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Reduced interhemispheric structural connectivity between anterior cingulate cortices in borderline personality disorder

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ABSTRACT

Functional and structural alterations of the anterior cingulate cortex (ACC), a key region for emotional and cognitive processing, are associated with borderline personality disorder (BPD). However, the interhemispheric structural connectivity between the left and right ACC and between other prefrontal regions in this condition is unknown. We acquired diffusion-tensor imaging data from 20 healthy women and 19 women with BPD and comorbid attention-deficit hyperactivity disorder (ADHD). Interhemispheric structural connectivity between both sides of the ACC, dorsolateral prefrontal cortices and medial orbitofrontal cortices was assessed by a novel probabilistic diffusion tensor-based fiber tracking method. In the BPD group as compared with healthy controls, we found decreased interhemispheric structural connectivity between both ACCs in fiber tracts that pass through the anterior corpus callosum and connect dorsal areas of the ACCs. Decreased interhemispheric structural connectivity between both ACCs may be a structural correlate of BPD.

1. Introduction

The anterior cingulate cortex (ACC) is a key region for emotion regulation and impulse control (Davidson et al., 2000), both prominent symptoms of borderline personality disorder (BPD). BPD is associated with alterations of ACC structure and function in terms of reduced ACC volume (Tebartz van Elst et al., 2003; Hazlett et al., 2005; Minzenberg et al., 2008; Soloff et al., 2008; Whittle et al., 2009), decreased activity during negative emotions and behavioral inhibition (Silbersweig et al., 2007), pain stimulation (Schmahl et al., 2006), response to fear stimuli (Minzenberg et al., 2007) and increased glutamate and *N*-acetylaspartate concentrations (Rüsch et al., 2009). Previous structural imaging studies assessed the ACC as a separate region. However, recent findings point to impaired interhemispheric connectivity in BPD (Williams et al., 2006; Rüsch et al., 2007a), which warrants further investigation of the ACC and other prefrontal areas involved in emotion regulation such as the orbitofrontal and dorsolateral prefrontal cortices.

We examined interhemispheric structural connectivity between these prefrontal regions in women with BPD and comorbid attention-deficit hyperactivity disorder (ADHD). This is a more homogeneous but representative subgroup of BPD because ADHD is very common in subjects with BPD (about 60% of adults with BPD have a lifetime history of ADHD; Fossati et al., 2002) and both disorders share key features such as emotional instability and impulsivity (Davids and Gastpar, 2005) that are linked to ACC function (Davidson et al., 2000). Because of ADHD comorbidity, recent findings of ACC volume reduction (Seidman et al., 2006) and alterations of functional connectivity (Tian et al., 2006) in ADHD add to the relevance of this brain region for our analyses (Makris et al., 2009). Based on these previous findings, our study was designed to test the hypothesis that interhemispheric structural connectivity between the ACC, orbitofrontal and dorsolateral prefrontal cortices is reduced in women with BPD and comorbid ADHD as compared with healthy women.

2. Materials and methods

2.1. Participants

Nineteen women with BPD were recruited at the Department of Psychiatry and Psychotherapy, University of Freiburg, Germany. The sample investigated in the study reported here, including healthy controls, is identical to the subjects of the above-mentioned study (for more details see Rüsch et al., 2007a,b, 2008), except for one patient whose imaging data were lost. All patients were free of psychotropic medication for at least 2 weeks before image acquisition, had BPD and

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currently fulfilled DSM-IV criteria for ADHD with onset in childhood. The following comorbid conditions were excluded to limit sample heterogeneity: current major depression, lifetime substance dependence or current substance abuse (Arnone et al., 2008); also a lifetime diagnosis of schizophrenia, bipolar I disorder, traumatic brain injury, or any medical disorder that might affect brain structure. Only women were studied in order to minimize possible variance due to gender differences and to reflect the greater prevalence of BPD among women (Schmahl and Bremner, 2006). Women with BPD on average had a history of approximately two suicide attempts ($M = 2.2$, S.D. = 2.6), two psychiatric hospitalizations ($M = 2.0$, S.D. = 2.3), and about three self-injurious behaviors per month during the past half year ($M = 3.1$, S.D. = 5.2). Of all 19 participants with BPD, seven had a current eating disorder; 13 had previously had major depression; five had a current posttraumatic stress disorder; and 10 had suffered from sexual abuse in childhood.

Twenty healthy female controls were group-matched with the patients for age, education and premorbid intelligence. Premorbid intelligence was measured by the Mehrfachwahl-Wortschatz-Intelligenz-Test (MWT-B, Lehrl et al., 1995; German version: Lehrl, 2005). All subjects in this study were right-handed women between 18 and 45 years of age and had completed at least 9 years of school education. The study was approved by the local ethics committee and all participants gave written informed consent.

2.2. Magnetic resonance imaging acquisition

Images were acquired with a standard circularly polarized radiofrequency head coil on a 3 Tesla Siemens Magnetom Trio MRI scanner equipped with a high performance gradient system capable of a maximal gradient strength of 40 mT/m. High resolution T1-weighted images were acquired using a magnetization prepared ultrafast gradient-echo sequence with the following parameters: FOV 240 mm^2 (FOV phase 100%), voxel size 1 mm^3, 1 slab; 160 slices; 30% slice oversampling, TR 2300; TI 1100; TE 3.68, flip angle 12°; band width 140 Hz/pixel. Diffusion-tensor imaging was performed with a diffusion-weighted single-shot spin-echo echo-planar sequence. The diffusion tensor was sampled by repeating the sequence along 12 different diffusion encoding directions. An effective *b*-value of 1000 mm^2/s was used for each of the 12 diffusion encoding directions. An additional measurement without diffusion weighting ($b = 0$ mm^2/s) was performed to allow calculation of the apparent diffusion coefficient values. Scan parameters were TR 8200 ms and TE 91 ms. A total of 52 contiguous 2.5-mm-thick axial slices were acquired, providing isotropic $2.5 \times 2.5 \times 2.5$ mm^3 voxels. Each diffusion tensor was sampled six times to optimize the signal-to-noise ratio (for more details, see Rüsch et al., 2007b).

