either standardized materials such as emotional slides, or personalized material such as autobiographical scripts, e.g., depicting traumatic experiences. Imaging studies in conjunction with sensory challenges, such as exposure to painful heat stimuli, can reveal insight into neural processing of sensory stimuli. Disturbed pain processing is a characteristic feature of BPD probably underlying self-injurious behavior in this population and neuroimaging techniques can be used to localize this disturbance neuroanatomically.

Using standardized emotional slides which are supposed to evoke emotional responses, FMRI investigations in healthy subjects found activation of the amygdala region, (Irwin et al., 1996; Morris et al., 1998), anterior cingulate cortex as well as ventromedial prefrontal cortex areas (Mayberg et al., 1999; Teasdale et al., 1999). PET studies revealed neural correlates of different emotional states, such as grief, shame, guilt, and anger, using scripts specific for each emotion (Dougherty et al., 1999; George et al., 1995; Shin et al., 2000). For example, during the imagination of situations associated with anger, alterations of prefrontal blood flow with increased activity in ACC were found (Dougherty et al., 1999; Kimbrell et al., 1999). Using standardized negative emotional material from the International Affective Picture System (IAPS) Herpertz et al. (2001) found increased activity in the amygdala of six patients with BPD without comorbid psychiatric disorders compared to controls. In a larger sample of 12 BPD patients with comorbid anxiety and depressive disorders, these findings could be replicated (Herpertz, personal communication).

Another method of emotional challenge consists of presenting standardized pictures of faces which express a specific emotion such as anger, fear, or sadness (Ekman, 1993). Donegan et al. (2003) used this paradigm to investigate BPD patients with and without PTSD and controls. They found different effects for the two BPD groups: For BPD patients with PTSD left-lateralized amygdala hyper-reactivity was found, whereas those BPD patients without PTSD showed bilateral amygdala hyper-reactivity. In the cingulate cortex, these investigators found deactivation in response to fearful faces for patients with BPD and comorbid PTSD but not for those BPD patients without PTSD. In frontal polar prefrontal cortex (BA 10), they found an opposite pattern of deactivation for BPD patients without but not for those with PTSD. These findings are consistent with findings of left-lateralized amygdala hyper-reactivity (Rauch et al., 2000) as well as decreased cingulate activation in PTSD, which will be discussed below.

With the aid of personalized autobiographical scripts, neuroimaging studies in PTSD following childhood abuse have also demonstrated abnormalities in prefrontal brain areas, with a failure of activation in anterior cingulate (Shin et al., 1999; Bremner et al., 1999). Using the method of script-driven symptom provocation in conjunction with fMRI, Lanius et al. (2001, 2003) found decreased function in medial prefrontal cortex, anterior cingulate and thalamus in patients with PTSD. However, these studies did not assess axis II pathology in traumatized patients. We

expanded the method of challenging autobiographical scripts to investigate processing of stressful memories in patients with BPD. With personalized scripts of childhood abuse situations, findings in BPD patients were similar to those described above for PTSD. Memories of abuse were associated with increases in blood flow in right dorsolateral prefrontal cortex as well as decreased blood flow in left dorsolateral prefrontal gyrus in women without BPD. There was also increased blood flow in right anterior cingulate and left orbitofrontal cortex in women without BPD. Women with BPD failed to activate anterior cingulate gyrus as well as orbitofrontal cortex. Also, no blood flow differences were seen in dorsolateral prefrontal gyrus in women with BPD (Schmahl et al., 2004). Since fear of abandonment is one of the characteristic features of BPD and situations of abandonment appear to be an important stressor in the development of BPD, we also tested the effects of memories of situations of abandonment, again with the aid of autobiographical scripts (Schmahl et al., 2003b). Memories of abandonment were associated with greater increases in blood flow in bilateral dorsolateral prefrontal cortex (middle frontal gyrus, areas 9 and 10) as well as right cuneus (area 19) in women with BPD than in women without BPD. Abandonment memories were associated with greater decreases in right anterior cingulate (areas 24 and 32) in women with BPD than in women without BPD. A larger decrease in blood flow in women with BPD was also seen in left temporal cortex and left visual association cortex.

