Disorder-Specific White Matter Alterations in Adolescent Borderline Personality Disorder

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Background: The pathogenesis of borderline personality disorder (BPD) is complex and not fully understood. Using diffusion tensor imaging, recent studies suggest that white matter abnormalities may occur in adult patients with BPD. However, deeper insight into the disorder-specific developmental psychobiology (e.g., analysis of adolescents with BPD; inclusion of clinical control groups) is missing.

Methods: Twenty adolescent patients with BPD (aged 14–18 years), 20 healthy, and 20 clinical control subjects were assessed using diffusion tensor imaging. All subjects were right-handed girls, matched for age and IQ. Microstructural parameters were analyzed via tractography of the main bundles in the limbic system and using Tract-Based Spatial Statistics, an explorative, global approach.

Results: BPD was associated with decreased fractional anisotropy in the fornix when compared with clinical ($p < .001$) or healthy (nonsignificant trend) control subjects. Using Tract-Based Spatial Statistics, significant disorder-specific white matter alterations were found in the long association bundles interconnecting the heteromodal association cortex and in connections between the thalamus and hippocampus.

Conclusions: The study strongly supports the hypothesis that white matter alterations play a key role in the pathogenesis of BPD. These disorder-specific alterations include white matter pathways involved in emotion regulation but also affect parts of the heteromodal association cortex that are related to emotion recognition. Our findings unify previously documented deficits in emotion recognition and regulation and suggest that a large-scale network of emotion processing is disrupted in BPD. Continued research is essential to evaluate the predictive value of these early disruptions in a clinical context.

Impaired behavioral control in the context of intense negative emotions is regarded as the core difficulty for patients with borderline personality disorder (BPD) (1) and predisposes them to emotional disinhibition and impulsive aggression (2,3). Neurobiologically, these core elements of BPD have been linked to failure of frontolimbic functions (4). The frontolimbic disconnectivity model of BPD (1,5–7) suggests that emotional dysregulation in BPD patients is caused by prefrontal deficits or hyperactivity of the limbic system, or a combination of both (8). This conceptualization of frontolimbic dysfunction in BPD resulted in a growing number of imaging studies using structural and functional methods [for review, see Schmahl et al. (9) or Lis et al. (10)], focusing mainly on frontolimbic areas (6,7) [see Ruocco et al. (11) for review]. A recent review by Ruocco et al. (12) highlighted increased functional activity in limbic structures (e.g., the insula cortex) and reduced activation in other brain regions (e.g., anterior cingulate, dorsolateral prefrontal cortex [DLPFC], and the left superior temporal gyrus [STG]). Some studies suggest that BPD is associated with macrostructural gray matter abnormalities, mainly in the orbitofrontal (OFC) and DLPFC, as well as the anterior cingulate cortex (9), whereas morphometric findings with regard to the amygdala and hippocampus remained inconsistent (13) [for review see Nunes et al. (14)]. In a voxel-based morphometric study, we recently found reduced gray matter in the DLPFC bilaterally and in the left OFC in adolescents with BPD compared with healthy control subjects (HC), whereas no group differences were found in the limbic system or in any white matter (WM) structures (15).

Diffusion tensor imaging (DTI), which has a strong potential in the sensitive detection of microstructural abnormalities (16) and could help gain a better understanding of the pathogenesis of BPD. To our knowledge, only four studies have analyzed DTI in BPD patients. Grant et al. (17) analyzed nine treatment-resistant adult patients with BPD who were engaged in extensive self-injurious behavior and seven control subjects using manual region of interest (ROI) analysis and reported alterations of inferior regions of the frontal cortex. Rüsch et al. (18) assessed 20 women with BPD and comorbid attention-deficit/hyperactivity disorder and 20 healthy women using manual ROI positioning. Increased mean diffusivity in inferior frontal WM correlated significantly with key aspects of psychopathology in BPD ($p < .05$, uncorrected). Additional analysis of the same sample revealed abnormalities of interhemispheric connectivity between both sides of the anterior cingulum as indicated by decreased fractional anisotropy (FA) (19). A recent study (20) using Tract-Based Spatial Statistics (TBSS) (21) revealed a decrease of FA in the genu and rostral areas of the corpus callosum as well as in left and right prefrontal WM in 28 adult patients with BPD compared with 26 HC.

