Psychological Medicine (2015), **45**, 3171–3180. © Cambridge University Press 2015
doi:10.1017/S0033291715001142

ORIGINAL ARTICLE

Structural alterations in white-matter tracts connecting (para-)limbic and prefrontal brain regions in borderline personality disorder

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Background. A dysfunctional network of prefrontal and (para-)limbic brain region has been suggested to underlie emotional dysregulation in borderline personality disorder (BPD). Abnormal activity in this network may be due to structural alterations in white-matter tracts connecting prefrontal and (para-)limbic brain regions. To test this hypothesis, we investigated the structural integrity of major white-matter tracts connecting these regions in BPD.

Method. Using diffusion tensor imaging, we investigated fractional anisotropy (FA), axonal anisotropy (AD) and radial diffusivity (RD) in the uncinate fasciculus, the major white-matter tract connecting (para-)limbic and prefrontal brain regions, in 26 healthy controls (HC) and 26 BPD participants. To clarify the specificity of possible white-matter alterations among HC and BPD participants, FA, AD and RD were also investigated in the cingulum.

Results. We found distinct structural alterations in the uncinate fasciculus but not in the cingulum of BPD participants. Compared to HC participants, BPD participants showed lower FA and higher RD in the uncinate fasciculus. By contrast, AD did not differ in the uncinate fasciculus of HC and BPD participants.

Conclusions. Our finding of abnormal FA and RD in the uncinate fasciculus indicates distinct white-matter alterations in BPD, presumably due to stress-induced myelin degeneration in the aftermath of stressful life events. Although these alterations may account for abnormal activity in brain regions implicated in emotion dysregulation, such as the amygdala, anterior cingulate cortex and prefrontal cortex, it remains to be determined whether these alterations are specific for BPD.

Received 27 August 2015; Revised 13 May 2015; Accepted 14 May 2015; First published online 19 June 2015

Key words: Amygdala, anterior cingulate cortex, borderline personality disorder, diffusion tensor imaging, prefrontal cortex, uncinate fasciculus, white matter.

Introduction

Emotion dysregulation, which is characterized by abnormalities in emotional sensitivity and abnormalities in emotion regulation (Crowell *et al.* 2009), has been suggested to be a core feature of borderline personality disorder (BPD), accounting for most if not all, symptoms of BPD, such as self-injurious behaviour, suicide attempts, aggressive outbursts and turbulent relationships (Crowell *et al.* 2009). Functional imaging studies indicate that a dysfunctional interplay between (para-)limbic and prefrontal brain regions may lead to emotion dysregulation in BPD (Mauchnik & Schmahl, 2010; Krause-Utz *et al.* 2014). During the processing of emotional stimuli, BPD patients frequently show hyperactivity in (para-)limbic brain regions (e.g. Herpertz *et al.* 2001; Niedtfeld *et al.* 2010; Schulze *et al.* 2011; Hazlett *et al.* 2012), such as the amygdala and hypoactivity in prefrontal brain regions (e.g. Koenigsberg *et al.* 2009*a*, *b*; Niedtfeld *et al.* 2010; Schulze *et al.* 2011), such as the anterior cingulate cortex (ACC), the orbitofrontal and dorsolateral prefrontal cortex (OFC, PFC). Moreover, the functional connectivity between these brain regions is also often impaired in BPD patients (e.g. New *et al.* 2007; Silbersweig *et al.* 2007; Niedtfeld *et al.* 2012), indicating that the interplay between prefrontal and (para-)limbic brain region is, indeed, disturbed in BPD. Structural imaging

