Altered white matter integrity in young adults with first-episode, treatment-naive, and treatment-responsive depression

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HIGHLIGHTS

► MDD may exhibit abnormalities of WM integrity in regions associated with emotional regulation.
► The patients enrolled in the present study were treatment-responsive young adults.
► TBSS method could detect WM tracts integrity alterations in patients and controls.
► Alterations of projection fibers and corpus callosum integrity attribute to pathogenesis of MDD.

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ABSTRACT

Abnormalities of the white matter (WM) tracts integrity in brain areas involved in emotional regulation have been postulated in major depressive disorder (MDD). However, there is no diffusion tensor imaging (DTI) study in patients with treatment-responsive MDD at present. DTI scans were performed on 22 patients with treatment-responsive MDD and 19 well-matched healthy subjects. Tract-based spatial statistics (TBSS) approach was employed to analyze the scans. Voxel-wise statistics revealed four brain WM tracts with lower fractional anisotropy (FA) in patients compared to healthy subjects: the bilateral internal capsule, the genu of corpus callosum, the bilateral anterior corona radiata, and the right external capsule. FA values were nowhere higher in patients compared to healthy subjects. Our findings demonstrate that the abnormalities of the WM tracts, major in the projection fibers and corpus callosum, may contribute to the pathogenesis of treatment-responsive MDD.

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1. Introduction

Major depressive disorder (MDD) is reported to be associated with reduced fractional anisotropy (FA) in the WM of the frontal lobe [17] and the temporal lobe [15] revealed by diffusion tensor imaging (DTI) studies using region-of-interest (ROI) analysis. Decreased FA has also been shown in the corpus callosum, internal capsule, superior longitudinal fasciculus (SLF), and sagittal stratum [24] in patients with MDD by using voxel-based morphometry (VBM) analysis.
Although the ROI- and VBM-based analyses have provided useful information, both have their weaknesses. It is difficult to manually and reproducibly place ROIs on thin WM tracts [18]. Besides, the ROI-based method can detect alterations only in the pre-selected ROIs and lacking global brain WM information. To VBM-based method, a large amount of smoothing and alignment problems can greatly affect the final results [11].

Recently, tract-based spatial statistics (TBSS) has been proposed to alleviate the alignment problem by applying both linear and nonlinear alignment to the data. It projects the FA values of individual subjects onto a given FA skeleton in a way that is not dependent on perfect nonlinear registration. Unlike with VBM, no spatial smoothing is necessary. Thus, this TBSS method minimizes the effects of misalignment [18,19].

The TBSS method has been used to evaluate WM alterations in patients with MDD with conflicting results. A trend of lower FA values was found in the left sagittal stratum in middle-aged patients with MDD [12] while altered white matter (WM) integrity of forebrain was observed in treatment-resistant depression [6]. Korgaonkar et al. [13] reported that the melancholic subtype of MDD patients showed decreased FA over WM regions associated with the limbic system, dorsolateral prefrontal cortex, thalamic projection fibers, corpus callosum, and other association fibers. Whereas in first-episode, treatment-naive patients with MDD, decreased FA values were detected in three WM tracts: the left anterior limb of the internal capsule, the WM of the right parahippocampal gyrus, and WM subjacent to the left posterior cingulate cortex [23]. The discrepancy of the above findings may partly be due to the heterogeneity of MDD in the previous studies, such as the patients’ age, illness duration, the severity of depression, medication, and the clinical subtypes. Hence, it is of particular importance to consider such factors when recruiting patients.

To address these factors, in this DTI study, we used a well-defined cohort of patients by recruiting merely the first-episode, treatment-naive, short-illness-duration, and treatment-responsive young adults with MDD. We hypothesized that the patients would show altered WM tracts integrity in the brain areas related to emotional regulation compared to healthy subjects. We also hypothesized that alterations of WM tracts integrity in the patients were positively associated with the severity of depression.