However, none of the imaging studies in BPD included clinical control subjects (CC) in their analysis. Thus, previously reported group differences may not necessarily be BPD-specific. Furthermore, studies

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of microstructural alterations in adolescents with BPD are unavailable. These are of particular interest because they allow us to understand the underlying psychobiology of this disorder, given the confounding influences of medication and knock-on effects (e.g., chronicity, drug abuse, duration, and number of comorbid diagnoses) on the original dysfunction are reduced (22). Moreover, previous DTI studies exclusively focused either on hypothesis-driven ROIs or on exploratory TBSS analysis, but both approaches are important and complementary. Thus, we focus on the early stage of onset of the disorder and include a clinical control group. Following the fronto-limbic disconnectivity model, we investigate the fornix as internal WM tract of the limbic system (23), the cingulum as major frontolimbic tract (23), and the uncinate fasciculus as major fronto-temporal tract (23) connecting the STG with the frontal lobe. Based on the described functional and volumetric changes, we hypothesized a reduced FA in these three WM tracts in BPD compared with HC and CC and investigated this using a fiber tractography–based analysis. This study also evaluated FA, radial (RD), and axial diffusivity (AD) using an explorative whole brain analysis, TBSS.

Methods and Materials

Participants and Recruitment

Participants were right-handed female adolescents aged between 14 and 18 years. Patients with a lifetime diagnosis of schizophrenia, schizoaffective disorder, bipolar disorder, pervasive developmental disorder, alcohol/drug dependence, significant neurological disease, a body mass index 16.0 or lower, and IQ 85 or lower were excluded. The adolescents comprised three groups: 20 patients with a DSM-IV defined diagnosis of BPD, 20 patients with mixed psychiatric diagnoses who did not fulfill more than one of the nine DSM-IV diagnostic criteria of BPD (CC), and 20 healthy controls with no current psychiatric disorder and who had never received a psychiatric diagnosis or undergone psychological or psychiatric treatment in their lifetime (HC). A family history of psychiatric illnesses a an exclusion criterion in the prescreening of HC.

Patients were consecutively recruited (February 2007–October 2008). Patients were informed about the study by their attending physicians. HC were recruited through advertisements in public schools. After assessment of handedness and confirmation of diagnosis, patients were included in the study. As with BPD patients, CC and HC were interviewed using a structured clinical interview to determine comorbid psychiatric disorders and the presence or absence of a psychiatric disorder, respectively. In addition, the adolescents of both control groups were interviewed using the BPD section of a structured clinical interview for personality disorders. Patients without a diagnosis of BPD and HC who fulfilled the inclusion criteria for the CC or HC group were matched with patients with BPD for age and school type. Of 159 patients admitted to the clinic during the recruitment period, 64 fulfilled the inclusion criteria and agreed to participate in the study. Four of the participants dropped out: one missed the appointment, and three where excluded from the magnetic resonance imaging (MRI) scan due to metallic objects on their bodies.

The study was approved by the local ethics committee. All adolescent subjects and their legal guardians assented and gave their written informed consent.

Psychiatric Measures

All subject groups were assessed using the German version (24) of the BPD section of the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (25). Psychiatric disorders were assessed with the German version (26) of the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present Version (K-SADS-P), a semistructured diagnostic clinical interview (27). Using these interviews, psychiatric disorders including BPD were excluded for the HC. In the CC group, a diagnosis of BPD was excluded and Axis I disorders were confirmed. BPD was diagnosed when at least five diagnostic criteria were fulfilled according to DSM-IV, and comorbid Axis I disorders were assessed. The German version (26) of the Childrens Global Assessment Scale (28) was used to measure the overall psychosocial functioning for the CC and BPD groups. Handedness was assessed by the Edinburgh Handedness Inventory (29). IQ was measured by the German version (30) of the Wechsler Abbreviated Scale of Intelligence (31). The extent of traumatic life experiences was determined using the pertinent section of the German version (32) of the Clinician Administered PTSD Scale, Child and Adolescent Version (33) that assesses the occurrence of a number of traumatic life events.

