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A comparative diffusion tensor imaging study of corpus callosum subregion integrity in bipolar disorder and schizophrenia

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ABSTRACT

Structural magnetic resonance imaging (MRI) studies have provided evidence for corpus callosum (CC) white matter abnormalities in bipolar disorder (BD) and schizophrenia (SZ). These findings include alterations in shape, volume, white matter intensity and structural integrity compared to healthy control populations. Although CC alterations are implicated in both SZ and BD, no study of which we are aware has investigated callosal subregion differences between these two patient populations. We used diffusion tensor imaging (DTI) to assess CC integrity in patients with BD ($n=16$), SZ ($n=19$) and healthy controls (HC) ($n=24$). Fractional anisotropy (FA) of CC subregions was measured using region of interest (ROI) analysis and compared in the three groups. Significant group differences of FA values were revealed in five CC subregions, including the anterior genu, middle genu, posterior genu, posterior body and anterior splenium. FA values of the same subregions were significantly reduced in patients with SZ compared with HC. FA values were also significantly reduced in patients with BD compared to the HC group in the same subregions, excepting the middle genu. No significant difference was found between patient groups in any region. Most of the alterations in CC subregions were present in both the BD and SZ groups. These results imply an overlap in potential pathology, possibly relating to risk factors common to both disorders. The one region that differed between patient groups, the middle genu area, may serve as an illness marker and is perhaps involved in the different cognitive impairments observed in BD and SZ.

1. Introduction

Bipolar disorder (BD) and schizophrenia (SZ) have long been considered as two distinct disorders; for example, BD and SZ often differ in their clinical course, associated levels of functional impairment, and response to medications (Goldberg et al., 1993; Gourovitch et al., 1999). Although the Kraepelinian dichotomy classifies BD and SZ as distinct entities, this concept has recently been challenged (Craddock and Owen, 2005), convergent evidence increasingly suggests that BD and SZ have overlapping features, such as symptomatology, persistent neurocognitive deficits, and shared susceptibility genes that frequently co-occur within relatives (Murray et al., 2004; Kato et al., 2005; Benes, 2007;Owen et al., 2007; Schretlen et al., 2007; Maier, 2008). Increasing evidence for greater commonalities in identified disorder mechanisms presents challenges for elucidating distinct neuropathophysiologies of BD and SZ.

The corpus callosum (CC) plays a pivotal role in higher cognitive functions via the integration of interhemispheric information. Since CC alterations may already be present in the early stages of BD (Atmaca et al., 2007; Lopez-Larson et al., 2010) and SZ (Douaud et al., 2007; Kyriakopoulos et al., 2008; White et al., 2009; Davenport et al., 2010; Henze et al., 2012), the CC has become a major structure of interest in BD and SZ research. Subsequent

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structural magnetic resonance imaging (MRI) studies have provided evidence for CC white matter abnormalities in BD (Brambilla et al., 2004; Atmaca et al., 2007; Yurgelun-Todd et al., 2007; Walterfang et al., 2009) and SZ (Downhill et al., 2000; Shenton et al., 2001; Bachmann et al., 2003; Innocenti et al., 2003; Nemes et al., 2005) including alterations in volume, signal intensity and structural integrity. Homologous findings in studies comparing either BD or SZ to healthy control populations have suggested alterations in callosal subregions that provide interhempshieric connections to the cortex, such as the genu (prefrontal areas), body (inferior temporal and superior parietal lobes) and isthmus (superior temporal and posterior parietal cortices) (Brambilla et al., 2003, 2004; Arnone et al., 2008; Bastin et al., 2008; White et al., 2008; Barnea-Goraly et al., 2009; Bellani et al., 2009; Walterfang et al., 2009; Henze et al., 2012).

Diffusion tensor imaging (DTI) (Basser et al., 1994) has made it possible to study microscopic characteristics of white matter and orientation of neural tissue in vivo by measuring the degree of water diffusion in the brain. DTI studies regularly employ a region of interest (ROI) methodology to measure fractional anisotropy (FA), an index of white matter integrity. Reduced FA indicates disruption of the organization of fiber tracts (Werring et al., 1999) and may be related to efficiency of interhemispheric signal transfer in the case of the CC. Given the longstanding implication of callosal volume, morphometry, and signal intensity differences in BD and SZ, many DTI studies have investigated CC FA in both disorders separately (Price et al., 2007; Wang et al., 2008 Gasparotti et al., 2009; Ha et al., 2011), results indicate that CC FA alterations are present in both BD and SZ. Meanwhile recent studies using DTI, which aim to investigate the specific white matter integrity in both disorders, have reported inconsistent findings including lower FA in posterior CC in BD (Lu et al., 2011), and no significant differences in CC regions (Sussmann et al., 2009; Cui et al., 2011). However, there is no study of which we are aware that uses DTI to compare BD and SZ directly to investigate the underlying subregion or subregions that differentiate the two disorders.

In the current DTI study, we applied a CC semi-automated segmentation approach to examine potential regionally and diagnostically specific CC abnormalities in patients with BD versus SZ, as indexed by ROI FA values, to discover possible distinct neural markers for both disorders.

2. Materials and methods

2.1. Ethics statement

We confirm that the research has been conducted in compliance with the appropriate ethical guidelines of the declaration of Helsinki. The study was approved by the Ethics Committee of the China Medical University. After complete description of the study, written informed consent was obtained from all participants. We confirm that all potential participants who declined to participate were not disadvantaged in any way by not participating in the study.

