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REVIEW

Brain structure and function in borderline personality disorder

Aisling O'Neill · Thomas Frodl

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Abstract The spotlight on borderline personality disorder (BPD) has been growing in recent years, with the number of papers discussing potential causes and triggers of the disorder rapidly on the increase. Also on the increase, though still lacking sufficient numbers to produce well-supported hypotheses, are studies employing neuroimaging techniques as investigative tools in BPD. In this review, we investigate the current state and findings of neuroimaging studies in BPD, focusing in particular, on the studies examining structural, functional, and neurometabolic abnormalities in the disorder. Some suspected trends in the data are highlighted, including reductions in the hippocampi and amygdalae of BPD patients compared to healthy controls, exaggerated amygdala activity in BPD patients when confronted with emotion-related stimulus, and negative correlations between increases in left amygdalar creatine and reductions in amygdalar volume, reductions in absolute *N*-acetylaspartate concentration in the dorsolateral prefrontal cortex of BPD patients, and increases in glutamate concentration in the anterior cingulate cortices of BPD patients. We also discuss the limitations of some of the current studies including hindrances due to sample effects and techniques used and the potential of future neuroimaging research in BPD.

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A number of research articles have discussed potential causes and factors which may lead to borderline personality disorder (BPD), though none has of yet produced any conclusive evidence in support of a single-cause theory. In fact, considering the heterogeneity of the disorder, it is more likely that a combination of factors is involved in its manifestation; each to different degrees within individuals (Asnaani et al. 2007; Wingenfeld et al. 2010). The main postulated theories cite the experience of early life trauma (e.g., childhood abuse or maternal separation), genetics, neurobiological alterations, or a combination of the above as being responsible, at least in part, along with external factors such as environmental and psychosocial stressors, for the onset of BPD (Goodman et al. 2004; Steele and Siever 2010).

A high correlation between childhood trauma and later development of BPD has been shown in numerous studies and it is generally accepted that such stressors are significant to the onset of the disorder, though the mechanisms involved are still under debate (Cohen et al. 2006). Abuse (physical and/or sexual) and neglect are common childhood experiences of adults with BPD, so, more than with other personality disorders. In one study, of the 358 BPD patients participating, 91% reported experiences of childhood abuse and 92% reported experiences of childhood neglect; much higher rates than those found amongst the patients with other personality disorders (Zanarini et al. 1997). In a later study, Zanarini et al. (2002) found a significant correlation between the severity of the reported child abuse and/or neglect of 290 BPD patients and the overall severity of the disorder.

Over the years, an increasing number of attempts have been made to produce a more genetic explanation of BPD, though the research is still far overshadowed by studies examining the relationship of early life adversity and BPD. A commonly discussed topic is the heritability of BPD, which has produced a number of twin studies, sibling environment/adoption studies, and self-report measures, though the findings from this approach have been less than consistent. Self-report measures, involving BPD patients, usually support an argument for at least a partial heritability, however, it is important to be mindful of the subjective nature of these measures and note that their findings do not always correspond with the relevant behavioural data (Williamson 2007; Jacob et al. 2010). The study of candidate genes is another popular genetic approach taken in BPD research and has produced a number of genes of particular interest. Genes currently under investigation include the 7-repeat polymorphism of the dopamine D4 receptor (DRD4), which has been linked to disorganized attachment, whilst the combined effect of the 7-repeat polymorphism and the 10/10 dopamine transporter (DAT) genotype has been linked to abnormalities in inhibitory control, both noted features of BPD (Congdon and Canli 2008; Friedel 2004).

Previous BPD research has consisted mainly of studies exploring the psychological aspects of the disorder from characteristic behaviours to psychosocial triggers and risk factors, with early life-stress proving to be strongly associated with the occurrences of the disorder. In recent years, however, appreciation has increased dramatically for the neurobiological abnormalities which have been associated with dimensions of personality dysfunction, with findings from a number of studies confirming the biological underpinnings of the disorder (Foti et al. 2010; Goodman et al. 2004). As incidents of early life trauma are so highly correlated with the occurrence of BPD, the disorder is quite often classed as being on a spectrum of trauma-related psychiatric disorders, of which post traumatic stress disorder (PTSD) is the core (Schmahl and Bremner 2006). Neuroimaging research exploring neurobiological abnormalities in PTSD has provided the building blocks for similar research in BPD, with the methodologies used in PTSD neuroimaging studies such as volumetry of different brain regions frequently transferred to studies in BPD; these methodologies themselves often originating in other better researched areas including Schizophrenia and Alzheimer's disease (Schmahl and Bremner 2006).

The regions of most interest in BPD research are generally those areas associated with the regulation of normal behaviours in healthy individuals, which are dysfunctional in those with BPD (Brambilla et al. 2004). A number of neuroimaging studies in BPD have reported findings of reductions in regions of the brain involved in the regulation of stress responses, emotion, and affect the hippocampus, the orbitofrontal cortex, and the amygdala, amongst other areas. Other studies have attempted to examine functional abnormalities in these same regions either at baseline or under emotion-inducing conditions, whilst a smaller number of studies have used magnetic resonance spectroscopy to explore changes in the concentrations of neurometabolites in certain brain regions of BPD patients, looking specifically at neurometabolites such as *N*-acetylaspartate, creatine, glutamate related compounds, and choline containing compounds.

In this review, we will discuss neuroimaging research relating to BPD thus far, considering the neurobiological aspects of the disorder, discussing the previous findings and their implications for future research.

Initially, a comprehensive literature search was conducted to locate all studies which used neuroimaging (structural MRI, PET, fMRI, MR-Spectroscopy) to study individuals with a primary diagnosis of BPD compared to healthy controls. PubMed, Science Direct, Web of Knowledge and Scopus were searched for publications dating from the databases' inceptions through to January 2011 using the keywords such as: "borderline personality disorder and MRI", "borderline personality disorder and (PET or fMRI)", "borderline personality disorder and spectroscopy". The search was confined to English language articles. The following study features were used as grounds for exclusion: Studies containing duplicated datasets (i.e., reported the same data in different manuscripts) were excluded, though meta-analyses which included a number of datasets were considered. Studies which employed only screening instruments and not diagnostic tools to confirm the diagnosis of BPD were also excluded. Two reviewers (AO'N, TF) independently applied these exclusion criteria to the databases. Inclusion criteria applied regulated the reporting of participant demographics, insuring that the included studies reported the participants with respect to age, gender, duration of symptoms and the study setting.