In a recent study (Driessen et al., 2004), neural correlates of traumatic memory versus aversive but nontraumatic memory were investigated in BPD patients with ($n = 6$) and without PTSD ($n = 6$). Comparing the reaction to the two memory types, differential responses for BPD patients with and without PTSD were found: Those without current PTSD showed a widespread activation of the orbitofrontal cortex (OFC) in both hemispheres, whereas those with current PTSD demonstrated only minor activation of the right more than the left OFC. Instead, there was a major right-sided activation of the anterior temporal lobe, including parahippocampal gyrus and amygdala. These results may indicate the existence of different neural networks in trauma-associated mental disorders. Taken together, a dysfunction of dorsolateral and medial prefrontal cortex may be associated with the recall of traumatic memories in women with BPD.

As mentioned above, alterations of pain perception and pain processing are a characteristic feature of BPD and may underlie self-injurious behavior in patients with the disorder. Neuroimaging studies revealed the neuroanatomical correlates of pain processing in the brain (Peyron et al., 2000). Two anatomically distinct pathways, distinguished according to their projections through thalamic nuclei, have been identified (Treede et al., 1999): a sensory-discriminative 'lateral' pathway projecting from the lateral thalamic nuclei to the primary and secondary somatosensory cortex, and an affective-motivational 'medial' pathway projecting from the medial thalamic nuclei to the insula and anterior cingulate cortex. Functional neuroimaging investigations of pain perception in healthy individuals using heat stimuli could demonstrate an involvement of lateral as well as medial pathways in pain processing of healthy human subjects (Bornhoevd et al., 2002; Davis, 2000). Dorsolateral prefrontal cortex appears to have an important pain control function (Lorenz et al., 2003). We used painful heat stimuli in combination with functional magnetic resonance imaging to examine neural processing of pain in BPD (Schmahl and Seifritz, 2003). Compared to normal subjects, BPD patients showed a specific pattern of cortical responses to pain, which was characterized by less activation in posterior parietal cortex and a stronger activation in dorsolateral prefrontal cortex. In addition, patients but not controls revealed a strong deactivation in the perigenual ACC. This pattern of neural activation may be related to disturbed evaluation of pain in patients with BPD.

6. Summary, conclusions, and outlook

Neuroimaging research in BPD started about 20 years ago, and the last decade has brought an enormous increase in structural as well as functional imaging research. This research has been stimulated by neuroimaging investigations in Posttraumatic Stress Disorder and methodologies have been transferred from neuroimaging research in PTSD, e.g., volumetry of hippocampus and amygdala, or challenge studies with stressful autobiographical scripts. Since PTSD and BPD are both characterized by stressful life events, and symptoms of both disorders are thought to be related to neurobiological alterations brought about by traumatic experiences, transfer of methodologies from research in PTSD to BPD seems to be justified.

The results of structural imaging studies are consistent with smaller hippocampal as well as amygdala volumes in adult patients with BPD. The finding of reduced hippocampal volume is consistent with many studies in PTSD, amygdala volume reduction, however, sets BPD apart from PTSD, where the amygdala seem to be structurally unaffected. Structural and functional neuroimaging has revealed a dysfunctional network of brain regions that seem to mediate much, if not all of the BPD symptomatology (Table 1). This frontolimbic network consists of anterior cingulate cortex, orbitofrontal and dorsolateral prefrontal cortex, hippocampus, and amygdala. FDG-PET studies have revealed