MRI Acquisition

A T_1-weighted sagittal isotropic magnetization prepared rapid acquisition gradient-echo sequence was obtained using a 3T scanner (Tim Trio, Siemens, Erlangen, Germany) and a 12-channel standard head coil (flip angle 9°, repetition time 2300 msec, echo time 2.98 seconds, field of view 256 mm, matrix size 256 × 256 pixels, slice thickness 1 mm). One hundred sixty slices with a voxel size of 1 × 1 × 1 mm were acquired. An axial T_2-weighted FLAIR (repetition time 9000 msec, echo time 129 msec) was performed. Both sequences were reviewed by an experienced radiologist to exclude clinically significant abnormalities. A single-shot echo-planar imaging sequence was applied for DTI assessment (repetition time 6400 msec, echo time 91 msec, 96 × 96 matrix size, field of view 240 mm). Fifty axial slices with a thickness of 2.5 mm and no gap, 12 gradient directions, two b values (0 and 1000 s/mm²), and 5 repetitions were acquired.

Quantitative Fiber Tracking

The DTI data sets were analyzed with NeuroQlab (MeVis, Bremen, Germany). The repeated DTI data sets were resampled to a matrix of 1.25 mm isotropic resolution, spatially matched, and averaged. Fiber tracking was performed with the following parameters: voxel size seed grid of 3, minimal value for anisotropy of .1, maximal curvature of .3 (107°), and maximal length of 400 mm. Missing data below the lower measurement threshold of .1 were taken as .1. Two clinical controls were excluded due to imaging artifacts.

As mentioned in the introduction, this study focused on three fiber tracts: 1) The fornix, a compact bundle of WM fibers, projecting from the hippocampus to the septum, anterior nucleus of the thalamus, and the mamillary bodies; 2) the cingulum, the most prominent WM fiber tract of the limbic system. It is located below the cingulate gyrus and is the only communication route between cingulate cortex and other areas of the brain, including prefrontal, parietal, temporal areas, and the thalamus; 3) the uncinate fasciculus, a major fiber tract connecting the inferior frontal and STG.

ROIs were drawn blind to group allocation. Slices for all ROI placements were determined on the basis of commonly identifiable anatomic landmarks as described subsequently. FA values were extracted along the cropped tracts.

The starting ROI for the fornix was placed in the coronal plane at the center of the body of the fornix (Figure 1A). From this ROI,
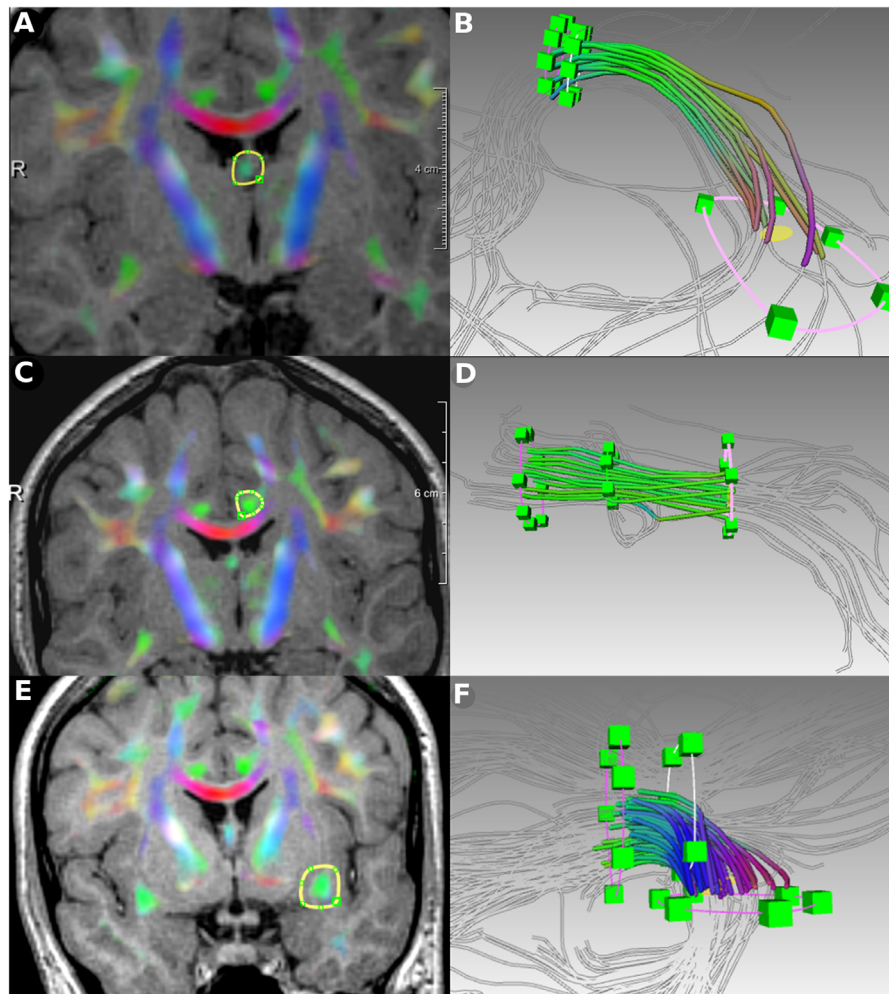
Figure 1. Exemplary fiber tractography of the fornix **(A, B)**, the cingulum **(C, D)**, and the uncinate fasciculus **(E, F)** with the starting regions of interest shown in yellow **(A, C, E)** and the two delineating regions of interest shown in pink **(B, D, F)** placed as described in the text. R, right.