Of the articles obtained, using the search term "borderline personality disorder and structural MRI", we carefully analysed 40, excluding ones those did not meet the needed criteria. Twenty-two articles were found to be appropriate for this review; articles that focused solely on specific traits associated with the disorder, solely on patients with comorbidities, or older articles whose results had been updated in more recent studies, were excluded. The search term "borderline personality disorder MRI meta-analysis" produced two includable meta-analyses. Using the search terms "(PET or fMRI) and borderline personality disorder", 100 studies were found. Ten of them met the inclusion criteria and are reported here; a large majority of the returned articles did not relate to BPD and were thus irrelevant, and the exclusion criteria for the

structural search were also employed here. For the search terms MR-Spectroscopy and BPD, eight articles were found, four of which are reported in this review, the rest were excluded based on the previous criteria for the structural and functional searches.

Structural brain changes

In volumetric studies, the two commonly used analytical techniques are voxel-based morphometry (VBM) and manual tracing. Manual tracing involves drawing the regions of interest (be it the whole brain or its subparts) on images obtained from brain scans and measuring the volume enclosed. It allows for the precise identification and delineation of regions of interest (Irle et al. 2005), though it can be time consuming and is of more use for larger areas. In voxel-based morphometry, each brain is mapped to a template then statistical tests are run across all voxels in the image to identify differences between testing groups. Though its results can be hard to validate, studies comparing the results of VBM to those of manual tracing or visual measurements have found relatively good correspondence (Whitwell 2009), though its validity when dealing with atypical brains (such as those containing severe pathologies) has been questioned, due to its core features of normalisation and segmentation to a template (Mechelli et al. 2005).

The most popular areas for volumetric research in BPD usually include the neural circuits in the prefrontal cortex, the limbic system, the anterior cingulate cortex (ACC), caudate nucleus, the brain areas of the HPA axis, and other related structures as abnormalities of these areas have been associated to varying degrees with the psychopathology of BPD. A summary of the reported alterations in brain structure in BPD can be found in Tables 1 and 2.

In general, the brain region which most consistently showed alterations in studies of BPD patients is the hippocampus, with a number of studies finding significant hippocampal volume reductions bilaterally in individuals with BPD compared to healthy controls (Brambilla et al. 2004; Schmahl et al. 2003; Tebartz van Elst et al. 2003). Interestingly, Brambilla et al. (2004) found with further examination that those BPD patients who had a history of childhood abuse, when compared to healthy controls, still displayed significant reductions in hippocampal volumes, whilst BPD patients without such a history did not display significant reductions. The researchers also found a significant negative correlation between hippocampal volume of the BPD patients with a history of childhood abuse and the length of duration of the abuse (Brambilla et al. 2004). A study by Driessen et al. (2000) reported similar findings with 16% reductions in the hippocampal volumes of the BPD patients being studied, compared to healthy controls, and a negative correlation being observed between hippocampal volume and duration of reported early trauma. In the Driessen et al. (2000) study, however, the negative correlation was only observed when the BPD and healthy control groups were considered together. Finally, Zetzsche et al. (2007) also found smaller grey-matter volume of the hippocampus in BPD patients compared to controls, with this volume decrease displaying a positive correlation with aggresive behavior and number of the previous hospitalizations.

Studies examining volumetric changes in other areas have been less consistent. With studies concerning the amygdala, for example, some researchers have argued that there are notable reductions in volume in patients with BPD compared to the healthy controls (Schmahl et al. 2003; Tebartz van Elst et al. 2003), whilst others have failed to show any differences (Brambilla et al. 2004; New et al. 2007), with yet others reporting an increase in the grey-matter of the amygdala of BPD patients (Minzenberg et al. 2008). Driessen et al.'s (2000) study also examined amygdala volumes in BPD patients, and reported a reduction of 8% in the BPD patient volumes compared to those of healthy controls. Another study compared cognition, hippocampal volumes, and amygdala volumes across a group of trauma-exposed women with BPD (some with and some without comorbid PTSD) and a group of healthy controls. The results showed decreases in both the hippocampus and amygdala volumes of the BPD women with PTSD compared to healthy controls (12 and 33% respectively), and also found cognition to be significantly impaired in this same group compared to the healthy controls (Weniger et al. 2009). The hippocampus and amygdala volumes of the BPD-women without PTSD were also found to be significantly reduced compared to healthy controls (11 and 22% respectively), though no significant differences in cognition were found between these two groups (Weniger et al. 2009). No significant volumetric differences were observed between the patients with and without PTSD, though the authors suggested that a larger patient-sample group may have shown significant differences in amygdala size between the two patient groups (Weniger et al. 2009). An interesting set of results which contradicted these findings of BPD amygdalar abnormalities found no significant differences in amygdala sizes between a BPD sample group and a healthy control group (Zetzsche et al. 2006). However, this same study did find a significant difference in the bilateral amygdala sizes of BPD patients with and without comorbid major depression (MDD). The amygdala volumes of the patients with MDD were found to be significantly larger than those of the patients without MDD, and a positive correlation was found between the volume of the left amygdala of the total BPD group and depressive symptoms (as measured by the

Table 1 Neurobiological structural changes seen in borderline personality disorder, and sample characteristics of each study

Study	Method	Sample characteristics; BPD/HC				Main results	
		Size	Age	Gender	Handedness	Volume reduction in BPD	Other results
Driessen et al. (2000)[a]	Manual tracing	21/21	29.9 ± 6/29.3 ± 6.7	21 (100)/21 (100) female	18(86)/18(86) RH	Amygdala, hippocampus	
Rusch et al. (2003)[b]	VBM	20/21	29.3 ± 3.9/28.4 ± 6.4	20(100)/21(100) female	Data unavailable	Grey matter of left amygdala	No reductions in grey matter of any other area
Schmahl et al. (2003)[c]	Manual tracing	10/23	27.4 ± 7.1/31.5 ± 8	10 (100)/23 (100) Female	10 (100)/20 (87) RH	Amygdala, hippocampus	
Tebartz van Elst et al. (2003)[d]	Manual tracing	8/8	33.5 ± 6.3/30.5 ± 5.1	8 (100)/8 (100) Female	Data unavailable	Amygdala, hippocampus, left OFC, right ACC	
Brambilla et al. (2004)[e]	Manual tracing	10/20	29.2 ± 9.25/data unavailable	6 (60) female/data unavailable	Data unavailable	ACC, hippocampus	No volume reduction of amygdala, caudate, temporal lobes, DLPFC
Hazlett et al. (2005)[f]	Manual tracing	50/50	33.2 ± 8.5/31.5 ± 9.9	23 (46)/20 (40) female	Data unavailable	ACC, posterior cingulate cortex	No volume reduction of whole cingulate, frontal lobe
Zetzsche et al. (2006)[g]	Manual tracing	25/25	26.1 ± 7.1/27.2 ± 6.3	25 (100)/25 (100) female	25 (100)/25 (100) RH		No difference in amygdala volumes between whole BPD group and HC group. Significantly larger amygdala volumes in BPD patients w. comorbid MDD compared to BPD patients w/o MDD
New et al. (2007)[h]	Manual tracing	26/24	BPD males: 35.7 ± 7.9 BPD females: 30.7 ± 8.6/HC males: 31.7 ± 7.9 HC females: 34 ± 11.2	9 (34.6)/9 (37.5) female	19(73)/19(79) RH		No volume reduction of amygdala
Tebartz van Elst et al. (2007)[i]	Manual tracing	12/10	27.7 ± 5.5/26.9 ± 4.4	12 (100)/10 (100) female	Data unavailable	Amygdala	Non-signif. reductions in hippocampus and OFC volumes
Zetzsche et al. (2007)[j]	Manual tracing	25/25	26.1 ± 7.1/27.2 ± 6.3	25 (100)/25 (100) female	25 (100)/25 (100) RH	Grey matter of hippocampus	
Chanen et al. (2008)[k]	Manual tracing	20/20	17.3 ± 1.1/19 ± 2.2	15 (75)/15 (75) Female	18 (90)/18 (90) RH	Right OFC	No volume reduction of amygdala, hippocampus