Table 1
Structural and functional imaging findings in frontolimbic regions

Region	Findings
Hippocampus	• Reduced volume (Driessen et al., 2000; Tebartz van Elst et al., 2003; Schmahl et al., 2003a) • Decreased baseline metabolism left (Juengling et al., 2003)
Amygdala	• Reduced volume (Driessen et al., 2000; Tebartz van Elst et al., 2003; Schmahl et al., 2003a) • Gray matter volume loss left (Ruesch et al., 2003) • Increased activity in response to affective pictures (Herpertz et al., 2001) and fearful faces (Donegan et al., 2003)
Anterior cingulate cortex	• Reduced volume right (Tebartz van Elst et al., 2003) • Decreased baseline metabolism (De la Fuente et al., 1997)/Increased baseline metabolism (Juengling et al., 2003) • Blunted response to fenfluramine (Siever et al., 1999) • Deactivation in response to *m*-cpp (New et al., 2002, 2003) • Reduced α-[(11)C]methyl-L-tryptophan trapping (Leyton et al., 2001) • Deactivation in response to fearful faces (Donegan et al., 2003) • Failure of activation in response to trauma scripts (Schmahl et al., 2004), deactivation in response to abandonment scripts (Schmahl et al., 2003b) • Decreased activity in response to pain stimuli (Schmahl and Seifritz, 2003)
Medial and orbital prefrontal cortex	• Reduced volume left orbital (Tebartz van Elst et al., 2003) • Decreased metabolism (Soloff et al., 2003) • Blunted response to fenfluramine (Siever et al., 1999; Soloff et al., 2000) and *m*-cpp (New et al., 2002, 2003) • Reduced alpha-[(11)C]methyl-L-tryptophan trapping (Leyton et al., 2001) • Failure of activation in response to trauma scripts (Schmahl et al., 2004)
Dorsolateral prefrontal cortex	• Reduced *N*-acteylaspartate concentration (Tebartz van Elst et al., 2001) • Decreased baseline metabolism (De la Fuente et al., 1997)/Increased baseline metabolism (Juengling et al., 2003) • Blunted response to fenfluramine right (Siever et al., 1999) • Failure of activation in response to trauma scripts (Schmahl et al., 2004), increased blood flow in response to abandonment scripts (Schmahl et al., 2003b) • Increased activity in response to pain stimuli left (Schmahl and Seifritz, 2003)

altered baseline metabolism in prefrontal regions including ACC. These brain areas also seem to be involved in dysfunctional serotonergic neurotransmission, which has been associated with disinhibited impulsive aggression in patients with BPD. Challenge studies using emotional, stressful, and sensory stimuli have consistently shown deactivation or failure of activation of ACC in patients with BPD. ACC may be viewed as a brain region mediating affective control, and dysfunction in this area could be related to affective dysregulation which is characteristic of BPD.

However, a number of open questions remain. Although deactivation of ACC in response to stress is found throughout most challenge studies, assessment of baseline metabolism with FDG-PET has not shown consistent results, with studies finding increased as well as decreased prefrontal metabolism. Different findings between FDG-PET studies may be due to subgroup differences as well as differences in gender distribution. Overall, gender effects seem to play a very important role in the neurobiology of BPD. This is particularly true for studies assessing serotonergic function. The studies by New et al. (2003) and Leyton et al. (2001) yielded large differences in serotonergic function in prefrontal areas between male and female BPD patients. This may be related to the fact that aggressive behavior is directed in different directions by male and female patients with BPD, with women showing mainly self-injurious behavior and men demonstrating more outwardly directed aggression. Another important conclusion from the research reviewed here is that frontolimbic dysfunction found in BPD is not a finding specific to the disorder, but can also be found in a variety of different disorders, such as PTSD, depression, or patients with impulsive and aggressive behavior. Thus, rather than being characteristic of a certain disorder, dysfunction of frontolimbic areas appears to underlie psychopathological clusters such as stress-related or impulsive syndromes.

Neuroimaging will certainly remain one of the most important methods for the study of the neurobiological underpinnings of BPD. Thus, future studies should focus on several points found to be important in the literature reviewed: different stress-related disorders, such as PTSD and BPD, should be compared directly using the same paradigms, such as emotional or stressful challenges. Also, given the large overlap of the two disorders BPD and PTSD, subgroups of BPD patients with and

without comorbid PTSD should be investigated. This clear separation of study groups may help to elucidate similarities as well as differences in the neurobiology of the two disorders. Another fruitful avenue of research is to take a look at gender effects in BPD. It seems to be crucial not to investigate mixed gender BPD groups since clinical as well as neurobiological differences between men and women with the disorder appear to be too large to investigate them together. However, only focussing on women with BPD would mean leaving out interesting findings. Thus, comparing male and female BPD patients is an interesting starting point for research which may help to clarify the role of gender in this disorder. PET studies using radioactively labelled tracers, e.g. opioid ligands, will become important to elucidate the contribution of different neurochemical systems to BPD symptomatology. Also, conditioning experiments in conjunction with functional imaging (Büchel and Dolan, 2000) may help to elucidate neural mechanisms underlying disturbed learning processes in BPD. Finally, an important question is whether the abnormalities found in imaging studies represent state or trait characteristics of the disorder. One possible way to answer this question is to investigate effects of therapeutic interventions by comparing patients before and after therapy.

