Impaired interhemispheric connectivity in medication-naive patients with major depressive disorder

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Background: Abnormalities in the anterior interhemispheric connections provided by the corpus callosum (CC) have long been implicated in major depressive disorder (MDD). The purpose of this study was to investigate interhemispheric connectivity in medication-naive patients with MDD by measuring fractional anisotropy in the CC with diffusion tensor imaging (DTI) techniques. **Methods:** We obtained DTI scans from medication-naive patients with MDD and from matched healthy controls. Fractional anisotropy values were compared using semiautomatic region of interest methods to localize the regional CC differences between these 2 groups. **Results:** We enrolled 27 patients and 27 controls in our study. Fractional anisotropy values were significantly lower in the anterior genu of the CC in the MDD group than in the control group (p = 0.009, corrected); results were not significantly different in any other CC subregions. **Limitations:** As patients with MDD were already experiencing acute episodes, future studies of individuals at risk for MDD are warranted to elucidate the interhemispheric connectivity abnormalities associated with the predisposition to MDD. **Conclusion:** The findings demonstrate abnormalities in the structural integrity of the anterior genu of the CC in medication-naive individuals with MDD, which may contribute to impairment of interhemispheric connectivity in patients with this disorder.

Introduction

Hemispheric asymmetry may be one of the most fundamental biological features in the human brain. Studies of mood and emotion processing in healthy and neuropsychiatric populations suggest processing of negative emotions relies mainly on the right cerebral hemisphere, whereas the left hemisphere is dominant for positive emotion processing.[1] Convergent evidence from investigations involving repetitive transcranial magnetic stimulation (rTMS),[2–4] electroencephalography (EEG)[5,6] and functional magnetic resonance imaging (fMRI)[7] suggest that an imbalance between left and right hemispheric activity may contribute to the pathophysiology of major depressive disorder (MDD). Abnormalities particularly in the functional balance between the left and right prefrontal cortices are implicated in the disorder. In addition, these data have raised the possibility that imbalanced functions between the left and right prefrontal cortices may result, at least in part, from impaired interhemispheric connections triggering the onset of pathological depressive episodes.[8]

Interestingly, brain connectivity abnormalities have also been increasingly reported in patients with first-episode MDD, suggesting that impaired connectivity may be an important trait feature of MDD. For example, functional connectivity analyses, which examine correlations in activity among different brain regions within and between hemispheres using fMRI, have shown abnormalities in the coordinated activity between brain regions at rest and during performance

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of emotional processing tasks in patients with first-episode MDD.[9,10] Preliminary studies using diffusion tensor imaging (DTI) have also demonstrated structural connectivity abnormalities in patients with first-episode MDD, further supporting impaired connectivity as an important trait feature of the disorder.[11,12]

The corpus callosum (CC), the largest white matter tract in the brain, provides substantial connections between the left and right cerebral hemispheres. This underscores its critical role in interhemispheric communication, particularly in the integration of emotional, high-level cognitive, linguistic and perceptual processing.[13,14] In recent years, advances in neuroimaging techniques have enhanced the field's ability to investigate white matter connections within the brain. Diffusion tensor imaging has been developed to probe the directional organization of white matter microstructure in vivo by measuring the magnitude and direction of water diffusion with a quantitative indicator, fractional anisotropy, and it has been successfully applied to investigate abnormalities within the white matter microstructure in patients with neuropsychiatric diseases. Increasingly, DTI studies have implicated the role of white matter abnormalities in MDD pathophysiology.[11,15–21] In recent DTI studies, Yuan and colleagues[22] found lower fractional anisotropy values in the genu of the CC in geriatric patients with remitted MDD using a region of interest (ROI)-based methodology. Both Korgaonkar and colleagues[23] and Kieseppä and colleagues[24] found that patients with MDD showed altered fractional anisotropy values in the posterior CC using tract-based spatial statistics (TBSS) methodology. These studies are important in supporting white matter abnormalities; however, patients were largely medicated and had experienced multiple episodes, possibly influencing the findings.

In the present study, we used a semiautomated ROI-based DTI technique to investigate interhemispheric connectivity in treatment-naive patients with MDD. We hypothesized that there would be abnormalities in the anterior genu of the CC, which provides connections between the left and right prefrontal cortices, in patients with MDD. Participants in our sample were not exposed to psychotropic medications and were early in their illness course, minimizing the potential confounding effects of medications and episodes that often complicate interpretation of findings in neuroimaging studies.