fiber tracking was performed using the aforementioned parameters. From this initial result, the fornix was then cropped using two delineating ROIs, one anteriorly, just before the separation in the two columns, and one posteriorly, just after the crus of the fornix on the right and left side, as indicated in Figure 1B. The starting ROI for the cingulum was placed in the coronal plane directly above the corpus callosum (Figure 1C). From the initial result, the cingulum was then cropped using two delineating ROIs, one anteriorly, at the midlevel of the body of the corpus callosum, and one posteriorly, just before the splenium of the corpus callosum, as indicated in Figure 1D. The starting ROI for the uncinate fasciculus was placed in the axial plane at the frontotemporal junction (Figure 1E), including both the uncinate and the inferior frontooccipital fasciculus (IFO). From the initial result, the uncinate fasciculus was then cropped using two delineating ROIs, one in the inferior frontal gyrus and one in the temporal lobe, as indicated in Figure 1F.

TBSS

Eddy currents and head motion were corrected using FSL FLIRT (www.fmrib.ox.ac.uk/fsl/) by affine registration of the baseline and diffusion-weighted volumes to the first baseline volume. Gradient directions were corrected according to the transformation. FSL bet was used to estimate brain masks. Tensors were fit

using the teem library (teem.sourceforge.net). Negative eigenvalues were corrected by adding the amount by which the smallest is negative, corresponding to increasing the non–diffusion-weighted image value. Registration, resampling to 1-mm isotropic voxel size, skeletonization (threshold: FA = .2), distance map calculation, and projection of the FA values as well as RD and AD onto the skeleton were performed using the standard FSL TBSS commands (21). Three subjects (one BPD patient and two clinical controls) were excluded because of failing image registration caused by major imaging artifacts. Pairwise group statistics were calculated as recommended using the "randomise" command for Monte Carlo permutation tests with $n = 5000$ repetitions and a confidence threshold of $p < .05$ for the corrected threshold-free cluster enhancement (TFCE) significance maps (34).

Statistical Analysis

Demographic and psychometric characteristics were compared using chi-square tests for categorical variables and analysis of variance for continuous variables. For pairwise post hoc comparisons of the groups, p values were corrected with Sidak's method to compensate for multiple testing. Statistical analyses were performed using Stata 12 (StataCorp LP, College Station, Texas). FA values of bilateral cingulums, fornices, and uncinate fasciculi were analyzed with multilevel mixed effects linear

regressions with the FA values as dependent variable, group as fixed factor, and subject and hemisphere as random factors. For post hoc pairwise group comparisons we used Sidak-corrected Wald tests.

Results

Demographic and Psychometric Data

As shown in Table 1, the BPD group and both control samples were matched for age and school type, and there was no significant between-group difference in either age ($F_{2,57} = 2.02$, $p = .141$) or IQ ($F_{2,57} = 1.70$, $p = .193$). Adolescents with a diagnosis of BPD displayed significant functional impairment (Childrens Global Assessment Scale) compared with the CC ($t_{38} = 5.45$, $p < .001$). In addition, adolescent patients with BPD reported a significantly higher number of traumatic experiences in their history compared with both the CC and the HC (analysis of variance: $F_{2,57} = 7.05$, $p = .0018$; pairwise comparisons: BPD vs. CC, $p = .021$; BPD vs. HC, $p = .002$; CC vs. HC $p = .824$).