References

Büchel C, Dolan RJ. Classical fear conditioning in functional neuroimaging. Current Opinion in Neurobiology 2000;10:219–23.

Bonne O, Brandes D, Gilboa A, Gomori JM, Shenton ME, Pitman RK, Shalev AY. Longitudinal MRI study of hippocampal volume in trauma survivors with PTSD. American Journal of Psychiatry 2001;158:1248–51.

Bornhoevd K, Quante M, Glauche V, Bromm B, Weiler C, Buechel C. Painful stimuli evoke different stimulus-response functions in the amygdala, prefrontal, insula and somatosensory cortex: a single-trial fMRI study. Brain 2002;125:1326–36.

Brambilla P, Soloff PH, Sala M, Nicoletti MA, Keshavan MS, Soares JC. Anatomical MRI study of borderline personality disorder patients. Psychiatry Research: Neuroimaging 2004;131:125–33.

Bremner JD. Does Stress damage the brain? New York: Norton; 2002.

Bremner JD, Randall P, Scott TM, Bronen RA, Seibyl JP, Southwick SM, Delaney RC, McCarthy G, Charney DS, Innis RB. MRI-based measurement of hippocampal volume in patients with combat-related posttraumatic stress disorder. American Journal of Psychiatry 1995;152:973–81.

Bremner JD, Randall P, Vermetten E, Staib L, Bronen RA, Mazure C, Capelli S, McCarthy G, Innis RB, Charney DS. Magnetic resonance imaging-based measurement of hippocampal volume in posttraumatic stress disorder related to childhood physical and sexual abuse – a preliminary report. Biological Psychiatry 1997;41:23–32.

Bremner JD, Narayan M, Staib LH, Southwick SM, McGlashan T, Charney DS. Neural correlates of childhood sexual abuse in women with and witout posttraumatic stress disorder. American Journal of Psychiatry 1999;156:1787–95.

Bremner JD, Vythilingam M, Vermetten E, Southwick SM, McGlashan T, Nazeer A, Khan S, Vaccarino LV, Soufer R, Garg PK, Ng CK, Staib LH, Duncan JS, Charney DS. MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. American Journal of Psychiatry 2003;160:924–32.

Chugani DC, Muzik O. α-[11C]Methyl-L-tryptophan PET maps brain serotonin synthesis and kynurenine pathway metabolism. Journal of Cerebral Blood Flow and Metabolism 2000;21:21–8.

Coccaro EF, Siever LJ, Klar H, Maurer G, Cochrane K, Cooper TB, Mohs RC, Davis KL. Serotonergic studies in patients with affective personality disorders: correlates with suicidal and impulsive-aggressive behavior. Archives of General Psychiatry 1989;46:587–99.

Coccaro EF, Kavoussi RJ, Cooper TB, Hauger RL. Hormonal responses to d- and d.l-fenfluramine in healthy human subjects. Neuropsychopharmacology 1996;15:595–607.

Davidson RJ, Irwin W. The functional neuroanatomy of emotion and affective style. Trends in Cognitive Science 1999;3:11–21.

Davis KD. The neural circuitry of pain as explored with functional MRI. Neurological Research 2000;22:313–7.

De Bellis MD, Keshavan MS, Clark DB, Casey BJ, Giedd JN, Boring AM, Frustaci K, Ryan ND. Developmental traumatology part II: brain development. Biological Psychiatry 1999;45:1271–84.

De la Fuente JM, Goldman S, Stanus E, Vizuette C, Morlán I, Bobes J, Mendlewicz J. Brain glucose metabolism in borderline personality disorder. Journal of Psychiatric Research 1997;31:531–41.