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studies suggest that this dysfunctional interplay may be due to macrostructural grey-matter alterations in prefrontal and (para-)limbic brain regions (e.g. Schmahl *et al.* 2003; Tebartz van Elst *et al.* 2003; Hazlett *et al.* 2005; Weniger *et al.* 2009; Bruehl *et al.* 2013; Niedtfeld *et al.* 2013), in particular in the ACC, OFC and amygdala. Microstructural white-matter alterations may also account for the dysfunctional interplay between these brain regions, implying that impairments in structural connectivity may account for impairments in functional connectivity. An analysis of structural alterations in white-matter tracts connecting (para-)limbic and prefrontal brain regions may help to elucidate whether impairments in structural and functional connectivity are, in fact, related to one another. The uncinate fasciculus (UF), the major white-matter tract connecting the amygdala to the ACC and PFC (Wakana *et al.* 2004), may be the ideal candidate to test this hypothesis; in particular because structural alterations in the UF have been linked to emotion dysregulation in mental disorders that share common features with BPD, such as social anxiety disorder (SAD; e.g. Phan *et al.* 2009), bipolar disorder (BD; e.g. Versace *et al.* 2008) or post-traumatic stress disorder (PTSD; e.g. Fani *et al.* 2012). Of note, previous studies investigating white-matter alterations in BPD have rarely focused on the UF (e.g. Grant *et al.* 2007; Rusch *et al.* 2007*a*, *b*; Carrasco *et al.* 2012; New *et al.* 2013), leaving open whether the UF is similarly implicated in BPD as in SAD, BD or PTSD.

The aim of the present study was to investigate the structural integrity of the UF in BPD by means of diffusion tensor imaging (DTI). DTI allows the measurement of the magnitude and direction of water diffusion in white-matter tracts like the UF (Mori & Zhang, 2006). Fractional anisotropy (FA), an index provided by DTI, represents the coherence of water diffusion in these tracts. Although FA is the primary index for structural integrity of white-matter tracts (Mori & Zhang, 2006), it does not differentiate between different causes for structural alterations in these tracts. Secondary and tertiary integrity indices, like axial diffusivity (AD; water diffusion along these tracts) and radial diffusivity (RD; water diffusion perpendicular to these tracts), on the contrary, are related to distinct structural alterations (e.g. Song *et al.* 2002, 2003; Sun *et al.* 2006), allowing a detailed depiction and quantification of white-matter alterations (e.g. axonal injuries, myelin degeneration). Such a detailed depiction and quantification of white-matter alterations, in particular in the UF, is still lacking in BPD, encouraging us to assess several diffusion measures (FA, AD, RD) in our study. Previous studies using these diffusion measures revealed increased FA and decreased RD of the UF in mental disorders associated with emotion dysregulation (e.g. Versace *et al.* 2008; Phan *et al.* 2009; Fani *et al.* 2012). Considering that emotion dysregulation appears to be the core feature of BPD, we expected to find similar structural alterations in BPD. In addition, we expected to find these structural alterations to be related to emotion dysregulation in BPD.

Table 1. *Co-morbid mental disorders among participants with borderline personality disorder*

	Current mental disorder		Lifetime mental disorder	
	n	%	*n*	%
Substance abuse	8	30.77	7	26.92
Major depressive disorder	17	65.38	21	80.77
Dysthmic disorder	9	34.62	11	42.31
Generalized anxiety disorder	5	19.23	5	19.23
Panic disorder without agoraphobia	2	7.69	2	7.69
Panic disorder with agoraphobia	5	19.23	5	19.23
Agoraphobia	2	7.69	2	7.69
Specific phobia	9	34.62	9	34.62
Social phobia	8	30.77	7	26.92
Obsessive compulsive disorder	2	7.69	2	7.69
Post-traumatic stress disorder	10	38.46	11	32.31
Undifferentiated somatoform disorder	10	38.46	10	38.46
Anorexia nervosa	0	0	2	7.69
Bulimia nervosa	4	15.38	4	15.38
Eating disorder not otherwise specified	1	38.46	1	38.46

Method

Participants

Twenty-six healthy females (healthy controls; HC) and 26 females with a DSM-IV diagnosis of BPD participated in the study. BPD participants were included in the study if they met at least five of nine DSM-IV criteria for a diagnosis of BPD, including criteria associated with emotional instability. BPD participants who met DSM-IV criteria for bipolar disorder, schizoaffective disorder or schizophrenia were excluded from the study. BPD participants who were included in the study met DSM-IV criteria for several other mental disorders, including substance-related disorders, mood disorders, anxiety disorders, somatoform disorders and eating disorders (see Table 1). HC participants were excluded from the study if they met DSM-IV criteria for any mental disorder. Additional exclusion criteria for all participants were severe cognitive impairment and mental retardation. None of the HC participants but nine of the BPD participants