Table 1 continued

Study	Method	Sample characteristics; BPD/HC				Main results	
		Size	Age	Gender	Handedness	Volume reduction in BPD	Other results
Minzenberg et al. (2008)[l]	VBM	12/12	30.3 ± 8/ 30.7 ± 10	5 (41.6)/6 (50) female	Data unavailable	Grey matter of ACC	Increased grey matter of amygdala
Soloff et al. (2008)[m]	VBM	34/30	27.5 ± 8/ 25.6 ± 7.7	22 (64.7)/19 (63.3) female	Data unavailable	(BPD women) medial temporal lobe (incl. Amygdala) (BPD men) grey matter of ACC	(BPD men) no reductions in medial temporal lobe (BPD women) no reductions in grey matter of ACC
Schmahl et al. (2009)[n]	Manual tracing	25/25	29 ± 6.7/ 28.5 ± 6.06	25 (100)/25 (100) female	25 (100)/25 (100) RH	(w. comorbid PTSD) hippocampus	(w/o comorbid PTSD) no reduction in hippocampus volume no volume reduction for amygdala in either patient group
Takahashi et al. (2009b)[o]	Manual tracing	Sample characteristics previously described by Chanen et al. (2008).					No signif. difference in insular cortex vols. between BPDs and HCs
Takahashi et al. (2009a)[o]	Manual tracing	Sample characterstics previously described by Chanen et al. (2008).					No differences in cavum septum pellucidum between BPD and HC. Significantly shorter adhesio interthalamica in BPD group, significantly larger 3rd ventricle in BPD
Vollm et al. (2009)[o]	VBM	7/6	17.3 ± 1.1/ 19 ± 2.2	7 (100)/6 (100) Male	7 (100)/6 (100) RH	Grey matter volumes in frontal, temporal, parietal cortices	
Weniger et al. (2009)[p]	Manual tracing	24/25	BPD w. PTSD: 32 ± 7 BPD w/o PTSD: 32 ± 5 HC: 33 ± 7	24 (100)/25 (100) Female	BPD w. PTSD: 10 (100) BPD w/o PTSD: 12 (85.7) HC: 25(200)RH	Amygdala, hippocampus	No signif. differences in vol. between patients with/without PTSD
Whittle et al. (2009)[q]	Manual tracing	Sample characterstics previously described by Chanen et al. (2008).				Left ACC	

Table 1 continued

Study	Method	Sample characteristics; BPD/HC				Main results	
		Size	Age	Gender	Handedness	Volume reduction in BPD	Other results
Brunner et al. (2010)[q]	VBM	20/20 CC: 20	16.7 ± 1.6/16.8 ± 1.2 CC: 16 ± 1.3	20 (100)/20 (100) CC: 20 (100)	20 (100)/20 (100) CC: 20(100) RH	DLPFC, left OFC	No differences found between BPD group and clinical control group

BPD and HC data presented as mean ± SD BPD/HC or number (percentage) BPD/HC

BPD Borderline personality disorder, *HC* Healthy controls, *CC* Clinical controls, *VBM* Voxel-based morphometry, *RH* Right handed, *MDD* Major depressive disorder, *PTSD* Post traumatic stress disorder, *OFC* Orbitofrontal cortex, *ACC* Anterior cingulate cortex, *DLPFC* Dorsolateral prefrontal cortex, *signif.* significant, *w.*with, *w/o* without

[a] All patients had been drug free for at least 7 days at the time of assessment. Nine patients had used psychotropic medications during the 7–1 weeks prior to the assessment. Data regarding psychotherapeutic treatments were unavailable

[b] All patients were free of psychotropic medication for at least the 2 weeks prior to the assessment. Data regarding psychotherapeutic treatments were unavailable

[c] Nine of the patients were being treated with psychotropic medication at the time of assessment. Data regarding psychotherapeutic treatments were unavailable

[d] All patients were free of psychotropic medication for at least the 2 weeks prior to the assessment. Data regarding psychotherapeutic treatments were unavailable

[e] All patients were free of psychotropic medications for at least the 2 months prior to the assessment. Six of the patients had been treated with psychotropic medication in the past, the other four were drug naïve. Data regarding psychotherapeutic treatments were unavailable

[f] All patients were free of psychoactive medications for at least 6 weeks prior to the assessment. Fourty-three of the 50 patients were drug naïve. Data regarding psychotherapeutic treatments were unavailable

[g] Twenty of the patients were taking psychotropic medications at the time of the assessment. Nineteen of the patients had been treated with psychotropic medications in the past. Five of the patients were not being treated with any medications at the time of the assessment, three of whom were drug naïve. Data regarding psychotherapeutic treatments were unavailable

[h] All patients were free of psychotropic medications for at least the 6 weeks prior to the assessment. Twenty-two of the 26 patients were drug naïve. Data regarding psychotherapeutic treatments were unavailable

[i] All patients were free of psychoactive medications for at least the 2 weeks prior to the assessment

[j] Twenty of the patients were taking psychotropic medications at the time of the assessment. Nineteen of the patients had been treated with psychotropic medications in the past. Five of the patients were not being treated with any medications at the time of the assessment, three of whom were drug naïve. Data regarding psychotherapeutic treatments were unavailable

[k] The patients included were teenagers with first presentation BPD. At the time of the assessment 17 of the patients were unmedicated, whilst 3 were being treated with psychotropic medications. One patient had been treated with psychotropic medication in the past. Sixteen of the patients had received non-specialised counsellingor psychotherapy in the past