Donegan NH, Sanislow CA, Blumberg HP, Fulbright RK, Lacadie C, Skudlarski P, Gore JC, Olson IR, McGlashan TH, WExler BE. Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation. Biological Psychiatry 2003;54:1284–93.

Dougherty DD, Shin LM, Alpert NM, Pitman RK, Orr SP, Lasko M, Macklin ML, Fischman AJ, Rauch SL. Anger in healthy men: a PET study using script-driven imagery. Biological Psychiatry 1999;46:466–72.

Driessen M, Herrmann J, Stahl K, Zwaan M, Meier S, Hill A, Osterheider M, Petersen D. Magnetic resonance imaging volumes of the hippocampus and the Amygdala in women with borderline personality disorder and early traumatization. Archives of General Psychiatry 2000;57:1115–22.

Driessen M, Beblo T, Mertens M, Piefke M, Rullkoetter N, Silva-Saavedra A, Reddemann L, Rau H, Markowitsch HJ, Wulff H, Lange W, Woermann FG. Posttraumatic stress disorder and fmri activation patterns of traumatic memory in patients with borderline personality disorder. Biological Psychiatry 2004;55:603–11.

Ekman P. Facial expression and emotion. American Journal of Psychology 1993;48:384–92.

George MS, Ketter TA, Parekh PI, Horwitz B, Herscovitch P, Post RM. Brain activity during transient sadness and happiness in healthy women. American Journal of Psychiatry 1995;152:341–51.

Gilbertson MW, Shenton ME, Ciszewski A, Kasai K, Lasko NB, Orr SP, Pitman RK. Smaller hippocampal volume predicts pathological vulnerability to psychological trauma. Nature Neuroscience 2002;5:1242–7.

Goyer PF, Andreason PJ, Semple WE, Clayton AH, King AC, Compton-Toth BA, Schulz SC, Cohen RM. Positron-emission tomography and personality disorders. Neuropsychopharmacology 1994;10:21–8.

Gurvits TV, Shenton ME, Hokama H, Ohta H, Lasko NB, Gilbertson MW, Orr SP, Kikinis R, Jolez FA, McCarley RW, Pitman RK. Magnetic resonance imaging study of hippocampal volume in chronic, combat-related posttraumatic stress disorder. Biological Psychiatry 1996;40:1091–9.

Herpertz SC, Dietrich TM, Wenning B, Krings T, Erberich SG, Willmes K, Thron A, Sass A. Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study. Biological Psychiatry 2001;50:292–8.

Irwin W, Davidson RJ, Lowe MJ, Mock BJ, Sorenson JA, Turski PA. Human amygdala activation detected with echo-planar functional magnetic resonance imaging. Neuroreport 1996;7:1765–9.

Jang KL, Livesley WJ, Vernon PA, Jackson DN. Heritability of personality disorder traits: a twin study. Acta Psychiatrica Scandinavica 1996;94:438–44.

Juengling FD, Schmahl C, Hesslinger B, Ebert D, Bremner JD, Gostomzyk J, Bohus M, Lieb K. Positron emission tomography in female patients with Borderline Personality Disorder. Journal of Psychiatric Research 2003;37:109–15.

Kimbrell TA, George MS, Parekh PI, Ketter TA, Podell DM, Danielson AL, Repella JD, Benson BE, Willis MW, Herscovitch P, Post RM. Regional brain activity during transient self-induced anxiety and anger in healthy adults. Biological Psychiatry 1999;46:454–65.

Lanius RA, Williamson PC, Densmore M, Boksman K, Gupta MA, Neufeld RW, Gati JS, Menon RS. Neural correlates of traumatic memories in posttraumatic stress disorder: a functional MRI investigation. American Journal of Psychiatry 2001;158:1920–2.

Lanius RA, Williamson PC, Hopper J, Densmore M, Boksman K, Gupta MA, Neufeld RWJ, Gati JS, Menon RS. Recall of emotional states in posttraumatic stress disorder: an fMRI investigation. Biological Psychiatry 2003;53:204–10.

