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Childhood abuse is associated with structural impairment in the ventrolateral prefrontal cortex and aggressiveness in patients with borderline personality disorder

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ABSTRACT

Volume reduction and functional impairment in areas of the prefrontal cortex (PFC) have been found in borderline personality disorder (BPD), particularly in patients with a history of childhood abuse. These abnormalities may contribute to the expression of emotion dysregulation and aggressiveness. In this study we investigated whether the volume of the PFC is reduced in BPD patients and whether a history of childhood abuse would be associated with greater PFC structural changes. Structural MRI data were obtained from 18 BPD patients and 19 healthy individuals matched for age, sex, handedness, and education and were analyzed using voxel based morphometry. The Child Abuse Scale was used to elicit a past history of abuse; aggression was evaluated using the Buss–Durkee Hostility Inventory (BDHI). The volume of the right ventrolateral PFC (VLPFC) was significantly reduced in BPD subjects with a history of childhood abuse compared to those without this risk factor. Additionally, right VLPFC gray matter volume significantly correlated with the BDHI total score and with BDHI irritability and negativism subscale scores in patients with a history of childhood abuse. Our results suggest that a history of childhood abuse may lead to increased aggression mediated by an impairment of the right VLPFC.

1. Introduction

Borderline personality disorder (BPD) is a psychiatric disorder characterized by instability in interpersonal relationships and self-image, deficiencies in emotion regulation and marked impulsivity which may lead to self-destructive or aggressive behaviors (American Psychiatric Association, 1994). BPD affects up to 5.9% of the population (Grant et al., 2008) and is associated with high levels of social disability, subjective distress and intensive mental health service utilization (Zanarini, 2005). There is therefore increased interest in studying the neural correlates of BPD in order to elucidate the pathophysiology of the disorder and the neural basis of its symptoms.

A number of brain imaging studies have examined volumetric and functional changes associated with BPD. Decreased volumes of the hippocampus and the amygdala have been consistently found (O'Neill and Frodl, 2012; Ruocco et al., 2012) and are possibly associated with exposure to physical and sexual abuse during childhood (Bremner et al., 1997; Brambilla et al., 2004). Furthermore, a number of neuroimaging studies in BPD have reported abnormalities within the prefrontal cortex (PFC) (Lyoo et al., 1998; McCloskey et al., 2005; Schmahl and Bremner, 2006; Lis et al., 2007). These include mainly gray matter volume reduction in the dorsal but mostly in the ventral PFC (Tebartz van Elst et al., 2003; Vollm et al., 2009; Brunner et al., 2010). It is also suggested that volume deficits within the ventral PFC are present even at the early stages of the disorder (Chanen et al.,

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2008; Brunner et al., 2010; Sala et al., 2011). Moreover, BPD patients show frontal hypoactivity as measured by positron emission tomography studies (De La Fuente et al., 1997; Soloff et al., 2000b; Soloff et al., 2003; Salavert et al., 2011) as well as attenuated ventral PFC engagement during tasks on inhibitory control (e.g. Go/noGo) in functional magnetic resonance imaging studies (Vollm et al., 2004; Silbersweig et al., 2007). Additionally, abnormalities in prefrontal regions in BPD patients are related to impairment in emotional regulation (Johnson et al., 2003), cognitive reappraisal (Schulze et al., 2011) and impulse control (Berlin et al., 2005), potentially contributing to impulsive aggressive and self-destructive behaviors (Soloff et al., 2003; Sala et al. 2011). We were particularly interested in exploring the role of structural PFC deficits in connection with aggression. Impulsive aggression is a core symptom of BPD caused by irritability states and by a lack of behavioral inhibition (Látalová and Prasko, 2010). A link between aggression in BPD and PFC deficits is likely given the established relationship between gray matter deficits in the ventral PFC and risk of reactive aggression (Blair, 2004; Li and Coccaro, 2005).

A history of sexual or physical abuse is one of the most robust risk factors for BDP as it is present in up 76% of patients (Zanarini, 2000) and is associated with the severity of psychopathology (Links and van Reekum, 1993; Silk et al., 1995; Soloff et al., 2002). Moreover, a recent review concluded that a history of childhood maltreatment is a predictor of aggression in BPD (Allen and Links, 2012). In BPD patients with a history of childhood abuse, reduced gray matter volume and hypoperfusion of the ventral PFC has been reported (Schmahl et al., 2004a; Soloff et al., 2008). Therefore, a potential effect of childhood abuse on ventral PFC volume in BPD can be hypothesized.