Methods

Participants

We recruited participants with MDD from the outpatient clinics of the Department of Psychiatry, The First Affiliated Hospital of China Medical University. The diagnoses of MDD in all patients were made independently by 2 trained psychiatrists (L.K. and Y.T.) using the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID).[25] Patients were required to fulfill DSM-IV criteria for MDD, have no comorbid Axis I diagnosis, have a score of at least 17 on the 17-item Hamilton Rating Scale for Depression (HAM-D)[26] and have no history of psychotropic medication, electroconvulsive therapy or psychotherapy. We recruited participants for the healthy control group from the community. The control participants were required to have no personal history of a DSM-IV Axis I disorder; this was confirmed using the SCID, version 2.0.[25] We also required that controls did not have first-degree relatives with a history of Axis I disorders.

The exclusion criteria for all participants were any contraindications for MRI, a history of head trauma with loss of consciousness for 5 or more minutes or any neurologic disorder and any concomitant major medical disorder. All participants were scanned within 48 hours of initial contact. The participants provided written informed consent after detailed description of the study. The study was approved by the Institutional Review Board of the China Medical University.

MRI acquisition

Diffusion-weighted images were acquired on a 3-T magnetic resonance scanner (General Electric) at The First Affiliated Hospital of China Medical University, Shenyang, China. Head motion was minimized with foam pads. A standard head coil was used for radiofrequency transmission and reception of the nuclear magnetic resonance signal. We acquired DTI scans using a spin-echo planar imaging sequence, parallel to the anterior commissure–posterior commissure (AC-PC) plane. The diffusion sensitizing gradients were applied along 25 noncollinear 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. We used a 3-dimensional fast-spoiled gradient-echo T_1-weighted sequence to acquire high-resolution structural images for anatomic 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, 1 average).

DTI processing

First, motion and eddy current correction were performed by aligning each diffusion-weighted image with the b0 image with an affine transformation within the FSL tool box (FMRIB Software Library, www.fmrib.ox.ac.uk/fsl/). A trilinear interpolation was then followed by resampling the image from 2 × 2 × 2 mm to 1 × 1 × 1 mm. Linear motion (Montreal Neurological Institute x, y, z planes) for all participants was below 2 mm, and rotational motion (pitch, roll, yaw) was below 2°. We completed additional DTI data processing and CC tracing using BioImage Suite software (www.bioimagesuite.org). We calculated diffusion tensor matrices and regional fractional anisotropy measures according to the methodology of Basser and colleagues.[27] The absolute red-green-blue colour-encoding scheme defined the directionality of the principal eigenvector:[28] left–right fibres in red, anterior–posterior fibres in green and superior–inferior fibres in blue (Fig. 1). The midsagittal slice was determined using AC-PC aligned high-resolution T_1 images.[29] Diffusion tensor imaging data were coregistered to high-resolution T_1 images with Bioimage Suite

software to identify the midsagittal slice. The entire CC was delineated manually on the midsagittal colour tensor map using BioImage Suite software by 2 operators (X.O. and F.W.) blind to participant characteristics. Then it was further subdivided into the genu, body, isthmus and splenium based on landmarks adapted from Keshavan and colleagues[30] and Witelson[31] using automated methods (Fig. 1). Inter-rater reliabilities for fractional anisotropy values in the 9 subregions (the anterior, middle and posterior genu; anterior body and posterior body; isthmus; and the anterior, middle and posterior splenium) presented as intraclass correlation coefficients ranged from 0.86 to 0.97.

Statistical analysis

All statistical analyses were conducted using SPSS for Windows software, version 16.0 (SPSS Inc.). We tested fractional anisotropy values for normality using Kolmogorov–Smirnov test statistics and normal probability plots. A linear mixed model was used in which the diagnostic group (control v. MDD) and sex represented between-subject factors, and the 9 CC subregions were included as a within-subject factor. The interaction between diagnostic group and sex was modelled. If the diagnostic group effect and interaction between diagnostic group and sex demonstrated significance, we performed analyses of covariance for the 9 subregions in the post hoc analyses, with results considered to be significant at $p < 0.05$ (Bonferroni corrected). If there was no significant interaction, sex was eliminated from the post hoc analyses. Least square means and standard errors were computed from the model and plotted to interpret diagnosis effects. We performed Spearman correlation analyses to test the relationships between fractional anisotropy values and illness duration.

Results

The MDD group included 27 participants (mean age 31.4 [standard deviation (SD) 9.1] yr, range 19–46 yr, 56% women). The control group included 27 participants (mean age 29.5 [SD 8.8] yr, range 20–46 yr, 56% women). All participants were right-handed. Table 1 presents detailed demographic and clinical characteristics of participants.