[l] All patients were unmedicated at the time of the assessment. Seven of the patients were drug naïve, whilst five had been free of psychotropic medications for the duration of 4 months to 10 years prior to the assessment. Data regarding psychotherapeutic treatments were unavailable

[m] All patients were free of psychoactive medications for the 2–6 weeks prior to the assessment. Data regarding psychotherapeutic treatments were unavailable

[n] All patients were free of psychotropic medications for at least the 2 weeks prior to the assessment. Data regarding psychotherapeutic treatments were unavailable

[o] All patients were unmedicated at the time of the assessment. Data regarding psychotherapeutic treatments were unavailable

[p] Seven of the patients were taking psychotropic medications at the time of the assessment. Data regarding psychotherapeutic treatments were unavailable

[q] The patients included were teenagers with first presentation BPD. None of the patients had taken psychotropic medications prior to their current admission to hospital. Nine of the BPD patients were taking psychotropic medication at the time of the assessment. Four of the CC patients were taking psychotropic medications at the time of the assessment. Data regarding psychotherapeutic treatments were unavailable

Table 2 Meta analyses of studies examining neurobiological structural changes seen in borderline personality disorder

Study	Method	Sample BPD/HC	Main results	
			Volume reduction	Other results
Hall et al. (2010)	MRI	–	Hippocampus, amygdala	No differences in whole brain volume
Nunes et al. (2009)	–	104/122	Hippocampus, amygdala	

Hamilton rating scale for depression) (Zetzsche et al. 2006).

The ACC is also known to play a role in the regulation of emotion and response inhibition (Wingenfeld et al. 2010), and the results of studies investigating volumetric abnormalities in the region, though few in number, have been relatively consistent. In a 2003 study by Tebartzan van Elst et al. (2003) a reduction in ACC volume was reported in BPD patients compared to the controls. This finding was supported by a number of later studies which observed significant reductions in grey-matter in the ACC of BPD patients (Hazlett et al. 2005; Minzenberg et al. 2008). A 2009 investigation of ACC volumes in adolescents with first presentation BPD and minimal exposure to treatment found a decrease in left ACC volume of the patient group compared to healthy controls (Whittle et al. 2009). In addition, the paper also reported a negative correlation between left ACC volume and parasuicidal behaviours and a positive correlation between left ACC volume and impulsivity in the patient group (Whittle et al. 2009).

Alterations in glucose metabolism and brain oxygenation

Other studies examining dysregulation in neural systems implicated in BPD have used techniques such as positron emission tomography (PET) or functional magnetic resonance imaging (fMRI) to investigate the activity in certain areas of interest. In PET studies, a positron emitting nucleotide is introduced into the body on a biologically active molecule, its activity in the brain is monitored, and this information is used to establish data about brain metabolism, blood flow, or receptor binding. FDG-PET is the most commonly used form of PET and uses FDG, a glucose analogue, to measure the rates of regional glucose uptake. fMRI studies are less-invasive than PET and are thus becoming a more popular technique, using magnetic fields and radio frequencies to measure changes in blood oxygenation which can be used as an indirect measure of neural activity, blood flow, or volume. Using PET, De la Fuente et al. (1997) found significant reductions in resting state glucose metabolism in the premotor areas and the dorsolateral prefrontal cortex (DLPFC), parts of the ACC (BA25), as well as the thalamus, caudate and lenticular nuclei of BPD patients compared to healthy controls. Interestingly, the BA25, which is connected to the amygdala and hypothalamus, is considered to be an important centre in the neural circuitry of depression and reductions in volume of BA25 are suspected to contribute to an increased risk for depression (Insel 2010). However, a later resting state PET study by Juengling et al. (2003) produced results contradictory to those of the De la Fuente study, reporting glucose hypermetabolism in the frontal and prefrontal cortices in patients with BPD relative to controls as well as significant hypometabolism in the hippocampus and cuneus, at baseline. Still another study found results which again varied from those of De la Fuente and Juengling's studies. Though said study did find glucose hypometabilsm at resting state in the frontal lobe, similar to the findings of De la Fuente et al., significant hypermetabolism was also seen in the motor cortex, the medial cingulate cortex, the ACC, the occipital lobe, and the temporal pole, amongst other regions, a finding not shown in either of the other FDG-PET studies mentioned (Salavert et al. 2011). Though mentioned earlier under the structural findings, the major findings of the New et al. (2007) related to dysfunctional connectivity between frontal brain areas and the amygdala in the brains of BPD patients. Using PET, the researchers found that in the HC group, there was a strong correlation between activity in the orbitofrontal cortex (OFC) and activity in the right ventral amygdala (New et al. 2007). In the BPD group, however, these same significant correlations between OFC and amygdala activity were absent (New et al. 2007). However, little research has been done to expand on these results.

The results of the fMRI studies, on the other hand, have been more consistent than those of the FDG-PET studies. The most common finding amongst these studies is that of exaggerated activity in the amygdala of patients with BPD compared to controls during procedures that involve the processing of emotionally aversive stimuli (Donegan et al. 2003a; Herpertz et al. 2001; Minzenberg et al. 2007a). Of particular interest is an emotional linguistic study by Silbersweig et al. (2007), which examined the brain function of BPD patients compared to controls under conditions associated with the interaction between behavioural inhibition and negative emotion. In the study, a significant reduction in activity was seen in the ventromedial

prefrontal cortex (including the medial orbitofrontal cortex and subgenual ACC) in the BPD patients compared to controls. A strong correlation was found between decreasing ventromedial prefrontal activity and decreasing constraint (impulsivity), whilst a strong correlation was also found for increased amygdalar ventral striatal activity and increased negative emotions in the patients (Silbersweig et al. 2007); impulsivity and the experience of exaggerated negative emotions being diagnostic features of the disorder. A summary of the functional findings of studies in BPD can be found in Table 3.