Based on the findings reported in the literature, we hypothesized that our sample of BPD patients would show reduced gray matter volume in the ventral PFC in comparison to healthy individuals. Furthermore, this volume decrement would be more pronounced in patients with a history of childhood abuse. Also, we hypothesized that volume reduction in the PFC would be associated with aggressiveness.

2. Methods

2.1. Participants and clinical assessment

Eighteen outpatients fulfilling criteria for BPD based on the Diagnostic and Statistical Manual of Mental Disorders, IV edition (DSM-IV) (American Psychiatric Association, 1994) were recruited from the Center for Research on Personality Disorders of the University of Pavia, Italy, which is an outpatient service dedicated to the treatment and study of Personality Disorders. Patients were screened to exclude current medical problems with known psychiatric consequences (Travers and King, 2005), namely medical evidence, current or past documented history of attention-deficit hyperactivity disorder (ADHD), learning disabilities, epilepsy, and history of encephalitis or significant head injury. BPD subjects were excluded if they had current or lifetime comorbidity with other personality disorders, or with schizophrenia, schizoaffective disorder, bipolar disorder or a history of alcohol or substance abuse within the 6 months preceding the study. Patients were matched on age, sex, handedness and years of education to 19 healthy individuals who were recruited by advertisement and were screened to ensure that they were free of any personal or family history (until the 2nd degree) of any Axis I or II disorders or personal history of childhood abuse. Demographic characteristics did not significantly differ between patients and healthy individuals (see Table 1). Twelve healthy controls and thirteen BPD patients were also tested in our prior region-of-interest study exploring volumes of dorsolateral PFC and hippocampus (Sala et al., 2010).

All participants were assessed by a specialist psychiatrist with the Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I) (Spitzer et al., 1992) and the SCID-II for DSM-IV Axis II disorders (Williams et al., 1992). Handedness was assessed using the Edinburgh Handedness Questionnaire (Oldfield, 1971). The Child Abuse Scale (CABUSE) (Soloff et al., 2002) was used to evaluate a past history of abuse. This consists of a 19-item interview which assesses independently experiences of physical and sexual abuse during childhood based on participants' recall. Participants' perception of abuse, legal and medical disclosure events, number of perpetrators and relationships, duration and overall life effect are assessed for each category. Severity of abuse is calculated by summing all items and ranges from 0 to 28, while duration is defined as the difference in age between offset and onset of abuse.

Table 1
Demographic characteristics of borderline personality disorder (BPD) patients and healthy controls.

	Patients with BPD ($n=18$)	Healthy controls ($n=19$)
Female, *n* (%)	13 (72.2)	13 (68.4)
Right-handed, *n* (%)	15 (83.3)	15 (78.9)
Age, mean (SD)	34.17 (9.4)	32.47 (7.9)
Years of education, mean (SD)	13.2 (1.4)	14.0 (2.1)

Aggression was evaluated using the Buss–Durkee Hostility Scale (BDHI) (Buss and Durkee, 1957). This is a 75 true–false item inventory consisting of the following scales: Assault, Indirect Hostility, Irritability, Negativism, Resentment, Suspicion, Verbal Hostility, and Guilt. The total score is calculated by summing the subscale scores and ranges from 1 to 75. Severity of current borderline psychopathology was assessed with the Zanarini Scale for Borderline Personality Disorders (ZAN-BPD) (Zanarini et al., 2003).

Fourteen patients had a current comorbid Axis I diagnosis (depressive disorder=10, dysthymia=4, panic disorder=1). Fourteen patients were medicated; 10 were on antidepressants (7 on selective serotonin reuptake inhibitors, 3 on serotonin-noradrenaline reuptake inhibitors); four were on mood stabilizers (2 on valproic acid, 2 on oxcarbazepine); and six were on atypical antipsychotics (4 in combination with an antidepressant, 1 in combination with a mood stabilizer, 1 on monotherapy). The Statistical Package for the Social Sciences 17.0 (SPSS, Inc., Chicago, IL) was used for analysis of demographics and psychopathological measures of aggressiveness.