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Table 2. *Group differences in demographical and clinical characteristics*

	HC ($n = 26$)		BPD ($n = 26$)	
	n	%	*n*	%
Education				
Basic	0	0.00	2	0.06
Intermediate	6	0.24	10	0.28
Advanced	20	0.77	14	0.54
	Mean	S.D.	Mean	S.D.
Age	26.80	6.582	26.45	7.037
Intelligence (MWT-IQ)	107.96	9.485	108.81	14.648
Anxious symptoms (STAI-T)	30.46	5.80	61.08	11.84
Depressive symptoms (BDI)	2.62	3.45	30.88	12.98
Borderline symptoms (BSL-23)	2.15	2.81	40.85	21.30

HC, Healthy control group; BPD, borderline personality disorder group; MWT-IQ, Multiple Choice Vocabulary Test – Intelligence quotient (Lehrl *et al.* 1995); STAI-T, State Trait Anxiety Inventory – Trait Version (Laux *et al.* 1981); BDI, Beck Depression Inventory (Hautzinger *et al.* 1995); BSL-23, Borderline Symptom List 23 (Bohus *et al.* 2009).

were using psychotropic medication at the time of the study (neuroleptics: $n = 2$; antidepressives: $n = 8$; mood stabilizers: $n = 1$). All participants provided written informed consent and were paid for their participation.

The study was carried out in accordance with the Declaration of Helsinki and was approved by the ethics committee of the University of Greifswald.

Measures

Structured clinical interviews were administered for the assessment of Axis I (Composite International Diagnostic Interview, CIDI; Wittchen & Pflister, 1997) and Axis II (Structured Clinical Interview for DSM-IV Axis II Disorders, SCID-II; Fydrich *et al.* 1997) disorders in HC and BPD participants. In addition, self-report questionnaires were applied to assess the severity of participants' anxious (State Trait Anxiety Inventory – Trait Version, STAI; Laux *et al.* 1981), depressive (Beck Depression Inventory, BDI; Hautzinger *et al.* 1995) and borderline (Borderline Symptom List 23, BSL-23; Bohus *et al.* 2009) symptoms. Besides this, a multiple choice vocabulary test was used as a proxy for participants' level of general intelligence (Multiple Choice Vocabulary Test, MWT; Lehrl *et al.* 1995)

Magnetic resonance imaging

Data acquisition

Magnetic resonance imaging was performed on a 3-T whole-body MR scanner (Verio, Siemens, Germany) equipped with a 32-channel head coil. Diffusion-weighted images were recorded with a multi-directional diffusion weighting sequence [repetition time (TR): 15 300 ms; echo time (TE): 107 ms; flip angle (FA): 90°; field of view (FOV): 230 × 230 mm^2; matrix: 128 × 128]. In all, 80 axial slices (slice thickness: 2 mm, no gap; voxel size: 1.8 × 1.8 × 2 mm^3) were acquired along 64 gradient directions with two *b* values (0 and 1000 mm/s^2) and one repetition. Additionally, high-resolution structural images were recorded with a T1-weighted coronal oriented magnetization-prepared rapid gradient echo (MPRAGE) sequence (TR: 2900 ms; TE: 2.52 ms; FA: 25°; FOV: 256 × 256 mm^2; matrix: 256 × 256), leading to the acquisition of 176 sagittal slices (voxel size: 1 × 1 × 1 mm^3).