Extensive psychometric testing was performed to characterize the sample and was reported previously (15). Current comorbid psychiatric diagnoses are listed in Table 1. None of the patients received medical treatment started before admission to our hospital excluding long-term medical treatment. Of the patients receiving medical treatment while hospitalized, nine patients in the BPD

Table 1. Demographic Information and Clinical Characteristics

Characteristics	BPD ($n = 20$)	CC ($n = 20$)	HC ($n = 20$)
Age, Mean $\pm$ SD (years)	16.7 $\pm$ 1.6	16.0 $\pm$ 1.3	16.8 $\pm$ 1.2
IQ, Mean $\pm$ SD	107.1 $\pm$ 10.7	114.0 $\pm$ 8.4	111.0 $\pm$ 15.7
School Type, n (%)			
Gymnasium	9 (45.0)	13 (65.0)	10 (50.0)
Realschule	4 (20.0)	5 (25.0)	5 (25.0)
Hauptschule	7 (35.0)	2 (10.0)	5 (25.0)
Clinical Setting, n (%)			NA
Inpatient	10 (50.0)	7 (35.0)	—
Day clinic	2 (10.0)	—	—
Outpatient	8 (40.0)	13 (65.0)	—
C-GAS	47.5 (8.2)	61.9 (9.3)	100.0
CAPS-CA	27.2 $\pm$ 13.8	17.1 $\pm$ 11.3	14.3 $\pm$ 8.4
Comorbid Psychiatric Diagnoses, n (%)			
Mood disorders	9 (45.0)	4 (20.0)	—
Anxiety disorders	9 (45.0)	4 (20.0)	—
PTSD	8/9	1/4	—
Substance abuse	9 (45.0)	6 (30.0)	—
Eating disorders	7 (35.0)	—	—
Conduct disorders	2 (10.0)	1 (5.0)	—
Somatoform disorders	—	3 (15.0)	—
Adjustment disorders	—	6 (30.0)	—
ADHD	—	1 (5.0)	—

IQ was measured using the Wechsler Abbreviated Scale of Intelligence (31). School-type: *Gymnasium*, 8 years of school after 4 years of elementary school, terminating with the general qualification for university entrance; *Realschule*, 6 years of school after 4 years of elementary school, terminating with a secondary-school level I certificate; *Hauptschule*, 9 years of elementary school. Patients could receive more than one psychiatric diagnosis concurrently.

ADHD, attention-deficit/hyperactivity disorder; BPD, subjects with borderline personality disorder; CAPS-CA, Clinician Administered PTSD Scale, Child and Adolescent Version; CC, clinical control subjects; C-GAS, Children's Global Assessment Scale; HC, healthy control subjects; NA, not applicable; PTSD, posttraumatic stress disorder.

Table 2. Group Means and Standard Deviations for Per Subject Means of Fractional Anisotropy Derived From Tractography

	Hemisphere		
	Left	Right	Total
Cingulum			
BPD	.347 $\pm$ .04	.313 $\pm$ .05	.330 $\pm$ .04
CC	.347 $\pm$ .07	.307 $\pm$ .08	.327 $\pm$ .07
HC	.349 $\pm$ .08	.327 $\pm$ .07	.338 $\pm$ .07
Total	.348 $\pm$ .06	.316 $\pm$ .07	.332 $\pm$ .06
Fornix			
BPD	.204 $\pm$ .08	.180 $\pm$ .07	.192 $\pm$ .07
CC	.274 $\pm$ .03	.237 $\pm$ .05	.256 $\pm$ .04
HC	.236 $\pm$ .06	.220 $\pm$ .07	.228 $\pm$ .06
Total	.237 $\pm$ .07	.212 $\pm$ .07	.224 $\pm$ .06
Uncinate Fasciculus			
BPD	.346 $\pm$ .10	.374 $\pm$ .04	.360 $\pm$ .06
CC	.357 $\pm$ .10	.346 $\pm$ .10	.352 $\pm$ .08
HC	.364 $\pm$ .09	.365 $\pm$ .07	.364 $\pm$ .06
Total	.356 $\pm$ .10	.362 $\pm$ .07	.359 $\pm$ .07

BPD, borderline personality disorder; CC, clinical control subjects; HC, healthy control subjects.

group were taking psychopharmacologic medication at the time of the scan. Seven patients were taking antidepressants: six patients were taking selective serotonin reuptake inhibitors (SSRIs), one patient was taking a tricyclic antidepressant, and one patient was taking two types of psychotropic medication (SSRI and tricyclic antidepressant) concurrently. Of the five patients in the clinical control group who took medication at the time of scanning, three patients were taking antidepressants: two patients were taking a SSRIs, one patient was taking a tricyclic antidepressant, one patient was taking a neuroleptic drug (olanzapine), and one patient was taking an antiepileptic drug (valproic acid).