All participants gave written informed consent in accordance with the Biomedical Ethics Committee of the IRCSS S. Matteo Hospital, which approved this study.

2.2. MRI data acquisition

Magnetic resonance imaging (MRI) scans were acquired using a 1.5 T Siemens Symphony Maestro Class. To verify head position of the participants and image quality, a T1-weighted sagittal scout image was acquired (TR=2300 ms, TE=3.93 ms). Proton density (PD) and T2-weighted images were obtained with the aim to exclude focal lesions (TR=2500 ms, TE1 =24 ms, TE2=121ms, FOV=230 × 230, slice thickness=5 mm). A coronal 3D T1-weighted multiplanar-reconstruction sequence according to Charcot's plane was performed (TR=1400 ms, TE=3.49 ms, FOV=176 × 235, slice thickness=1 mm) in order to obtain 144 partitions providing whole-brain anatomical data.

2.3. MRI data analysis

All images were first checked manually for gross structural abnormalities which were not observed in any participant. Images were then pre-processed and analyzed using voxel-based morphometry (VBM) as implemented in Statistical Parametric Mapping 8 (SPM8) software (http://www.fil.ion.ucl.ac.uk/spm/) and run in a MATLAB 7.5 environment (The Mathworks Inc, Natick, MA). As a first step, we manually reoriented the images to position the anterior commissure to the origin of the three-dimensional Montreal Neurological Institute (MNI) coordinate system. The unified segmentation procedure was used to segment the T1 weighted images into white (WM) and gray matter (GM) and cerebrospinal fluid (CSF) partitions (Ashburner and Friston, 2005). This procedure provides the native space versions as well as the DARTEL imported versions of each tissue partition. We then used the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) algorithm (Ashburner, 2007) to warp the GM segment into a new study-specific reference space representing an average of all the subjects included in the analysis. This was achieved by iteratively matching the DARTEL imported versions to an increasingly crisp template generated from their own mean. The final template image was then used to generate smoothed (with an 8-mm Gaussian filter), modulated and spatially normalized GM images in MNI space (Modi et al., 2012). The total intracranial volume (TIV) was calculated by summing the total GM, WM, and CSF fractions of the whole brain according to the SPM algorithm. As previous studies found loss of GM volume in the ventral PFC in BPD patients, we used a region of interest (ROI) approach. ROIs in Brodmann Areas (BA) 11, 44, 45, 47 (Petrides, 2005; Uylings et al., 2010) were created using the WFU Pick Atlas toolbox (www.fmri.wfubmc.edu) (Maldjian et al., 2003) and smoothed GM volumes were extracted with the Marsbar toolbox (www.marsbar.sourceforge.net) for further analyses in SPSS 17.0 (SPSS, Inc, Chicago, IL).

To test our hypotheses, we performed analyses of covariance (ANCOVAs) where GM volumes of the selected ROIs were entered as dependent variables, with diagnosis as factor and TIV as covariate. A separate ANCOVA was conducted within the patient sample only with the same dependent variables and covariate but childhood abuse as the independent factor. ROIs for which significant between-groups differences were found based on a history of childhood abuse were then examined in terms of their correlation with the BDHI scale scores. As these analyses were hypothesis-driven, no Bonferroni correction was applied. In addition, the effect size of the volumetric differences between groups was quantified using Cohen's *d* (Cohen, 1988). We also conducted an exploratory analysis comparing the volumes of the selected ROIs between those patients who had a current depressive disorder and healthy participants as morphological changes have been reported in depression (Yeh et al., 2010).

3. Results

3.1. Psychopathological data

In the whole sample, 11 BPD patients reported a history of childhood abuse. Among them, six reported combined physical and sexual abuse, four reported only physical abuse and one reported only sexual abuse. The range of CABUSE scores was 4.0–23.0, with a mean ($\pm$SD) of 8.9 ± 7.06. Duration was not considered as in all cases childhood abuse experiences started before the age of 5. The proportion of patients on medications did not differ between subjects with and without a past history of childhood abuse ($P > 0.05$). The BDHI total and subscale scores were higher in BPD patients than controls (all $p < 0.02$) (Table 2). The key difference between patients with and without a history of childhood abuse was in the Irritability dimension of the BDHI, which was significantly higher in those who had been abused (Table 2). Moreover, in the subsample of BPD patients with a history of childhood abuse, the severity of the abuse, as rated by the CABUSE, positively correlated with the BDHI Irritability dimension ($r=0.69$, $P=0.03$). BDHI total scores and subscale scores did not differ between patients who were medicated and the patients who were not (all $P > 0.09$).