Data processing

Following established procedures (Domin *et al.* 2014), the diffusion-weighted images were preprocessed with tools from the Functional Magnetic Resonance Imaging of the Brain Software Library (http://www.fmrib.ox.ac.uk/fsl). After correction of eddy currents and head motion, skull stripping was performed with *bet*. Next, *flirt* was used for a linear co-registration of the diffusion-weight image and the structural image as well as for a linear co-registration of the structural image and the MNI template. Then, *nflirt* was used for a nonlinear co-registration of the structural image and the MNI template. The transformation information obtained during the linear and nonlinear co-registration was combined using *convertwarp* and subsequently inversed using *invwarp*. The inversed transformation information was used for the de-normalization of the ICBM-DTI-81 white-matter labels atlas (Mori *et al.* 2008, Oishi *et al.* 2008), which contained anatomical masks in MNI space. De-normalization of this atlas was necessary because the diffusion-weighted images were deliberately left in native space to avoid unnecessary image transformations during normalization to MNI space. Finally, the gradient vectors for the diffusion weighting gradients were corrected by the rotation matrix calculated during motion correction and linear co-registration.

Data analysis

JavaDTI (Domin *et al.* 2014) was used for diffusion tensor calculation and diffusion tensor tractography. For diffusion tensor calculation, a diffusion tensor model was fitted at each voxel to provide a voxel-wise calculation of FA, AD and RD. For diffusion tensor tractography, tracts were determined by a continuous path originating

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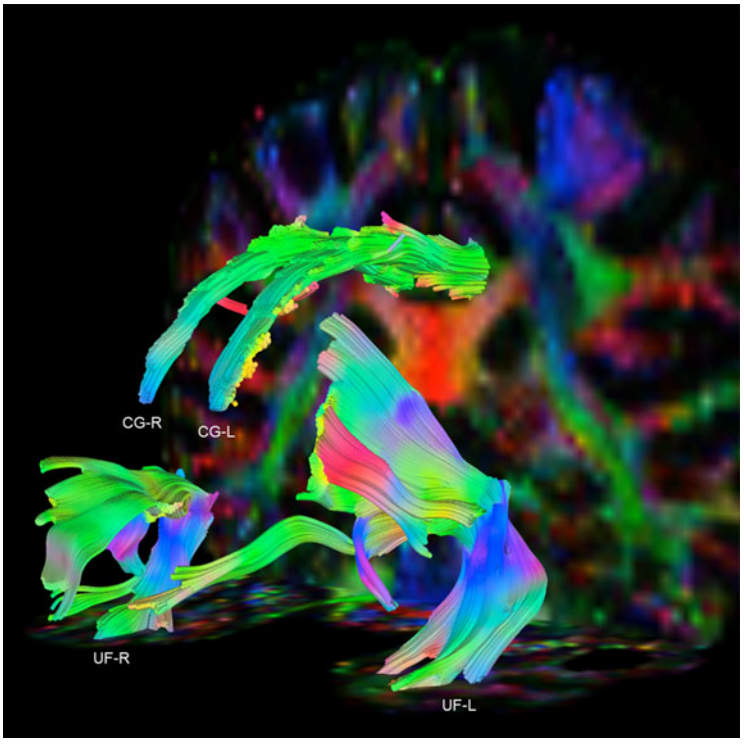

Fig. 1. Tracts of the bilateral uncinate fasciculus (UF) and the bilateral cingulum (CG) projected on the diffusion-weighted image of one healthy control (HC) participant. Red, green, and blue represent left to right, anterior to posterior and superior to inferior directions, respectively.

from a seed voxel in a region of interest (ROI) and following the tensor direction. Parameter thresholds for tract determination were FA values greater than 0.20 and turning angles smaller than 45°. Tracts were determined in pre-defined ROIs using de-normalized masks of the ICBM-DTI-81 white-matter labels atlas (Mori *et al.* 2008; Oishi *et al.* 2008). In line with previous procedures (e.g. Versace *et al.* 2008; Zhang *et al.* 2012), the bilateral UF comprised the primary ROI, whereas the bilateral cingulum (CG) served as a secondary ROI to clarify the specificity of findings. The mean FA, AD and RD were extracted from each of these ROIs and used for the statistical analyses.

Data visualization

For visualization purposes (see Fig. 1), tracts of the bilateral UF and bilateral CG were projected on the diffusion-weighted image of one HC participant using DSI Studio (http://dsi-studio.labsolver.org/).