Neurometabolites

Though the number of studies examining structural and functional abnormalities in BPD is increasing, revealing more about the dysfunctional frontolimbic brain regions involved in the neuropathology of the disorder, only a handful of studies have examined the concentration of neurometabolites in the brains of patients with BPD. Magnetic resonance spectroscopy (MRS) is a technique related to MRI which allows for the study of metabolic changes in diseases affecting the brain and other organs. It is being used with increasing frequency in brain research as it is the only method that allows non invasive in vivo observation of various neurometabolites, including glutamate (Glu), glutamine (Gln), phosphocreatine (PCr) and creatine (Cr) (total creatine [tCr]), *N*-acetylaspartate (total NAA [tNAA]), and choline-containing compounds (tCho). Studies examining alterations in NAA concentration have yet to yield consistent results, though the limited number of studies is a major obstacle in achieving this goal. The earliest study of NAA concentrations in BPD, by van Elst et al. (2001), found a significant 19% reduction of absolute NAA concentration in the DLPFC of BPD patients compared to controls. Reductions in NAA have been shown to reflect a state of neuronal damage that often precedes cell death, thus NAA concentrations are of particular interest as they could be indicative of neuronal integrity (van Elst et al. 2001) The researchers also reported non-significant reductions in striatal Cr concentrations, though no differences were found in frontal or striatal NAA/Cr and Cho/Cr ratios. They explained the lack of difference in neurochemical ratios between groups as being due to the non-significant reductions seen in Cr concentrations; positing that, contrary to the previous assumptions, in fact, there is limited usefulness in measuring the relative concentrations of NAA/Cr and Cho/Cr as the concentration of Cr is not constant (van Elst et al. 2001). Consequently, a decrease in both NAA and Cr concentrations may result in false negative findings. Additional findings of reductions in tNAA and tCr were produced in a BPD study of the amygdala by Hoerst et al. (2010b), further opposing the assumption that Cr is a constant term and providing further evidence supporting a role for tNAA reductions in the mechanisms underlying the disorder.

In a 2007 pilot study by Tebartz van Elst et al. (2007), not only was further evidence produced to counter the traditional view of Cr as a stable neurometabolite, the study was also the first to discovered a relationship between neurometabolic abnormalities and structural abnormalities in a brain-region associated with BPD. The study found a significant 11–17% reduction in amygdalar volume of patients with BPD accompanied by a 17% increase in the Cr concentration of the left amygdala. The Cr concentration was found to be negatively correlated with amygdala volume, but positively correlated with measures of anxiety. The nature of the relationship between these volumetric and neurometabolic abnormalities, and any others that have yet to be shown in BPD, are still unclear, though Tebartz van Elst et al. (2007) suggest that it is likely to be linked to the pathology and neurochemical abnormalities of the disorder, specifically in terms of Cr-related processes. PCr and Cr levels make up the total Cr visible in MRS, and both play important roles in the phosphate bound energy metabolism which is essential in the brain. There is evidence to suggest that Cr and PCr/Cr kinase system are involved in neuronal growth cone activity and axonal elongation. From this perspective, increases in the Cr signal in the amygdala could reflect disturbances in local energy metabolism which in turn may result in amygdalar volume loss and consequently irregularities in the neuronal network for affect regulation (Tebartz van Elst et al. 2007). Alternatively, the observed increases in Cr concentrations may be a coping strategy of the brain to compensate for a structurally compromised emotional information processing network, though not enough research exists to confirm either theory yet (Tebartz van Elst et al. 2007). However, the findings of the Tebartz van Elst et al. study clash with those of the previously mentioned Hoerst et al. study, which not only found an opposing decrease in tCr in the amygdala but also failed to find a significant correlation between the neurochemical concentrations and psychometric measures taken. Recently, another separate study by Hoerst et al. (2010a) found significantly elevated levels of Glu in the ACCs of patients with BPD compared to that of controls. Furthermore, the levels of Glu were found to be positively correlated with the measures of impulsivity irrespective of diagnosis, whilst other positive correlations were found between Glu concentrations and levels of dissociation, as well as Glu concentrations and severity of symptoms within the patient group. It is worth noting, however, that similar neurochemical abnormalities have been found in the studies of non-human primates exposed to early life stress and in studies of adolescents with PTSD,

Table 3 Neurobiological functional abnormalities seen in borderline personality disorder, and sample characteristics of each study

Study	Method	Sample characteristics; BPD/HC				Patient State	Results
		Size	Age	Gender	Handedness		
De la Fuente et al. (1997)[a]	FDG-PET	10/15	34.2 ± 7.2/30.7[b]	8 (80)/7 (46.6) female	10 (100)/15 (100) RH	Resting	BPD group showed signif. hypometabolism in the premotor area, DLPFC, parts of the ACC, thalamus, caudate, and lenticular nuclei
Herpertz et al. (2001)[c]	fMRI	6/6	26.2 ± 8.1/ 27.2 ± 4.5	6 (100)/6 (100) female	6 (100)/6 (100) RH	Viewing emotionally aversive slides	BPD group showed activation bilaterally of the amygdala, medial and inferolateral prefrontal cortex, and fusiform gyrus
Donegan et al. (2003b)[d]	fMRI (only amygdala)	15/15	35 ± 11.7/ 34.9 ± 10	13 (86)/9 (60) female	15 (100)/15 (100) RH	Viewing facial expressions of emotion	Significantly greater left amygdala activation in the BPD group
Juengling et al. (2003)[e]	FDG-PET	12/12	25 ± 4/30 ± 9	12 (100)/12 (100) female	Data unavailable	Resting	BPD group showed signif. hypermetabolism in the frontal and prefrontal cortices, and significant hypometabolism in the left hippocampus and cuneus
Minzenberg et al. (2007b)[f]	fMRI	12/12	30.3 ± 8/ 30.7 ± 10	5 (41.6)/6 (50) female	Data unavailable	Viewing facial expressions of emotion and making gender discriminations	In relation to fear stimuli the BPD group showed exaggerated activation in the amygdala, impaired activation of ACC
New et al. (2007)[g]	FDG-PET	26/24	BPD males: 35.7 ± 7.9 BPD females: 30.7 ± 8.6/HC males: 31.7 ± 7.9 HC females: 34 ± 11.2	9 (34.6)/9 (37.5) female	19 (73)/19 (79) RH	Resting and placebo or resting and m-CPP	Placebo HC: signif. pos. correl. b/w right OFC and ventral amygdala Placebo BPD: weak correl. b/w amygdala and anterior PFC m-CPP HC: pos. correl. b/w OFC and amygdala regions m-CPP BPD: pos. correl. b/w DLPFC and amygdala
Silbersweig et al. (2007)[h]	fMRI	16/14	31.25[i]/23.8[i]	15 (93.7)/10 (71.4) female	15 (93.7)/12 (85.7) RH	Performing emotional linguistic go/ no go task	BPD group showed decrease in ventromedial prefrontal activity
Koenigsberg et al. (2009a)[j]	fMRI	18/16	32.6 ± 10.4/ 31.8 ± 7.7	10 (55.5)/9 (56.2) female	17 (94.4)/14 (87.5) RH	Distancing from/Casual viewing of images depicting social interactions	Whilst viewing negative images the BPD group showed less signal change in the dorsal ACC and intraparietal sulcus, less deactivation in the amygdala, and increased activation in the superior temporal sulcus and superior frontal gyrus
Koenigsberg et al. (2009b)[k]	fMRI	19/17	34.9 ± 11.1/ 31.2 ± 10.6	7(36.8)/ 8(47.05) female	14(73.6)/ 15(88.2) RH	Viewing emotion inducing images	Whilst viewing negative social emotional images, the BPD group showed exaggerated activation in the amygdala and visual processing regions
New et al. (2009)[l]	FDG-PET	38/36	30.5 ± 8.5/ 28.4 ± 7.1	16(42.1)/ 18(50) female	32(84.2)/ 32(88.8) RH	Performing aggression provoking task	BPD group showed hypermetabolism in OFC and amygdala during provocation; hypometabolism in anterior, medial, and prefrontal regions during provocation