3.2. Effect of diagnoses and child abuse on PFC volume

Details of all volumetric measurements and effect sizes corresponding to differences between diagnostic groups and between BPD patients with and without childhood abuse are shown in Table 3. TIV did not significantly differ between BPD patients and healthy participants ($t_{35}=-0.4$, $P=0.69$) and between BPD patients with and without a history of childhood abuse ($t_{16}=1.1$, $p=0.3$).

The ANCOVAs showed no overall effect of diagnosis (BDP vs. controls) ($F_{1,35}=0.97$, $P=0.3$) but a significant effect of childhood abuse ($F_{1,15}=5.21$, $P=0.04$). Follow-up pairwise tests showed that the reduction in the GM volume was significant in right VLPFC (BA47) (Fig. 1). History of childhood abuse explained 27% (partial eta squared $=0.27$) of the variance in the GM volume in this area. No other pairwise comparisons were significant (all $P > 0.07$). The exploratory comparison between BPD patients with depression and healthy controls did not show any significant main effect of diagnosis ($F_{1,16}=0.77$, $P=0.4$).

3.3. Correlations between PFC volumes and aggressiveness

The GM volume in right VLPFC (BA47) negatively correlated with BDHI total score ($r=-0.87$, $P=0.002$), Irritability subscale ($r=-0.67$, $P=0.05$) and Negativism subscale ($r=-0.72$, $P=0.03$) in patients with a history of childhood abuse. No significant correlations were found between GM volume in right VLPFC and medication dosages ($P > 0.05$).

4. Discussion

Our results confirmed our hypothesis that in patients with BPD ventral prefrontal gray matter volume reduction, particularly in right BA47, would be associated with a history of childhood abuse. This is consistent with the study by Soloff et al. (Soloff et al., 2008), who found bilateral volume reduction of the VLPFC in female BPD patients with a history of childhood abuse in comparison to patients who had not been abused. Our study confirms the importance of the VLPFC in the pathophysiology of BPD and extends our understanding of the role of these brain structural changes in symptom generation. Specifically, we show that in BPD patients with a history of childhood abuse the VLPFC gray matter volume correlated with levels of aggression as measured by the Buss–Durkee Hostility Scale (BDHI) and severity of childhood abuse correlated with the BDHI Irritability dimension.

The VLPFC plays a key role in neural circuitries involved in emotional control. This region, with its connections with the amygdala, the anterior cingulate cortex and other areas of the PFC, is involved in the inhibitory control of behaviors that can occur as a result of arousal relating to anger and other negative emotions (Davidson et al., 2000). Impulsive aggression emerges when the ventral PFC fails in inhibiting acts that are triggered by irritability and anger-provoking stimuli (Siever, 2008). Therefore, the inhibition of aggressive acts after the experience of strong emotions requires the integrity of the neural systems subserving regulation of emotion, namely regions of dorsal and ventral regions of lateral PFC (Coccaro et al., 2011). Moreover, a disruption of frontolimbic circuitry has been associated with emotion dysregulation in BPD, the ventral PFC being disturbed in its effortful regulation of emotional states that arise as automatic responses from subcortical limbic regions (Minzenberg

Table 2
Buss–Durkee Hostility Inventory scores in patients with borderline personality disorder (BPD) and in healthy controls (HC); patients were also subdivided based on childhood abuse (CA) in those with (BPD+CA) and without such a history (BPD-CA).