Leyton M, Okazawa H, Diksic M, Paris J, Rosa P, Mzengeza S, Young SN, Blier P, Benkelfat C. Brain regional α-[^{11}C]Methyl-L-Tryptophan trapping in impulsive subjects with borderline personlaity disorder. American Journal of Psychiatry 2001;158:775–82.

Lieb K, Zanarini M, Schmahl C, Linehan M, Bohus M. Borderline personality disorder. Lancet 2004;364:453–61.

Lorenz K, Minoshima S, Casey KL. Keeping pain out of mind: the role of the dorsolateral prefrontal cortex in pain modulation. Brain 2003;126:1079–91.

Lucas PB, Gardner DL, Cowdry RW, Pickar D. Cerebral structure in borderline personality disorder. Psychiatry Research 1989;27: 111–5.

Lyoo IK. A brain MRI study in subjects with borderline personality disorder. Journal of Affective Disorders 1998;50:235–43.

Mayberg HS, Liotti M, Brannan SK, McGinnis S, Mahurin RK, Jerabek PA, Silva JA, Tekell JL, Martin CC, Lancaster JL, Fox PT. Reciprocal limbic – cortical function and negative mood: converging PET findings in depression and normal sadness. American Journal of Psychiatry 1999;156:675–82.

Morris JS, Öhman A, Dolan RJ. Conscious and unconscious emotional learning in the human amygdala. Nature 1998;393: 467–70.

New AS, Hazlett EA, Buchsbaum MS, Goodman M, Reynolds D, Mitropoulou V, Sprung L, Shaw RB, Koenigsberg H, Platholdi J, Silverman J, Siever LJ. Blunted prefrontal cortical ^{18}fluorodeoyglucose positron emission tomography response to meta-chlorophenylpiperazine in impulsive aggression. Archives of General Psychiatry 2002;59:621–9.

New AS, Hazlett EA, Buchsbaum MS, Goodman M, Koenigsberg HW, Iskander L, Mitropoulou V, Siever LJ. *m*-CPP PET and impulsive aggression in borderline personality disorder. Biological Psychiatry 2003;53:S104.

New AS, Buchsbaum MS, Hazlett EA, Goodman M, Koenigsberg HW, Lo J, Iskander L, Newmark R, Brand J, O 'Flynn K, Siever LJ. Fluoxetine increases relative metabolic rate in prefrontal cortex in impulsive aggression. Psychopharmacology 2004;176:451–8.

Peyron R, Laurent B, Garcia-Larrea L. Functional imaging of brain responses to pain. Clinical Neurophysiology 2000;30:263–88.

Rauch SL, Whalen PJ, Shin LM, McInerney SC, Macklin ML, Lasko NB, Orr SP, Pitman RK. Exaggerated amygdala response to masked facial stimuli in posttraumatic stress disorder: a functional MRI study. Biological Psychiatry 2000;47:769–76.

Rinne T, de Kloet R, Wouters L, Goekoop JG, DeRijk RH, van den Brink W. Hyperresponsiveness of hypothalamic-pituitary-adrenal axis to combined dexamethasone/corticotropin-releasing hormaone challenge in female borderline personality disorder subjects with a history of sustained childhood abuse. Biological Psychiatry 2002;52:1102–12.

Ruesch N, Tebartz van Elst L, Wilke M, Thiel T, Ludaescher P, Huppertz H-J, Schmahl C, Bohus M, Lieb K, Hesslinger B, Hennig J, Ebert D. A voxel-based morphometric MRI study in female patients with borderline personality disorder. NeuroImage 2003;20:385–92.

Schmahl CG, Seifritz E. Functional MRI in the assessment of pain in patients with borderline personality disorder. Biological Psychiatry 2003;53:S104.

Schmahl CG, McGlashan TH, Bremner JD. Neurobiological correlates of borderline personality disorder. Psychopharmacology Bulletin 2002;36:69–87.

Schmahl CG, Vermetten E, Elzinga BM, Bremner JD. Magnetic resonance imaging of hippocampal and amygdala volume in women with childhood abuse and borderline personality disorder. Psychiatry Research: Neuroimaging 2003a;122:109–15.