Table 3 continued

Study	Method	Sample characteristics; BPD/HC				Patient State	Results
		Size	Age	Gender	Handedness		
Salavert et al. (2011)[m]	FDG PET	8/8	35.5 ± 9.27/32 ± 7.86	6 (75)/5 (62.5) female	8 (100)/8 (100) RH	Resting	BPD group showed hypometabolism in the frontal lobe; hypermetabolism in the motor cortex, medial and anterior cingulus, occipital lobe, temporal pole, left superior parietal gyrus and right superior frontal gyrus

BPD and HC data presented as mean ± SD BPD/HC or number (percentage) BPD/HC

BPD Borderline personality disorder, *HC* Healthy controls, *fMRI* Functional magnetic resonance imaging, *FDG-PET* Fludeoxyglucose positron emission tomography, *RH* Right handed, *m-CPP* Meta-chloropiperazine, *OFC* Orbitofrontal cortex, *PFC* Prefrontal cortex, *ACC* Anterior cingulate cortex, *DLPFC* Dorsolateral prefrontal cortex, *signif.* significant, *correl.* correlation, *pos.* positive, *b/w* between

[a] SD data unavailable for HC group

[b] All patients were free of psychoactive medications for the 2–6 weeks prior to the assessment. Data regarding psychotherapeutic treatments were unavailable

[c] All patients were free of psychoactive medications at the time of the assessment. Data regarding psychotherapeutic treatments were unavailable

[d] Eleven of the patients were taking psychotropic medications at the time of the assessment. Data regarding psychotherapeutic treatments were unavailable

[e] All patients were free of psychotropic medications for at least the 4 weeks prior to the assessment. Data regarding psychotherapeutic treatments were unavailable

[f] All patients were unmedicated at the time of the assessment. Seven of the patients were drug naïve, whilst the remaining five had discontinued treatments with psychotropic medications from 4 months to several years before the assessment. Data regarding psychotherapeutic treatments were unavailable

[g] All patients were free of psychotropic medications for at least the 6 weeks prior to the assessment. Twenty-two of the 26 patients were drug naïve. Data regarding psychotherapeutic treatments were unavailable

[h] Eleven of the patients were taking psychotropic medications at the time of the assessment. Data regarding psychotherapeutic treatments were unavailable

[i] SD data unavailable for group

[j] All patients were free of psychotropic medications for at least the 2 weeks prior to the assessment. Data regarding psychotherapeutic treatments were unavailable

[k] All patients were free of psychotropic medications for at least the 2 weeks prior to the assessment. Data regarding psychotherapeutic treatments were unavailable

[l] All patients were free of psychotropic medications for at least the 2 months prior to the assessment. Data regarding psychotherapeutic treatments were unavailable

[m] All patients were free of psychotropic medications for at least the 1 month prior to the assessment. Data regarding psychotherapeutic treatments were unavailable

suggesting that these abnormalities are related to the experiences of trauma and are not BPD specific (Mathew et al. 2003). A summary of the above findings in neurometabolite studies can be found in Table 4.

Discussion

The articles examined here, though not always in agreement with each other, have produced some interesting results which shall surely bring us closer to uncovering the mechanisms underlying BPD. In relation to the studies of structural abnormalities in patients with BPD, the cited meta-analyses both concluded that there were significant reductions in the volumes of the amygdalae and hippocampi of the BPD patients analysed. Despite this, individual studies appear to have produced more varied results, e.g., of the 11 studies which examined amygdala volume 6 found significant reductions in volume for the patient group, 4 found no significant differences between patient group and control, and 1 found a significant increase in grey matter of the amygdalae of the patient group. More difficulties arise with the amygdala in particular as Minzenberg et al. (2008) pointed out that a change in either direction could in theory be linked to different features of the disorder; for example a smaller amygdala in patients with BPD could potentially provide an explanation for the emotional dysregulation associated with the disorder, whilst an increase in grey-matter concentration could account for the exaggerated responses to emotional stimulus seen in the amygdala. Despite the reductions in the amygdalae of BPD patients being a somewhat controversial finding, and many reports of similar amygdalar reductions existing for other trauma-related disorders, it

Table 4 Neurometabolite changes seen in borderline personality disorder

Study	Sample characteristics; BPD/HC				MRS details	Findings
	Size	Age	Gender	Handedness		
van Elst et al. (2001)[a]	12/14	31.6 ± 7.1/ 30.1 ± 3.8	12 (100)/ 14 (100) female	Data unavailable	2.0 Tesla 2 cm^3 voxel size Std. quadrature head coil	19% reduction in NAA conc. in DLPFC Non-significant reductions of 15% in frontal and 16% in striatal Cr conc NAA/Cr and Cho/Cr ratios showed no differences
Tebartz van Elst et al. (2007)[b]	12/10	27.7 ± 5.5/ 26.9 ± 4.4	12(100)/ 10(100) Female	Data unavailable	2.0 Tesla 1.5 cm^3 voxel size Std. quadrature head coil	11–17% reductions in amygdalar volume 17% increase in left amygdalar Cr Left amygdalar Cr conc. pos. correlated with measures of anxiety Left amygdalar Cr conc. neg. correlated with amygdalar volume
Hoerst et al. (2010a)[c]	30/30	29.33 ± 7.6/ 28.6 ± 8	30 (100)/ 30 (100) Female	30 (100)/30 (100) RH	3.0 Tesla 15 × 20 × 12 mm^3 voxel size 12 channel receive only head coil	Increased Glu conc. in ACC Pos. correlation between Glu conc. and impulsivity (independent of BPD diagnosis) Neg. correlation between Glu conc. and BPD severity (within patient group)
Hoerst et al. (2010b)[d]	21/20	27.24 ± 5.5/ 28.55 ± 8.7	21 (100)/ 20 (100) Female	21 (100)/20 (100) RH	3.0 Tesla 12 × 10 × 12 mm voxel size 12 channel receive only head coil	Reduction in tNAA and tCr in left amygdala BPD patients with comorbid PTSD showed lower levels of tCr compared to Single diagnosis BPD patients and controls No significant correlation between neurochemical conc. and psychometric measurements