Imaging Findings

The tractography-based analysis (see Table 2) revealed significant group differences in FA values in the bilateral fornices ($\chi^2_2 = 13.29$, $p = .001$). Further statistical testing revealed lower FA values in BPD patients compared with CC ($\chi^2_1 = 13.11$, $p = .0009$) and HC (not significant: $\chi^2_1 = 4.52$, $p = .097$). HC and CC did not exhibit different FA values in the fornix ($\chi^2_1 = 2.41$, $p = .32$). No group differences were apparent in FA of the uncinate fasciculus ($\chi^2_2 = .38$, $p = .825$) and the cingulum ($\chi^2_2 = .32$, $p = .851$).

Six voxelwise statistical tests were carried out for each of the 3 measures (FA, RD, AD) using TBSS: BPD > HC (value of BPD patients higher than in HC), BPD < HC, BPD > CC, BPD < CC, HC > CC, and HC < CC.

Statistical analysis was performed with and without the subjects' age as covariate and led to similar results. No significant differences were found between the CC and HC group.

Figure 2 gives an overview of the BPD-specific WM alterations. Except for one isolated region within the right superior fronto-occipital fasciculus (SFOF), BPD patients showed no significant reduction in FA compared with the CC (Figure 2A). An increased RD was found bilaterally in parts of the IFO with projections to the OFC, the internal capsule, the superior longitudinal fasciculus (SLF), and the SFOF when comparing BPD patients with CC (Figure 2B). AD was increased only in the left SLF when comparing BPD patients with CC (Figure 2C). These differences
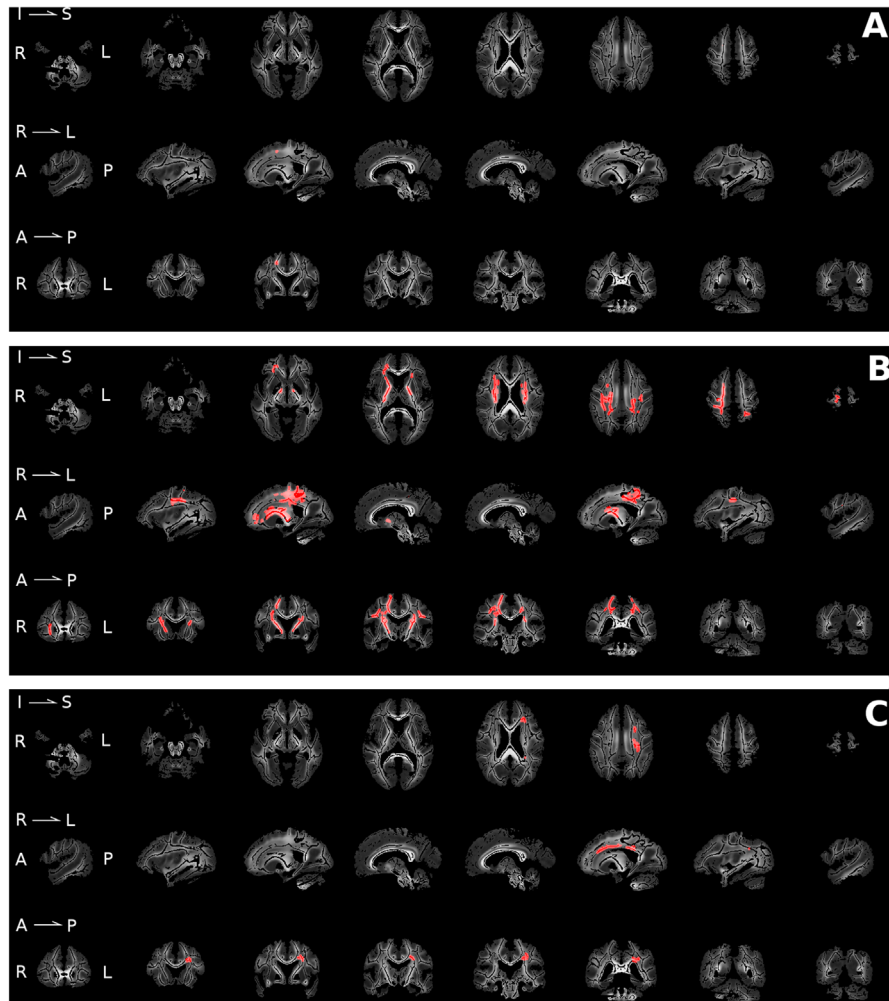
Figure 2. Areas of significantly **(A)** decreased fractional anisotropy, **(B)** increased radial diffusivity, and **(C)** increased axial diffusivity in borderline personality disorder identified by Tract-Based Spatial Statistics (TBSS) analysis. The figure shows slices through the mean fractional anisotropy image with an overlay of the TBSS tract skeleton in black (no significant differences) and red (significant differences). Statistical maps were dilated from the TBSS skeleton for visualization purposes. No differences were found between the healthy and clinical control subjects. A, anterior; I, inferior; L, left; P, posterior; R, right; S, superior.