Scale core	BPD ($n=18$)	HC ($n=19$)	BPD vs. HC	BPD+CA ($n=11$)	BPD−CA ($n=7$)	BPD+CA vs. BPD−CA
Buss–Durkee Hostility Inventory						
Assault	3.8 ± 2.4	1.8 ± 1.4	$t_{35}=-3.1$, $P=0.004$	4.5 ± 2.5	2.9 ± 1.8	ns
Indirect hostility	7.1 ± 2.3	3.4 ± 1.6	$t_{35}=-5.5$, $P=0.001$	6.6 ± 2.5	7.7 ± 1.8	ns
Irritability	6.0 ± 2.8	3.2 ± 1.6	$t_{35}=-3.6$, $P=0.001$	7.3 ± 2.7	4.0 ± 1.1	$t_{16}=3.1$, $P=0.006$
Negativism	3.9 ± 0.8	2.7 ± 1.6	$t_{35}=-2.7$, $P=0.01$	4.2 ± 0.6	3.7 ± 1.1	ns
Resentment	4.4 ± 2.7	1.6 ± 1.0	$t_{35}=-4.2$, $P=0.001$	5.4 ± 2.2	3.4 ± 3.1	ns
Suspicion	2.5 ± 1.8	1.2 ± 0.8	$t_{35}=-2.9$, $P=0.006$	3.7 ± 2.6	1.7 ± 1.2	ns
Verbal hostility	7.8 ± 2.4	3.6 ± 2.1	$t_{35}=-5.5$, $P=0.001$	8.5 ± 2.3	7.1 ± 2.3	ns
Guilt	4.9 ± 2.3	2.6 ± 1.6	$t_{35}=-3.5$, $P=0.001$	5.1 ± 2.4	5.1 ± 2.5	ns
Total	40.5 ± 10.2	20.0 ± 6.7	$t_{35}=-7.1$, $P=0.001$	45.3 ± 11.2	35.7 ± 6.6	ns
Zanarini Scale for Borderline Personality Disorders						
Total score	13.1 ± 3.6	–		14.4 ± 2.38	12.3 ± 2.38	ns

ns = $P > 0.05$, not significant

Table 3
Mean regional volumes and effect size (Cohen's *d*) of differences in patients with borderline personality disorder (BPD) compared to healthy controls (HC) and in patients with (BPD+CA) and without (BPD−CA) a history of childhood abuse (CA).

Brain volume cm^3	BPD ($n=18$)	HC ($n=19$)	BPD vs. HC Effect size	BPD+CA ($n=11$)	BPD−CA ($n=7$)	BPD+CA vs. BPD−CA effect size
Total intracranial volume	1.43×10^3 (0.14)	1.45×10^3 (0.10)	1.17	1.39×10^3 (0.07)	1.48×10^3 (0.09)	1.15
BA 11 (left)	3.87 (0.29)	3.88 (0.35)	0.03	3.8 (0.29)	3.96 (0.27)	0.6
BA 44 (left)	3.2 (0.31)	3.31 (0.25)	0.41	3.11 (0.22)	3.31 (0.38)	0.73
BA 45 (left)	3.19 (0.4)	3.29 (0.33)	0.28	3.06 (0.29)	3.33 (0.4)	0.85
BA 47 (left)	3.72 (0.3)	3.63 (0.36)	0.28	3.61 (0.16)	3.77 (0.33)	0.71
BA 11 (right)	3.86 (0.31)	3.88 (0.39)	0.06	3.78 (0.25)	3.93 (0.3)	0.59
BA 44 (right)	3.35 (0.34)	3.38 (0.24)	0.11	3.24 (0.23)	3.46 (0.42)	0.74
BA 45 (right)	3.4 (0.4)	3.5 (0.37)	0.27	3.24 (0.25)	3.56 (0.44)	0.7
BA 47 (right)	3.97 (0.3)	3.86 (0.33)	0.36	3.84 (0.2)	4.16 (0.36)	1.38

BA=Brodmann area; volumes are shown as mean (S.D.)

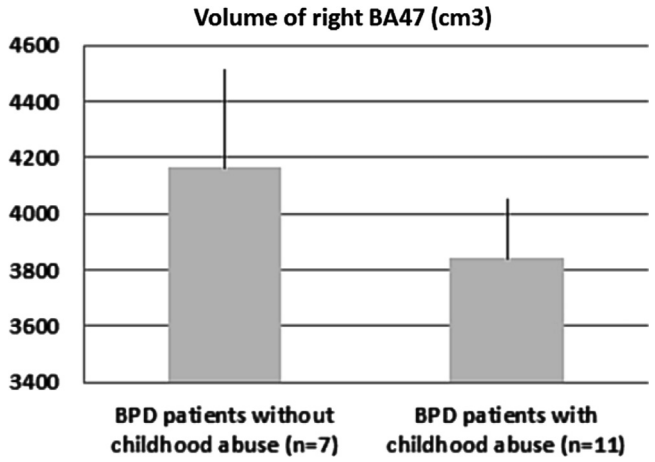

Fig. 1. Gray matter volume in cubic centimeters (cm^3) of right Broadmann area (BA) 47 in borderline personality disorder patients without ($n=7$) and with ($n=11$) a history of childhood abuse. Error bars: ± 1 S.D.