2.2. Subjects

Participants included 16 subjects with BD I (mean age 30.3 ± standard deviation [S.D.] 5.6 years, mean age of onset 25 ± S.D.5.88 years, 9 females), 19 with paranoid SZ (mean age 29.2 ± S.D. 8.8 years, mean age of onset 24.89 ± S.D.8.04 years,10 females), and 24 healthy control comparisons (HC) (mean age 29.1 ± S.D.7.3, 14 females). Both outpatients and inpatients were recruited from the First Affiliated Hospital of China Medical University and Shenyang Mental Health Center. All participants were evaluated by two psychiatrists for diagnosis using the Structured Clinical Interview for DSM-IV. Mood states in BD were assessed on the basis of the Hamilton Depression Rating Scale (HDRS) (Hamilton, 1960) and Young Mania Rating Scale (YMRS) (Young et al., 1978). Psychotic symptoms in SZ were assessed on the basis of the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962). Three BD patients were on lithium, six were on anticonvulsants, 10 were on atypical antipsychotics, four were on antidepressants, and one was unmedicated, as well as one patient with unclear medication. One SZ patient was on typical antipsychotics, 13 were on atypical antipsychotics and six were unmedicated. No presence of DSM-IV Axis I was confirmed in the HC participants and their first-degree family members. All participants were right handed, except two SZ patients, one BD patient and two HCs who had mixed hand dominance. Detailed demographic and clinical data are presented in Table 1.

Table 1
Demographic and clinical characteristics.

Characteristics	HC ($n=24$)	BD ($n=16$)	SZ ($n=19$)
Age (years, mean ± S.D.)	29.1 ± 7.3	30.3 ± 5.6	29.2 ± 8.8
Gender (male: female)	10:14	7:9	9:10
Course of disease (months, mean ± S.D.)	N/A	65.9 ± 82.0	52.9 ± 79.5
BPRS (mean ± S.D.)	N/A	N/A	27.2 ± 8.9
HDRS (mean ± S.D.)	0.7 ± 0.9	5.1 ± 6.2	N/A
YMRS (mean ± S.D.)	0	5.7 ± 9.2	N/A
Medication (Yes, N)	N/A	15	13

BD: Bipolar disorder.
SZ: Schizophrenia.
S.D.: Standard deviation.
BPRS: Brief psychiatric rating scale.
HDRS: Hamilton depression rating scale.
YMRS: Young mania rating scale.

Exclusion criteria for all participants included (1) general MRI-contraindications, (2) history of head injury with loss of consciousness over 5 min or any neurological disorders, (3) any concomitant major medical disorders, and (4) IQ <70.

2.3. MRI acquisition

Diffusion-weighted images were acquired on a GE Signa HDX 3.0T magnetic resonance image (MRI) scanner at the First Affiliated Hospital of China Medical University, Shenyang, China. Head motion was minimized with restraining foam pads. A standard head coil was used for radiofrequency transmission and reception of the MRI signal. DTI data were acquired using spin-echo planar imaging sequence, parallel to the anterior–posterior (AC–PC) plane. The diffusion sensitizing gradients were applied along 25 non-collinear directions ($b=1000$ s/mm^2), together with an axial acquisition without diffusion weighting ($b=0$). Scan parameters were repetition time (TR)=17,000 ms; echo time (TE)=85.4 ms; field of view (FOV)=240×240 mm^2; image matrix=120×120; 65 contiguous slices of 2 mm without gap. A 3D Fast Spoiled Gradient-Echo (FSPGR) T1-weighted sequence was used to acquire high resolution structural images for anatomical determinations (TR=7.1 ms, TE=3.2 ms, FOV=240×240 mm^2, matrix=240×240, slice thickness=1.0 mm without gap, 176 slices, one average).

2.4. DTI processing and analysis

Images were processed with FSL (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl/) and BioImage Suite software (http://www.bioimagesuite.org) using our previous protocol (Xu et al., 2012). Briefly, motion and eddy current correction were performed with FSL (FMRIB Software Library, http://www.fmrib.ox.ac.uk/fsl/). Linear motion (x, y, z planes) for all participants was below 2 mm and rotational motion (pitch, roll, yaw) was below 2°. A tri-linear interpolation was then followed by resampling the image from $2\times2\times2$ mm^3 to $1\times1\times1$ mm^3 resolution. Additional DTI data processing, such as diffusion tensor matrices, FA and color tensor maps, and CC tracing were done using BioImage Suite software (http://www.bioimagesuite.org). First, the mid-sagittal slice was determined using AC–PC aligned high resolution T1-images. DTI data was coregistered to high resolution T1-images which was used to identify the mid-sagittal slice. Then, the entire CC was delineated manually on the mid-sagittal color tensor map with two raters blind to participant characteristics. The corpus callosum was then subdivided into the genu, body, isthmus and splenium according to the definition by Keshavan et al. (2002) (Fig. 1). Inter-rater reliabilities for FA values in the nine subregions including the anterior, middle and posterior genu, anterior body, posterior body, isthmus, as well as the anterior, middle and posterior splenium, presented as intra-class correlation coefficients, ranged from 0.86 to 0.97.

2.5. Statistical analysis

All statistical analyses were conducted using SPSS for Windows software, version 16.0 (SPSS Inc., Chicago, 2008). FA values were tested for normality using Kolmogorov–Smirnov test statistics and normal probability plots. Nine analysis of variance (ANOVAs) were performed to test the three groups for differences in FA values across the nine subregions and $p<0.05/9$ (Bonferroni corrected) was