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.

Key Words: Connectivity, diffusion-weighted imaging, diffusion tensor imaging, heteromodal association cortex, Tract-Based Spatial Statistics (TBSS), tractography

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 frontolimbic 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 frontotemporal 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/mm^2), 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,

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