BPD Borderline personality disorder, *HC* Healthy controls, *RH* Right handed, *DLPFC* Dorsolateral prefrontal cortex, *NAA* *N*-acetylaspartate, *tNAA* Total *N*-acetylaspartate, *Cr* Creatine, *tCr* Total creatine, *Cho* Choline, *Glu* Glutamate, *conc.* concentration, *neg.* negative, *pos.* positive, *w.*with, *w/o* without

[a] All patients were unmedicated at the time of the assessment. All patients were receiving a specialised treatment for BPD which followed the principles of dialectic behavioural therapy

[b] All patients were free of psychoactive medications for at least the 2 weeks prior to the assessment. Data regarding psychotherapeutic treatments were unavailable

[c] All patients were free of psychotropic medications for at least the 3 months prior to the assessment. Data regarding psychotherapeutic treatments were unavailable

[d] All patients were free of psychotropic medications for at least the 14 days prior to the assessment. Data regarding psychotherapeutic treatments were unavailable

has been suggested that, if it was possible to consistently find such abnormalities, reductions in the amygdala volumes of BPD patients could be a stronger feature of the disorder than other structural abnormalities and could provide important markers for intervention and treatment (Weniger et al. 2009). In addition, although amygdala abnormalities are not specific to BPD, observations of differences in the magnitude of such reductions between BPD groups with and without severe depressive symptoms, comorbid MDD, and other disorders may prove to be useful when distinguishing subtypes of the disorder (Zetzsche et al. 2006).

Overall, the brain region most consistently found to display alterations in BPD patients is the hippocampus. The hippocampus plays an important role in memory consolidation, declarative memory, and is highly sensitive to the effects of stress, with stress-related increases in glucocorticoid levels being associated with smaller hippocampal volumes in animal studies (Brambilla et al. 2004). It has been suggested that volumetric reductions of the hippocampus, the most frequently produced result in human studies, may lead to the neurocognitive deficits, dissociative symptoms, perceptual distortions, and identity instability seen in BPD patients (Brambilla et al. 2004).

Although the reductions in regions of the brain known to play important roles in emotional regulation, processing, and other functions usually impaired in individuals with BPD are largely accepted, it is worth noting again that reductions in the hippocampus, amygdala, and ACC are not specific to BPD. Reductions in these areas have also been shown in trauma-exposed individuals, both with and without psychiatric disorders (most commonly PTSD and MDD) (Cohen et al. 2006; Macqueen and Frodl 2010; Karl et al. 2006), and in the same neural structures of non-human primates that have experienced early life stress (Bremner 1999; Bremne and Vermetten 2001; Cohen et al. 2006). However in the human studies, the magnitude of these reductions is generally greater in those with the psychiatric disorders than in those without. As these structural abnormalities are not specific to BPD, Wingenfeld et al. (2010) suggest that these findings in BPD patients support the theory that early life stress does indeed have a damaging effect in certain brain regions. However, the exact cause of the volume reductions observed and whether the high incidence of BPD patient comorbidity with PTSD and MDD is due predominantly to trauma-related aspects of the disorder remain to be seen. It is important to also acknowledge at this point that the depth of the interaction between traumatisation and other factors such as familial/genetic factors, environment, and pharmacological intervention on long-term neurobiological changes as yet is not well understood (Bremne and Vermetten 2001; Kaufman and Charney 2001). The different techniques used in the studies (i.e., VBM or manual tracing) did not appear to affect the outcome, though other methodoligical issues which may have influenced the results of not only the volumetric studies but also the functional and spectroscopic studies include the large disparity seen between sample sizes; gender differences, of which very little is understood; and the comorbidities of the participant samples, with some samples consisting of patients suffering from other disorders in addition to BPD, which although being true to the general BPD population, may produce misleading results; whilst other samples consist of individuals with a sole diagnosis of BPD, which may not accurately reflect the general BPD population. Another potential issue worth noting regarding sample characteristics is the age of the participants. As the brain goes through maturation, it is known to undergo both increases and decreases in the white and grey matter of various areas continuing into the early 20s (Giedd et al. 1999; Paus 2005). Of the studies cited, only the samples of the Brunner et al. (2010) and Chanen et al. (2008) studies consisted solely of teenagers with first presentation BPD (although both the Takahashi et al. studies and the Whittle et al. study used the same sample as Chanen et al.). The findings of these adolescent studies were generally in keeping with those of the adult-sample studies, thus there does not appear to be any pressing anomalies in the BPD brain attributable to age or level of brain maturation. Limitation of this matter is the lack of longitudinal studies in BPD. An increase of such studies is vital for the researchers to gain a fuller understanding not only of the potential effect of brain immaturity on adolescent BPD but also the long-term effects of the progression of the disorder and of treatment on the adult brain.

An as yet unexplored explanation of the volumetric reductions seen in particular brain areas of BPD patients involves dysregulation on a cellular level. Support for this theory includes studies which have shown that both chronic stress and peripheral chronic inflammation are linked to the down regulation of hippocampal-brain derived neurotrophic factor (Karl et al. 2006); a growth factor found in high concentrations in the hippocampus, amongst other areas. In addition, increases in inflammatory mediators of the immune system, linked to chronic dysregulation of the hypothalamic–pituitary–adrenal axis (HPA axis), which is itself linked to chronic stress, have been found to increase atherosclerotic processes in blood vessels (Karl et al. 2006). In turn, these processes can lead to hypertension which has also been linked to reductions in hippocampal volume (Wiseman et al. 2004). Studies in PTSD, which like BPD is strongly related to stressful and traumatic events, have investigated a potential cellular basis for the disorder and have found associations between the disorder and alterations in immune system and cardiovascular

function (Karl et al. 2006). In addition, experimental stress was shown to result in depressive-like behavior and neuronal changes including atrophy of neurons and downregulation of neurogenesis (Duman 2002). It is possible that similar findings could be made in BPD research, however, such an approach has not yet been explored. Further details may potentially also be gleaned from post mortem studies, however these studies for various reasons do not exist in BPD.

The fMRI studies examining neurobiological functional abnormalities in BPD patients produced results which were largely consistent with each other. The most prominent finding was that of exaggerated activity in the amygdala whilst passively viewing emotionally aversive slides or the slides depicting negative facial expressions. The one PET study that involved an aggression-invoking task produced similar results, finding hypermetabolism in the amygdalae and orbitofrontal cortices of the BPD group when provoked. These findings would suggest that individuals with BPD have different neural dynamics compared to their healthy counterparts when passively viewing negative images or being provoked into a negative emotional state (Koenigsberg et al. 2009a). Indeed in the individuals with BPD, these abnormal activations may cause impaired utilization of cognitive control regulations leading to the difficulties in behaviour modulation and in the ability to regulate emotional reactions during negative emotional states which characterize the disorder (Silbersweig et al. 2007; Koenigsberg et al. 2009a).