Statistical analyses

All statistical analyses were conducted using SPSS v. 22 (SPSS Inc., USA). Differences in HC and BPD participants' demographic (age, intelligence) and clinical (anxious, depressive, borderline symptoms) characteristics were analysed with χ^2 tests and analyses of variance (ANOVAs). Differences in diffusion measures (FA, AD, RD) indicating structural alterations in the bilateral UF or CG of HC and BPD participants were analysed by means of mixed-design ANOVAs with group as between-subjects factor and hemisphere as within-subjects factor. Diffusion measures (FA, AD, RD) that differed between HC and BPD participants were considered as covariates in the above-mentioned ANOVAs. Associations between diffusion measures (FA, AD, RD) indicating structural alterations in the bilateral UF or CG and clinical characteristics were analysed with Pearson's product-moment correlations, separately for HC and BPD participants. The significance level for these analyses was set at $p < 0.05$ (two-tailed) and if necessary corrected for multiple comparisons by applying the Bonferroni method. In addition to the significance level p, the effect size measures η_p^2 and d are reported to facilitate interpretation of (marginally) significant effects.

Results

Group differences in demographic and clinical characteristics

Several ANOVAs and χ^2 tests were run to investigate whether HC and BPD participants differed in their demographic and clinical characteristics (see Table 2). HC and

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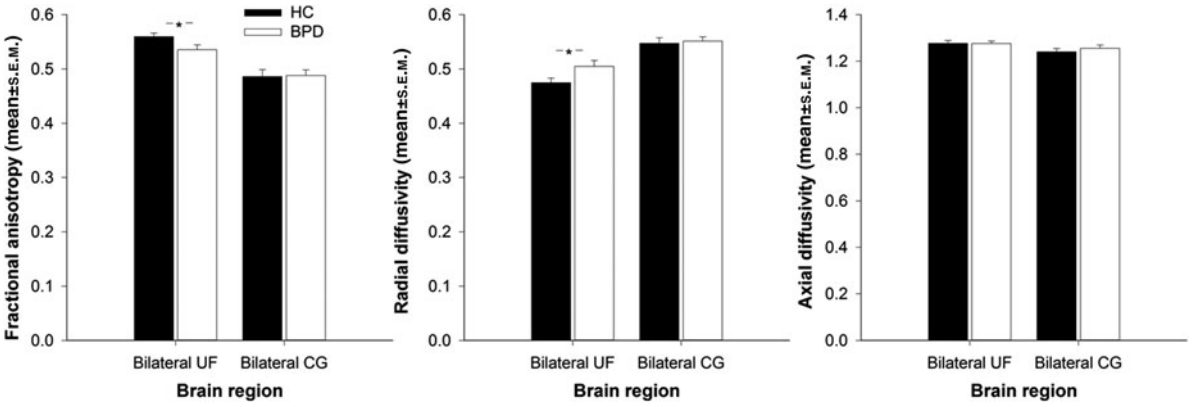

Fig. 2. Structural integrity of the bilateral uncinate fasciculus (UF) and bilateral cingulum (CG). Bars represent mean fractional anisotropy (FA), mean radial diffusivity (RD) and mean axial diffusivity (AD) in the bilateral UF and bilateral CG of healthy control (HC) participants and participants with borderline personality disorder (BPD). Error bars indicate S.E.M. $^{*}p < 0.05$.

BPD participants did not differ in terms of age ($F_{1,50} = 0.03$, $p = 0.85$, $\eta^2_P = 0.001$), education [$\chi^2(1, N = 52) = 4.06$, $p = 0.13$] or intelligence ($F_{1,50} = 0.06$, $p = 0.81$, $\eta^2_P = 0.001$). BPD participants, however, reported more anxious ($F_{1,50} = 140.18$, $p < 0.001$, $\eta^2_P = 0.74$), depressive ($F_{1,50} = 115.16$, $p < 0.001$, $\eta^2_P = 0.70$) and borderline ($F_{1,50} = 84.31$, $p < 0.001$, $\eta^2_P = 0.63$) symptoms than HC participants.