Schmahl CG, Elzinga BM, Vermetten E, Sanislow C, McGlashan TH, Bremner JD. Neural correlates of memories of abandonment in women with and without borderline personality disorder. Biological Psychiatry 2003b;54:142–51.

Schmahl CG, Vermetten E, Elzinga BM, Bremner JD. A PET study of memories of childhood abuse in Borderline Personality Disorder. Biological Psychiatry 2004;55:759–65.

Schulz SC, Koller MM, Kishore PR, Hamer RM, Gehl JJ, Friedel RO. Ventricular enlargement in teenage patients with schizophrenia spectrum disorder. American Journal of Psychiatry 1983;140: 1592–5.

Shin LM, McNally RJ, Kosslyn SM, Thompson WL, Rauch SL, Alpert NM, Metzger LJ, Lasko NB, Orr SP, Pitman RK. Regional cerebral blood flow during script-driven imagery in childhood sexual abuse-related PTSD: a PET investigation. American Journal of Psychiatry 1999;156:575–84.

Shin M, Dougherty DD, Orr SP, Pitman RK, Lasko M, Macklin ML, Alpert NM, Fischman J, Rauch SL. Activation of anterior paralimbic structures during guilt-related script-driven imagery. Biological Psychiatry 2000;48:43–50.

Siever LJ, Buchsbaum MS, New AS, Speigel-Cohen J, wei T, Hazlett EA, Sevin E, Nunn M, Mitropoulou V. d,l-fenfluramine response in impulsive personality disorder assessed with [^{18}F]fluorodeoyglucose positron emission tomography. Neuropsychopharmacology 1999;20:413–23.

Skodol A, Siever L, Livesley J, Gunderson JG, Pfohl B, Widiger T. The borderline diagnosis II: biology, genetics, and clinical course. Biological Psychiatry 2002;51:951–63.

Snyder S, Pitts Jr WM, Gustin Q. CT scans of patients with borderline personality disorder. American Journal of Psychiatry 1983;140: 272.

Soloff PH. Borderline personality disorder: psychopharmacology of borderline personality disorder. Psychiatric Clinics of North America 2000;23:169–92.

Soloff PH, Meltzer CC, Greer PJ, Constantine D, Kelly TM. A fenfluramine-activated FDG-PET study of borderline personality disorder. Biological Psychiatry 2000;47:540–7.

Soloff PH, Meltzer CC, Becker C, Greer PJ, Kelly TM, Constantine D. Impulsivity and prefrontal hypometabolism in borderline personality disorder. Psychiatry Res: Neuroimaging 2003;123: 153–63.

Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B. Hippocampal volume in women victimized by childhood sexual abuse. Psychological Medicine 1997;27:951–9.

Teasdale JD, Howard RJ, Cox SG, Ha Y, Brammer MJ, Williams SCR, Checkley SA. Functional MRI study of the cognitive generation of affect. American Journal of Psychiatry 1999;156: 209–15.

Tebartz van Elst L, Hesslinger B, Thiel T, Geiger E, Haegele K, Lemieux L, Lieb K, Bohus M, Hennig J, Ebert D. Frontolimbic brain abnormalities in patients with borderline personality disorder. A volumetric MRI study. Biological Psychiatry 2003;54:163–71.

Tebartz van Elst L, Thiel T, Hesslinger B, Lieb K, Bohus M, Hennig J, Ebert D. Subtle prefrontal neuropathology in a pilot magnetic resonance spectroscopy study in patients with borderline personality disorder. Journal of Neuropsychiatry and Clinical Neurosciences 2001;13:511–4.

Torgersen S, Lygren S, Øien PA, Skre I, Onstad S, Edvardsen J, Tambs K, Kringlen E. A twin study of personality disorders. Comprehensive Psychiatry 2000;41:416–25.

Treede R-D, Kenshalo DR, Gracely RH, Jones AKP. The cortical representation of pain. Pain 1999;79:105–11.

Zanarini MC, Gunderson JG, Frankenburg FR, Chauncey DL. The revised diagnostic Interview for Borderlines: discriminating BPD from other Axis II disorders. Journal of Personality Disorders 1989;3:10–8.