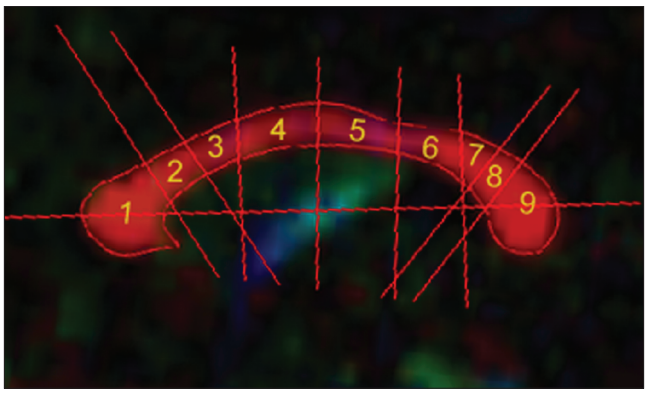

Fig. 1: Sagittal image from the tensor colour map displays in red the scheme used to subdivide the corpus and the left–right coursing fibres of the corpus callosum.

The MDD and control groups did not differ significantly in age or sex (all $p > 0.05$). Analysis of fractional anisotropy values showed that the main effect of diagnosis was statistically significant ($F_{1,50} = 4.39$, $p = 0.041$), suggesting that the overall fractional anisotropy levels in patients with MDD were significantly different from those of controls. The difference of least square means between the diagnostic groups across subregions indicated that overall fractional anisotropy levels in patients with MDD were lower than those of controls and that the contribution to group difference was derived mainly from decreased fractional anisotropy values in the anterior genu of the CC ($F_{1,53} = 11.63$, $p = 0.009$, Bonferroni-corrected) in the MDD compared with the control group. Fractional anisotropy decreases in other CC subregions were not significant (all $p > 0.05$, Bonferroni corrected). These findings are illustrated in Figure 2 and Table 2. In addition, there was a significant overall effect of sex on fractional anisotropy values ($F_{1,50} = 4.89$, $p = 0.032$); however, there was no significant group × sex interaction ($F_{1,50} = 0.35$, $p = 0.56$). Exploratory analyses did not reveal significant correlations between illness duration and fractional anisotropy values in the 9 subregions (all $p > 0.05$).

Table 1: Demographic and clinical characteristics of study participants

	Group; mean (SD)*	
Characteristic	Controls, $n = 27$	MDD, $n = 27$
Age, yr	31.4 (9.1)	29.5 (8.8)
Sex, male:female	12:15	12:15
Education, yr	13.3 (3.1)	13.0 (2.7)
HAM-D score	0.8 (1.1)	28.5 (5.3)
Duration of illness, mo	NA	15.6 (17.8)

HAM-D = Hamilton Rating Scale for Depression;[28] MDD = major depressive disorder; NA = not applicable; SD = standard deviation.
*Unless otherwise indicated.

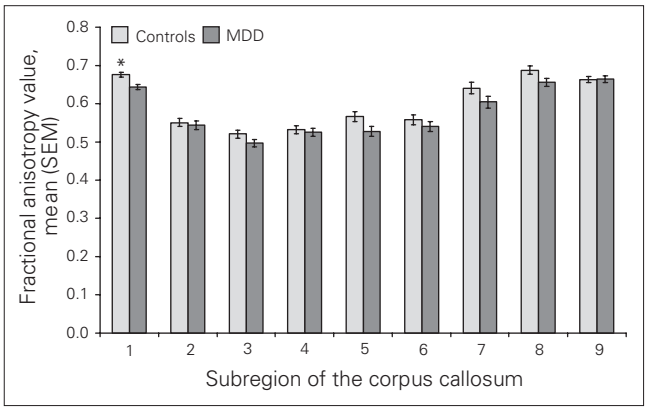

Fig. 2: Least square mean anisotropy values in the 9 subregions of the corpus callosum and standard errors of the mean (SEM) for the major depressive disorder (MDD; $n = 27$) and the control ($n = 27$) groups. *The effect of diagnosis was significant in the anterior genu of the corpus callosum ($p = 0.009$, corrected).