Group differences in structural integrity

Primary analyses

A series of mixed-design ANOVAs (group×hemisphere) was performed to investigate whether HC and BPD participants showed different FA, AD and RD in the primary ROI, the bilateral UF (see Figs 1 and 2). BPD, as compared to HC participants, showed lower FA (effect of group: $F_{1,50} = 4.85$, $p = 0.03$, $\eta^2_P = 0.09$; all other effects involving group or hemisphere: $F < 2.74$, $p > 0.10$, $\eta^2_P < 0.05$) and higher RD (effect of group: $F_{1,50} = 4.91$, $p = 0.03$, $\eta^2_P = 0.09$; all other effects involving group or hemisphere: $F < 2.72$, $p > 0.14$, $\eta^2_P < 0.04$) in the bilateral UF. By contrast, AD did not differ in the bilateral UF of HC and BPD participants (all effects involving group or hemisphere: $F < 0.10$, $p > 0.89$, $\eta^2_P < 0.001$). To further investigate how FA and RD in the UF were related to one another, FA or RD were entered as covariates in the above-mentioned mixed-design ANOVAs (group×hemisphere). Controlling for individual differences in FA or RD, eliminated FA and RD differences in the bilateral UF of HC and BPD participants (all effects involving group or hemisphere for FA or RD: $F < 1.42$, $p > 0.24$, $\eta^2_P < 0.03$). Moreover, correlation analyses revealed a negative relationship between FA and RD in the bilateral UF (all $r > |0.78|$, $p < 0.001$), suggesting a common pathophysiological process underlying structural alterations in the bilateral UF of BPD participants. Of note, excluding BPD participants with co-morbid PTSD from the above analyses revealed a similar pattern of results (see Supplementary Material S1).

Secondary analyses

Another series of mixed-design ANOVAs (group× hemisphere) was run to investigate whether HC and BPD participants showed different FA, AD and RD in the secondary ROI, the bilateral CG (see Figs 1 and 2). This analysis revealed no differences in FA, AD or RD in the bilateral CG of HC and BPD participants (all effects involving group or hemisphere for FA: $F < 2.89$, $p > 0.10$, $\eta^2_P < 0.06$; all effects involving group for AD and RD: $F < 3.34$, $p > 0.07$, $\eta^2_P < 0.06$; all effects involving hemisphere for AD and RD: $F > 5.60$, $p < 0.02$, $\eta^2_P > 0.101$), indicating the specificity of the structural alterations in the bilateral UF of BPD participants. As above, excluding BPD participants with co-morbid PTSD from the analysis did not change the results (see Supplementary Material S1)

Associations between clinical characteristics and structural integrity

Primary analyses

Several correlation analyses were run to investigate whether FA, RD and AD in the bilateral UF of HC and BPD participants were related to participants' anxious, depressive or borderline symptoms. None of these analyses revealed a relationship between structural alterations in the UF and self-reports of anxious, depressive or borderline symptoms, neither among BPD nor among HC participants (all $r < |0.33|$, all $p > 0.10$).

Secondary analyses

Further correlation analyses were run to investigate whether FA, RD and AD in the bilateral CG of HC

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and BPD participants were related to participants' anxious, depressive or borderline symptoms. Mirroring the findings of the above-mentioned correlation analyses, structural alterations in the CG were unrelated to HC and BPD participants' self-reported symptoms (all $r < |0.35|$, all $p > 0.08$).

Discussion

The aim of the present study was to investigate the structural integrity of the UF, the major white-matter tract connecting (para-)limbic to prefrontal brain regions, in BPD. In consideration of previous studies revealing structural alterations in the UF in mental disorders that share common features with BPD (e.g. Versace *et al.* 2008; Phan *et al.* 2009; Fani *et al.* 2012), we expected to find similar alterations in BPD. In addition, we expected these alterations to be related to emotion dsyregulation in BPD.