in diffusion-derived metrics showed a similar but more extensive pattern of changes when comparing BPD patients with HC.

When relating the results from tractography and TBSS, the following was noted: both the fornix and the uncinate fasciculus, especially at the frontotemporal junction, were not represented in the TBSS skeleton; thus the tractography approach provided complementary results to TBSS. The cingulum was well represented in both methods and did not show any significant changes in either the tract-based or the voxel-based method.

Discussion

Comparing BPD patients with HC, morphometric studies have indicated gray matter alterations in the amygdala, hippocampus, OFC, DLPFC, and cingulate cortex, as reviewed previously (35). These studies have motivated more recent investigation of potential WM alterations in BPD using DTI. None of these studies (morphometric and DTI) were designed to reveal disorder-specific effects in BPD. A recent voxel-based morphometric analysis (15) that included CC did not reveal disorder specific effects in gray or

WM. However, DTI may be more sensitive to microstructural alterations in WM architecture.

On the basis of these studies, we focused the hypothesis-driven tractography part of our study on the main WM tracts of the limbic system and the inferior frontal WM. However, two recent functional MRI studies (12,36) indicate that a larger-scale network beyond the hippocampal and frontal regions may be involved in BPD, and we used TBSS as complementary approach to investigate the potential presence of subtle, more widespread WM changes. Using TBSS, important WM tracts, for example, the uncinate fasciculus and the fornix, were poorly or not at all represented in our study. Thus, both approaches were essential to obtain an integrative view of limbic, frontal, and more widespread involvement.

Using this combination of evaluation methods, we show for the first time that there are BPD-specific WM changes in the limbic system (fiber tracking), the inferior frontal WM (TBSS) as well as more widespread changes (TBSS) in areas that may be related to the heteromodal association cortex (HASC). We now discuss these findings in detail and relate them to previous studies.

In BPD patients, the fornix exhibited a reduced FA in our tractography-based analysis. Previous ROI-based DTI studies did not evaluate the fornix, and Carrasco et al. (20), who used TBSS, did not report any findings in the fornix. However, it is unclear whether the fornix was represented in their skeleton. This is highly dependent on the FA threshold, which was set to the recommended value of .2 as a trade-off between skeleton completeness and suppression of low mean FA areas and/or high intersubject variability. In this study, we applied the same recommended threshold, and the fornix was not represented at all.

In previous studies, alterations of the OFC were found in BPD and were associated with emotional dysregulation (15). In accordance with Rüsch et al. (18), our current analysis does not reveal changes in FA in the inferior frontal WM, a finding that both TBSS and tractography supported. However, using TBSS, a significant increase in RD bilaterally in parts of the IFO/uncus complex with projections to the OFC demonstrates for the first time prefrontal WM involvement in BPD.

Although alterations in the frontal WM, mainly located in regions in close proximity of the DLPFC (Brodmann's area 46), were expected, TBSS also revealed prominent differences between BPD and CC as well as HC in the SLF and SFOF complex. The SLF—or more precisely, the arcuate fasciculus—is associated with language tasks through interconnection of Broca's and Wernicke's areas, but it also connects the DLPFC as a frontal component of the HASC with the temporoparietal components of the HASC, including the planum temporale and the inferior parietal cortex (37). Thus, it seems that the underlying structural fingerprint of BPD is more widespread than commonly assumed. Besides the disturbed emotion regulation related to the frontolimbic disconnectivity model, the interpretation of emotional cues in visual information in the temporoparietal aspects of the HASC may also be impaired. Concurring with our findings, a recent study using resting state functional MRI (36) and a meta-analysis of functional MRI studies (12) also suggest a more widespread extent of the disorder beyond the frontal lobe. Furthermore, clinical studies also indicate that emotion recognition is impaired in BPD (38,39).