Another PET study which produced prominent results was that of New et al. (2007). The study found that a correlation between activity in the prefrontal cortex and the amygdala seen in HC participants was absent in BPD participants. New et al. expanded on this and suggested that the correlation seen in the HC group indicated the intact coupling between the prefrontal cortex and the right ventral amygdala. Though the directionality of the associations between the amygdala and the prefrontal cortex is still controversial, in this case the directionality of the correlation would indicate that the coupling may be the underlying neural substrate responsible for down regulation of the amygdala in response to aversive stimuli; the absence of which explaining the failure of those with BPD to down regulate the amygdala when faced with aversive stimuli (New et al. 2007).

The other PET studies examined patients only during a resting state, though the results of these studies produced very little consistency. One reason for the lack of consistency amongst these PET studies could be that at resting state, the patients' emotional state is not known thus the range of neural activity could be vast, whereas in the studies involving specific tasks or images, the patients' emotional states can be more accurately predicted and the resulting images compared with more reliability. This would suggest that when investigating neurobiological functioning in BPD patients, studies which employ emotion-related stimuli provide a more reliable measure than resting state studies; a fitting theory considering that the characteristic features of the disorder include emotional dysregulation and irregular emotional response behaviours. Another potential cause of inconsistencies in functionality studies is sample characteristics, specifically gender differences. Gender effects are particularly relevant in investigations of emotional states such as aggression, as aggression in particular is known to be directed differently in males and females and this could result in different neural activation between the genders (Schmahl et al. 2003; Schmahl and Bremner 2006). Another potentially confounding variable in functional studies is the past and present treatment (including both pharmacological and psychotherapeutic) received by the patients. Such treatments have been shown to affect regional cerebral functioning to a certain extent in different psychiatric disorders (Salavert et al. 2011), however studying untreated BPD patients can be very difficult due to the patient predisposition in BPD to self harm or attempt suicide. Although some patients may have never received treatment of any kind, as we can see from Table 3 the majority of patient participants in the studies cited here had at least a history of treatment with psychotropic medications, with others being treated with psychotropic medications at the time of the assessment. Unfortunately, very little data were reported by the studies regarding details of the psychotherapeutic treatment of the patients, which is in itself a major limitation of the research. Nevertheless, Salavert et al. (2011) suggest that although the influence of pharmacological and psychotherapeutic treatments cannot be ruled out conclusively, it is accepted that both treatments tend to improve the neurofunctional deficits observed in the disorder. Thus, finding significant differences in functioning between BPD patients and healthy controls, despite the potential influence of various treatments, gives credence to the effects found (Salavert et al. 2011). Nonetheless, these studies still confirm the importance of the areas of interest established by structural studies, e.g., the ACC and hippocampus (Schmahl and Bremner 2006).

The neurometabolite studies, however, have thus far been inconclusive purely because of the small number of studies that tackle the subject. The fewer the number of studies, the less comparisons can be made and the weaker the conclusion drawn. The few studies in existence have investigated concentrations of neurometabolites such as glutamate, glutamine, phosphocreatine and creatine, *N*-acetylaspartate, and choline-containing compounds. These metabolites have been described as markers for and associated with a number of neuronal features and occurrences such as neuronal

integrity (tNAA), energy-dependent functions (Cr), and demyelination (Cho), though these associations are still under debate (Jung et al. 2002). Though still requiring further validation, these studies have produced some interesting results. For example, the study by Tebartz van Elst et al. in 2007 found two interesting irregularities in the BPD patients; increases in left amygdalar creatine and reductions in amygdalar volume (Tebartz van Elst et al. 2007). Adding to this, the researchers also found a negative correlation between left amygdalar creatine concentration and amygdalar volume and a positive correlation between these creatine concentrations and psychometric measures of anxiety. A reduction in left amygdalar creatine levels was then also produced in a later study, lending support to the above Tebartz van Elst et al. findings, though the later study did not find any correlations between neurometabolite concentrations and any psychometric measurements (Hoerst et al. 2010b). These findings tie in very well with the structural studies which have found reductions in amygdala volumes in BPD patients, though much more spectroscopy research is needed to support these results and further any theories. The results of the other Hoerst et al. (2010a) study from the same year are in keeping with the theory that elevated levels of Glu in the ACC are significantly associated with both severity of BPD symptoms and subjective impulsivity ratings, the latter independent of a BPD diagnosis. These findings, along with the finding of increased levels of Glx in non human primates exposed to early life stress, also support the suggested associated between HPA axis activation and heightened glutamate neurotransmission in the prefrontal cortex (Mathew et al. 2003).

As the research stands, it is evident that much more concrete findings are needed to gain a firm understanding of the neurobiological underpinnings of the disorder. The abnormalities found thus far in the volumetric and functional studies overlap dramatically with those found in studies of individuals who have experienced trauma, those with trauma-related disorders, and those with MDD. The neural abnormalities found in individuals with PTSD in particular are very similar to those seen in the BPD studies cited here. As both disorders share a range of etiological factors and symptomology, the shared biological features are perhaps an inevitability. Studies examining brain abnormalities in BPD patients with and without comorbid attention deficit hyperactivity disorder (ADHD), however, remain largely absent. This is indeed surprising considering that there is a clear overlap of symptoms between the disorders (including emotional instability and impulsivity) and that around 60% of adults with BPD have a lifetime history of ADHD or ADHD symptoms (Fossati et al. 2002). This lack of data regarding BPD and comorbid ADHD is a severe limitation of the previous research and it is strongly recommended that if possible the issue be addressed in future studies, along with the further study of other prominent comorbidities. By furthering the study of BPD and its comorbid disorders, it may be possible to establish biological markers to distinguish the disorders from each other. An additional goal would be to establish markers to differentiate the subtypes of the disorder. Another direction for studies examining abnormalities in terms of potential markers would be to investigate abnormalities in first presentation BPD patients, as these could lead to effective methods for intervention and treatment. As yet, the studies examining the neurobiology of BPD have been solely cross-sectional, which as mentioned earlier, is a major limitation in the quest to expand our knowledge of the disorder. Longitudinal studies examining the course of the disorder from the first presentation into adulthood and equally as importantly examining the ongoing effects of pharmacological and psychotherapeutic intervention are vital to gain a better understanding of the disorder and for indexing and improving current treatments. To achieve these goals employing a combination of volumetric, functional, and spectroscopic methods, cross-sectionally and longitudinally, though expensive and time consuming, may prove to be essential, as alone their findings may only provide snippets of the broader picture.

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