2.3. DTI data preprocessing

Seed regions for fiber tracking were defined using the WFU-Pickatlas and the MARINA tool (MAsks for Region of Interest Analysis, Version 0.6.1, B. Walter, Giessen, Germany, 2002) implemented in SPM5 (Statistical Parametric Mapping, Wellcome Department of Imaging Neuroscience, University College London). We chose the following bilateral regions of interest (ROIs, cf. Fig. 1): anterior cingulate, medial orbitofrontal and dorsolateral prefrontal cortices. T1-weighted images were first coregistered with the b0 images and then segmented using the unified segmentation step implemented in SPM5 (Ashburner and Friston, 2005). This procedure provided us with normalization parameters for forward and backward transformations between the individual native space and Montreal Neurological Institute (MNI) space. All six seed regions were transferred into native space using the inverse normalization parameters that were individually determined from the T1-weighted dataset of each single subject in SPM5 (for more details, see Bracht et al., 2009).

For computing probabilistic maps, we chose an innovative and well-validated approach (Kreher et al., 2008) that allows quantification of structural connectivity between defined seed regions without a priori assumptions about connecting pathways (Bracht et al., 2009). In this probabilistic streamline-based approach, streamlines spread from each seed voxel through the tensor field. The local direction is determined by

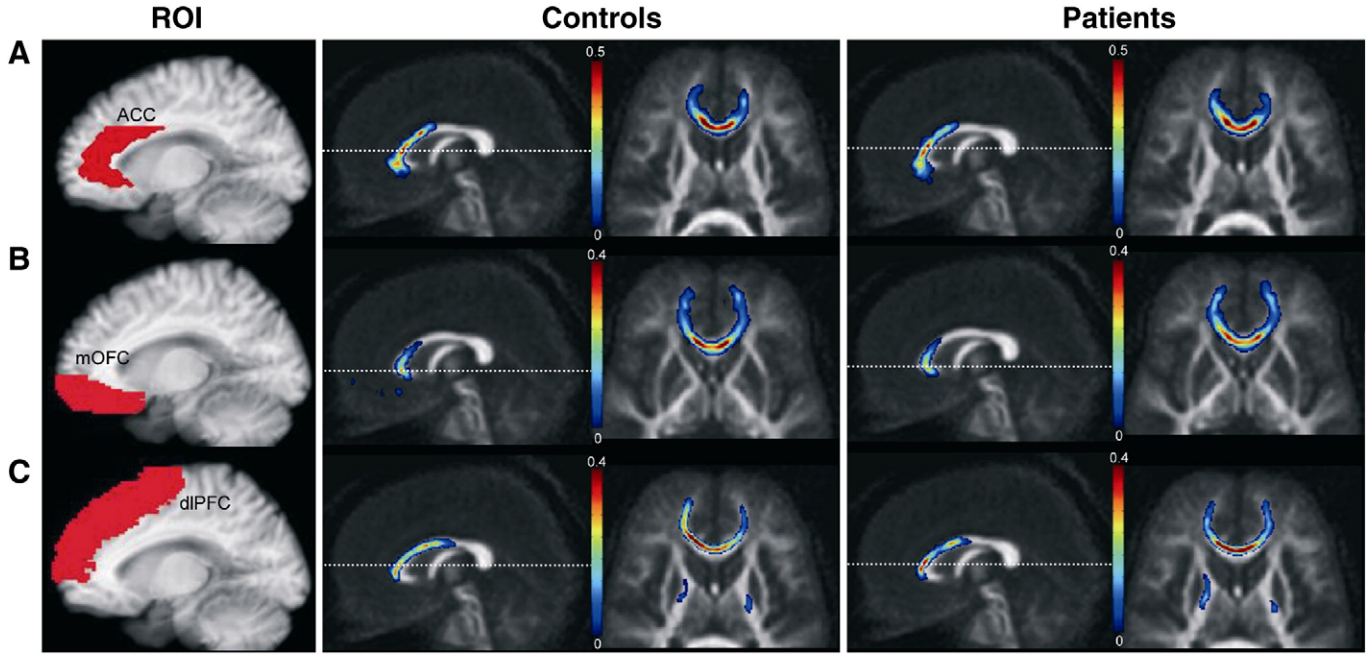

Fig. 1. Group mean maps of the three interhemispheric connections for 20 healthy controls (middle column) and 19 women with BPD (right column). Connections between both anterior cingulate cortices (ACC) are shown in row A, between both medial orbitofrontal cortices (mOFC) in row B, and between both dorsolateral prefrontal cortices (dlPFC) in row C. Voxel-wise values represent the arithmetic mean (0–1) of the probability that a voxel is part of the fiber bundle of interest (in short: *p*robability *i*ndex forming part of the *b*undle of *i*nterest, PIBI; for details see Kreher et al., 2008). Maximum PIBI values are displayed at the top of each color bar, lower PIBI threshold was 0.01 in all connections. Maps are overlaid on a mean fractional anisotropy map derived from the control subjects. In the left column, regions of interest (ROIs) are displayed in red as maximum intensity projections in sagittal direction. In the middle and right columns, dotted white lines in the sagittal projections indicate the positions of the corresponding axial sections.