From an anatomic point of view, the most surprising finding of this study is the increased RD in the internal capsule, which consists of the thalamic radiations, frontopontine-, corticospinal-, and parieto-occipital pontine tract. Its predominant function can be related to central motor control and sensory function, but especially the anterior and lateral dorsal nuclei of the thalamus are connected with the limbic system through the thalamic radiations (23). Through this connection, these findings may be related to disturbed emotional regulation as seen in BPD. This hypothesis is strengthened by a recent study on functional connectivity of the amygdala (40).

In summary, beyond the microstructural alterations in the fornix and the WM in proximity to the DLPFC and OFC, we found subtle but significant changes in structures that we did not suspect to be relevant in BPD, such as the SLF and the SFOF. The overall picture that emerges from our study is that a large-scale network of emotion processing, which integrates emotion regulation and emotion recognition, is impaired in BPD.

Limitations

A direct correlation of diffusion-derived indices with specific microstructural parameters such as axon density or myelin degeneration is challenging for several reasons, such as large voxel size and absent histologic confirmation [for a review on this topic, see Chapter 6 in Johansen-Berg et al. (41)]. The widespread increase in RD and AD seems to cancel each other out in their contribution to the FA, resulting in minimal FA changes. Another potential source of ambiguity is introduced by the usage of tractography, a method that still lacks proper validation techniques (42). Thus, the influence on our results of the choice of tractography algorithm is unclear. Even though the microstructural interpretation of the results is challenging, the mere existence of substantial and disorder-specific alterations in diffusion-derived indices in early BPD, as shown by TBSS, is striking.

Our sample size may be seen as a further limitation of this study. In combination with the absence of chronic disease, this limitation may explain the lack of FA reductions in the inferior frontal WM and the lack of significant FA reduction in the fornix when comparing BPD with HC. The same may apply to the cingulum in which, unexpectedly, neither fiber tracking nor TBSS showed significant changes in our patient population. Larger, longitudinal studies need to be performed to elucidate the potential effect of chronification on DTI-derived metrics.

Because we focused on examining a homogeneous sample and because both gender and handedness are known to be potential confounders for brain structures (43), we restricted the study to right-handed female subjects. This selection implies that the findings cannot be generalized to male patients and patients with different hemispheric lateralization. Additionally, differences in pubertal status (44,45) as well as comorbid psychiatric diagnoses, especially mood and anxiety disorders (13) and substance use disorders, may be potential confounding factors. On the one hand, given that it is rare to find patients with BPD who do not have comorbid diagnoses, our sample adequately represents BPD. On the other hand, subgroup analysis is of great importance to evaluate the potential effects of comorbid diagnoses. In this context, the relation between BPD and major depressive disorder could be of particular interest because they share disrupted emotion regulation as a key feature and TBSS studies (46–48) indicate changes in inferior frontal WM in major depressive disorder. Of further interest is the evaluation of the two other large subgroups in our sample, BPD with posttraumatic stress disorder and BPD with substance abuse. A preliminary analysis of these subgroups solely revealed increased DA in patients with BPD and PTSD in regions of the right and left SLF. However, because of the limited size of the subsets, the analysis of larger samples is required to obtain a solid understanding of these effects.

Conclusion

Overall, this study demonstrates disorder-specific widespread microstructural alterations in BPD. It strongly supports the hypothesis that WM alterations play a key role in the pathogenesis of BPD. These disorder-specific alterations include WM pathways involved in emotion regulation but also affect parts of the HASC that are related to emotion recognition. In contrast to the isolated frontolimbic disconnectivity hypothesis, our findings unify previously documented deficits in emotion recognition and regulation and suggest that a large-scale network of emotion processing is disrupted in BPD. These findings may be seen as a structural template that explains previously described functional deficits in both emotion regulation and recognition. This opens a new perspective on the pathogenesis of BPD in which deficits in emotion regulation and recognition simultaneously contribute to the disorder. Continued research is essential to evaluate the

predictive value of these early disruptions in the emotion-processing network in a clinical context.

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