Table 2: Fractional anistropy values in healthy controls and patients with major depressive disorder

Brain region	Group; mean (SD)		*p* value, uncorrected*
	Controls	MDD	
Anterior genu	0.68 (0.03)	0.64 (0.04)	0.001
Middle genu	0.55 (0.06)	0.54 (0.05)	0.63
Posterior genu	0.52 (0.05)	0.50 (0.06)	0.11
Anterior body	0.53 (0.06)	0.53 (0.06)	0.67
Posterior body	0.57 (0.07)	0.53 (0.07)	0.044
Isthmus	0.56 (0.06)	0.54 (0.08)	0.36
Anterior splenium	0.64 (0.09)	0.60 (0.08)	0.11
Middle splenium	0.69 (0.05)	0.66 (0.06)	0.040
Posterior splenium	0.66 (0.04)	0.66 (0.05)	0.92

MDD = major depressive disorder; SD = standard deviation.
* Bonferroni corrected.

Discussion

We found decreased fractional anisotropy values in the anterior genu of the CC in patients with MDD compared with controls. To our knowledge, this study provides the first evidence of anterior genu CC abnormalities in a sample of medication-naive adults with MDD. Additionally, most of our participants had relatively short illness durations (80% of participants had illness duration < 2 yr). Therefore, our findings were not influenced by treatment, and chronicity-related confounds were minimized.

Corpus callosum abnormalities have been increasingly implicated in MDD in neuroimaging studies. Structural MRI studies have demonstrated area and shape changes in the CC in patients with MDD.[32–34] Lacerda and colleagues[35] found that patients with familial MDD (first-degree relatives with unipolar or bipolar disorder) had a significantly larger middle genu area than healthy controls and significantly larger middle genu, anterior splenium and middle splenium areas than patients with nonfamilial MDD. Additionally, magnetization transfer ratio (MTR) imaging has shown a lower MTR in the splenium of the CC in geriatric patients with MDD in comparison with nondepressed elderly people.[36] The present study provided additional evidence of abnormal structural integrity in the CC in unmedicated patients with MDD.

The anterior genu of the CC is the major white matter commissure connecting homologous regions of the left and right prefrontal cortices, anterior cingulate and insula. Both the anterior cingulate cortex and insula have connections with limbic structures, such as the amygdala, and are involved in affective processing and cognitive functioning.[37] Convergent studies have increasingly implicated both regions in MDD. For example, alterations in volume and functional activation in both these regions have been reported in studies of patients with MDD.[38–42] Also, the anterior genu of the CC plays an important role in interhemispheric communication and hemispheric asymmetry of emotional and cognitive functioning.[43] Abnormalities in interhemispheric functioning have been reported previously in patients with MDD.[2–7,44–46] Lesions in the anterior CC have been implicated in emotional dysregulation[47] and the hemispheric lateralization of prefrontal abnormalities associated with acute depressive episodes.[48] Mechanisms that may underlie the development of abnormalities in anterior genu CC white matter organization are suggested by recent postmortem studies.[49,50] Such studies have demonstrated associations between susceptibility to MDD and decreases in frontal oligodendrocyte density and myelin-related factors in patients with MDD.

Our present findings of decreased fractional anisotropy in the anterior genu of the CC further support the involvement of this region in the neural dysfunction that occurs in patients with MDD. Moreover, they suggest that MDD may be associated with structural deficits in interhemispheric white matter tracts that connect the prefrontal cortices at comparatively early stages of illness, as most of the study participants had relatively short durations of illness. Furthermore, the findings reported herein and prior findings of lower fractional anisotropy in the genu of the CC in geriatric patients with remitted MDD[22] suggest that abnormal genu integrity might be a common feature for both adult and late-onset MDD. Additionally, the presence of lower fractional anisotropy in the genu of the CC in patients with active and remitted MDD, as well as in medication-naive and medicated patients with MDD, suggest that decreased structural integrity of the genu of the CC may be a trait-related marker of MDD and may have important implications for early identification of those at risk for the disorder. However, definitive conclusions cannot be drawn based on the current findings. Future investigation of populations at increased genetic risk for MDD who have not yet experienced depressive episodes is needed to help elucidate the onset of white matter alterations. Longitudinal and systematic treatment studies could help to clarify the effects of episodes and treatment.

Limitations

As the patients with MDD included in our study were already experiencing an acute episode, future studies of individuals at risk for MDD are warranted to elucidate the interhemispheric connectivity abnormalities associated with predisposition to the disorder.

Conclusion

Our findings demonstrate abnormalities in the structural integrity of the anterior genu of the CC in medication-naive patients with MDD, which may contribute to impairment of interhemispheric connectivity in patients with this disorder.

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designed the study. W. Jiang, L. Ren and L. Kong accquired data. X. Ouyang, Y. Jiang, F. Womer and Z. Liu analyzed the data. X. Ouyang, H. Blumberg, Y. Tang and F. Wang wrote the article. All authors reviewed the article and provided approval for publication.

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