We revealed distinct structural alterations in the UF of BPD but not HC participants as indicated by multiple diffusion measures. Compared to HC participants, BPD participants showed increased FA and decreased RD but normal AD in the UF. Whereas differences in FA indicate structural alterations, differences in RD and AD help to depict and quantify the causes for these alterations (Mori & Zhang, 2006). Differences in AD reflect alterations due to axonal injury (Song *et al.* 2002, 2003; Sun *et al.* 2006) and differences in RD reflect alterations due to myelin degeneration (Song *et al.* 2002, 2003; Sun *et al.* 2006). Since differences in FA were closely related to differences in RD but not AD, the observed alterations were probably due to demyelination. Demyelination has been shown to be associated with inflammation (Merrill & Benveniste, 1996), which often occurs in the aftermath of stressful life events (Garcia-Bueno *et al.* 2008). Considering that BPD patients frequently experience stressful life events (e.g. Pagano *et al.* 2004; Lobbestael *et al.* 2010; McGowan *et al.* 2012), it may be possible that these experiences lead to inflammation. A dysregulation of pro- and anti-inflammatory cytokines, presumably as a consequence of stress-dependent alterations of the hypothalamus-pituitary-adrenal axis (Wingenfeld *et al.* 2009), has already been reported in BPD patients (e.g. Kahl *et al.* 2006; Diaz-Marsa *et al.* 2012). Studies are now needed that further investigate the relationship between stress-induced inflammation and myelin degeneration in BPD. Of note, demyelination appeared to be specific for the UF because similar alterations were not evident in the CG, another white-matter tract connecting (para-)limbic brain regions (Wakana *et al.* 2004).

Although we found, for the first time, white-matter alterations in a tract connecting BPD patients' (para-)limbic and prefrontal brain regions, white-matter alterations in tracts connecting prefrontal brain regions have already been shown (e.g. Grant *et al.* 2007; Rusch *et al.* 2007*a*, *b*; Carrasco *et al.* 2012). Moreover, grey-matter alterations in BPD patients' (para-)limbic and prefrontal brain regions have also been reported (e.g. Schmahl *et al.* 2003; Tebartz van Elst *et al.* 2003; Hazlett *et al.* 2005; Weniger *et al.* 2009; Bruehl *et al.* 2013; Niedtfeld *et al.* 2013), implying structural alterations on the microscopic and macroscopic level in BPD. These alterations are most pronounced in prefrontal regions (e.g. Tebartz van Elst *et al.* 2003; Hazlett *et al.* 2005; Grant *et al.* 2007; Rusch *et al.* 2007*a*, *b*; Carrasco *et al.* 2012; Bruehl *et al.* 2013), such as the ACC and OFC, and (para-)limbic regions, such as the amygdala (e.g. Schmahl *et al.* 2003; Weniger *et al.* 2009; Niedtfeld *et al.* 2013). Of note, BPD patients often show abnormal activity (e.g. Herpertz *et al.* 2001; Koenigsberg *et al.* 2009*a*, *b*; Niedtfeld *et al.* 2010; Schulze *et al.* 2011; Hazlett *et al.* 2012) and abnormal connectivity (e.g. New *et al.* 2007; Silbersweig *et al.* 2007; Niedtfeld *et al.* 2012) in these regions, indicating a dysfunctional interplay between (para-)limbic and prefrontal brain regions in BPD (Mauchnik & Schmahl, 2010; Krause-Utz *et al.* 2014). Since these regions are implicated in the experience and regulation of emotions (Ochsner *et al.* 2012), emotion dysregulation may be due to structural and functional alterations in these regions (Mauchnik & Schmahl, 2010; Krause-Utz *et al.* 2014). Accordingly, structural and functional alterations in BPD patients' (para-)limbic and prefrontal regions have been related to abnormalities in emotional sensitivity and abnormalities in emotion regulation (e.g. Hazlett *et al.* 2005; Rusch *et al.* 2007*b*; Niedtfeld *et al.* 2010, 2013; Hazlett *et al.* 2012; Bruehl *et al.* 2013). Nonetheless, it remains open whether structural alterations, in fact, account for functional alterations in the same regions as suggested by the present and previous findings (e.g. Tromp *et al.* 2012). Further studies combining structural and functional imaging procedures may help to elucidate the interdependence of structural and functional alterations in BPD.