et al., 2007; Ruocco et al., 2010). In particular, the right lateral PFC hypoactivation in BPD patients was found to be associated with difficulty in suppressing negative affect (Ruocco et al., 2010); this abnormal cortical response may underlie symptoms of emotion dysregulation in BPD and may arise from gray matter alterations in these structures (Minzenberg et al., 2008).

Thus, reduced VLPFC gray matter volume in patients with BPD and childhood abuse may accentuate difficulties in regulating emotional states of irritability which could in turn lead to aggression towards others or own self in the form of self-harm. BPD patients with a history of childhood abuse show greater emotional instability linked to impaired memory control, probably due to abnormalities in the prefrontal-hippocampus circuitry (Sala et al., 2009). This impairment may lead to flashbacks and intrusive thoughts of traumatic experiences such the childhood abuse (Schmahl et al., 2003; Anderson et al., 2004; Schmahl et al., 2004b) which are likely to generate painful emotional states. Furthermore, BPD patients with a history of childhood abuse may be less successful in inhibiting responses when irritated or angry, as it has been found that trauma exposure is associated with less successful regulation of negative emotions (New et al., 2009) and with alterations in PFC activity (Lang et al., 2012). Therefore it could be argued that childhood abuse increases the vulnerability of BPD patients to irritability states and aggressive reactions and that brain structural alterations within the VLPFC may mediate this effect.

A limitation of this study is the small sample size, especially when comparing the subgroups of BPD patients with and without a history of childhood abuse. Examination of the effect size of group differences shown in Table 3 suggests that difference of right VLPFC volume in BPD patients with childhood abuse versus BPD patients without childhood abuse have a large effect size. The study of the relationship between childhood abuse in BPD patients and PFC volume is still at an early stage, so even a result from a limited sample might be valuable and reproducible; a larger sample could validate and strengthen this finding. The small sample size may also preclude the possibility of finding volume differences in other areas with smaller effect size. Another potential limitation is the comorbidity with other Axis I diagnoses within BPD patients. However, since comorbidity is present in the majority of BPD patients seen in routine clinical practice (Soloff et al., 2000a, 2002; Skodol et al., 2002), the exclusion of BPD patients with comorbid diagnoses would limit the generalizability of the findings. A strength of the present study is that no BPD patient had a current or lifetime history of post-traumatic stress disorder (PTSD), the presence of which would potentially have confounding effects. Indeed these disorders have a high degree of lifetime co-occurrence (Pagura et al., 2010), and PTSD itself is associated with volumetric alterations within the ventral prefrontal cortex (Bremner et al., 1997; Shin et al., 2006). BPD usually shows important comorbidity on Axis II (Grant et al., 2008), which was not found in our sample. The absence of this comorbidity may represent both a limitation and a strength of the study, in that it limits the generalizability of the findings but also makes them more specific to BPD; comparing VLPFC volumes between patients with different personality disorders in future studies might be informative. A further limitation of the study is that the inter-reliability of BPD diagnosis was not available.

Another limitation of this study is that the histories of childhood abuse were measured retrospectively as reported by the patients, which could be biased by patients' subjective recollections, and could not be confirmed by means of reliable sources (e.g., .records from hospital, police, or courts). More research is thus needed to understand how duration, frequency and type of abuse might play a role in volume reductions in the VLPFC. Finally, it is important to mention that in psychiatric diseases other than BPD childhood abuse has been found to be associated with PFC volume reduction, namely psychotic disorders (Sheffield et al., 2013). Future investigations into the effect of childhood abuse on PFC volumes independently of diagnostic category are needed.

In conclusion, childhood abuse in BPD may be associated with right VLPFC gray matter volume reduction and higher levels of aggressiveness. Further studies might focus on the functional consequences of VLPFC volume reduction during paradigms of emotion regulation.

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