Although we assume that structural alterations in the UF account for abnormalities in emotional sensitivity and abnormalities in emotion regulation, we have to admit that we were unable to show a specific relationship between structural alterations and emotion dysregulation in BPD participants. BPD participants' scores on the self-report questionnaires assessing psychopathological symptoms (BDI, STAI, BSL) indicated abnormalities in emotional sensitivity and abnormalities in emotion regulation, but none of these scores was related to structural alterations in BPD participants' UF. We did not expect to find a relationship between structural alterations and anxiety or depression scores because the BDI and STAI do not explicitly

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assess symptoms related to emotion dysregulation (Laux *et al.* 1981; Hautzinger *et al.* 1995). A relationship between structural alterations and borderline scores, on the contrary, was expected because symptoms related to emotion dysregulation are, amongst others, assessed by the BSL (Bohus *et al.* 2009). However, we employed a shortened version of the BSL, which may be less sensitive to capture abnormalities in emotional sensitivity and abnormalities in emotion regulation than the original version (Bohus *et al.* 2007, 2009). Notably, the BSL assess emotion dysregulation as typically displayed by BPD patients. The non-existent relationship between structural alterations and borderline symptoms, may, thus, indicate that these alterations are not specific for BPD. Similar alterations have already been found in other mental disorders, such as BD, SAD or PTSD (e.g. Versace *et al.* 2008; Phan *et al.* 2009; Fani *et al.* 2012). Considering that these disorders are also characterized by abnormalities in emotional sensitivity and abnormalities in emotion regulation (e.g. Goldin *et al.* 2009; New *et al.* 2009; Schulze *et al.* 2011; Townsend *et al.* 2013), it may be possible that structural alterations in the UF reflect emotion dysregulation in general. To determine the specificity of these alterations, further studies are needed that compare these alterations between different disorders known to be associated with emotion dysregulation. Of these disorders, PTSD may be of particular relevance because BPD is often associated with PTSD (e.g. Zanarini *et al.* 1998, 2004, 2011; McGlashan *et al.* 2000; Shea *et al.* 2004). It may, thus, be possible that structural alterations in the UF of BPD participants were due to the presence of PTSD rather than BPD. BPD participants, however, still showed alterations in the UF after controlling for the presence of PTSD, indicating that these alterations were most likely due to the presence of BPD. Further studies investigating BPD patients with different degrees of trauma exposure and trauma-related symptoms by means of appropriate measures may help to clarify how stressful life experiences lead to structural alterations in the UF. Considering that these alterations are already present in adolescents with BPD features (New *et al.* 2013), it may be worthwhile to investigate BPD patients across the life span in these studies, preferably before and after pharmacological or psychotherapeutic interventions to determine the effects of these interventions on the structural integrity of the UF.

Taken together, we found, for the first time, distinct white-matter alterations in the UF of BPD as compared to HC participants. These alterations were due to myelin rather than to axonal degeneration, possibly as a consequence of stress-induced inflammation in the aftermath of stressful life events. These alterations were present in a white-matter tract connecting (para-)limbic and prefrontal brain regions that have been related to abnormalities in emotional sensitivity and abnormalities in emotion regulation. Although we suppose that these alterations account for emotional dysregulation in BPD, it remains to be determined whether these alterations are specific for BPD. It may be possible that these alterations can generally be found in mental disorders that are characterized by emotion dysregulation.

Supplementary material

For supplementary material accompanying this paper visit http://dx.doi.org/10.1017/S0033291715001142.

Acknowledgements

Funding for the study was provided by in-house grants from the Department of Psychiatry and Psychotherapy of the University of Greifswald and from the Center for Diagnostic Radiology and Neuroradiology of the University of Greifswald. The funding source had no further role in study design, in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication. The authors thank Anna Buchheim for valuable suggestions regarding the design of the study and Alfons Hamm for valuable suggestions regarding the analysis and interpretation of results of the study.

Declaration of Interest

None.

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