2. Methods

2.1. Subjects

Twenty-nine right-handed, first-episode, and treatment-naive outpatients were recruited from Mental Health Institute, the Second Xiangya Hospital, Central South University, China. Current MDD attack was diagnosed by using the Structured Clinical Interview according to the DSM-IV criteria [4]. The severity of depression was evaluated using 17-item Hamilton Rating Scale for Depression (HRSD) [9]. Only those with HRSD score of $\geq 18$ were eligible for the study. Exclusion criteria were any history of neurological diseases or other physical diseases, and comorbidities with other disorders (no evidence for schizoaffective disorder, bipolar disorder or Axis II, personality disorders and mental retardation). Patients of age younger than 18 years or older than 50 years old were also excluded. Additionally, the current illness duration was no more than six months. DTI scans were performed at the day when the patients were enrolled. Then all patients took antidepressants at a minimum dose of 150 mg/day of imipramine equivalents (dose converted using a conversion table [10]) for 6 weeks. To ensure that the study sample is representative of the “real world”, the patients were treated randomly according to random number table. The drugs included one of the three typical classes of antidepressants: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitor (SSRI) and serotonin–norepinephrine reuptake inhibitors (SNRIs). Detailed treatment can be found in Supplementary Table S1. The treatment-response was termed as a more than 50% reduction in the HRSD scores after antidepressant treatment, consistent with previous studies [5,7,8].

Nineteen right-handed healthy subjects were recruited from the community. They were also interviewed by the same psychiatrists using the Structured Clinical Interview for DSM-IV, nonpatient edition [4]. None of them had a history of serious medical or neuropsychiatric illness or a family history of major psychiatric or neurological illness in their first-degree relatives, and all were well matched with the patients in terms of age, gender and years of education.

All subjects were given information about the procedures. Written informed consent was obtained via forms approved by the local Ethics Committee.

2.2. Scan acquisition

Imaging was performed on a 1.5T GE scanner (General Electric, Fairfield, CT, USA) equipped with high-speed gradients. The patients were informed to remain motionless and to keep their eyes closed. Single-shot echo planar diffusion-weighted imaging with alignment of the anterior commissure-posterior commissure plane was performed.

The DTI parameters were as follows: repetition time $= 12,000$ ms; echo time $= 105$ ms; acquisition matrix $= 128 \times 128$; field of view $= 240 \times 240 \text{mm}$; slice thickness $= 4 \text{mm}$, no gap; $30$ contiguous axial slices. The diffusion sensitizing gradients were applied along $13$ non-collinear directions ($b = 1000 \text{s/mm}^2$) with an acquisition without diffusion weighting ($b = 0$).

2.3. Data processing

All diffusion tensor images were processed using software tools from the FMRIB software library (FSL, version 4.1.8; http://www.fmrib.ox.ac.uk/fsl). First, each dataset was corrected for head movement and eddy current distortions using an affine transformation of each diffusion weighted image to the reference volume of the nondiffusion weighted ($b = 0$) image. Second, a binary brain mask was generated from the nondiffusion weighted image by using brain extraction tool. Following these steps, diffusion tensor models were fitted independently for each voxel within the brain mask and images of FA were generated for each participant.

Each subject’s FA images were then non-linearly aligned into $1 \text{mm} \times 1 \text{mm} \times 1 \text{mm}$ MNI standard space using a FMRIB58_FA template. This results in a standard space version of every subject’s FA image. After aligning all of the individual FA images to the standard space template by using nonlinear registration, a mean FA image is calculated and thinned to create a mean FA skeleton embodying the center of all tracts derived from the whole group. An FA threshold value of 0.2 or higher was set to exclude peripheral tracts. Next, each subject’s aligned FA data was projected onto this skeleton by assigning each skeleton voxel by the maximum FA value found in a direction perpendicular to the tract.

2.4. Statistical analysis

Distributions of age and years of education of the two groups were compared by using two-sample t-test, and distributions of gender were compared by using Chi-square test. For the imaging data, analyses were carried via voxel-wise cross-subject statistics of the independent two-sample t-test, by FSL Randomise tool (version 2.1) using 5000 permutations with the threshold-free cluster.
Fig. 1. White matter structures showing significantly lower FA in first-episode, treatment-naive, short-illness-duration, and treatment-responsive young adults with MDD (P<0.01, corrected for multiple comparisons) in (1) the left anterior corona radiata, (2) the right anterior corona radiata, (3) the right external capsule, (4) genu of corpus callosum, (5) the left internal capsule, and (6) the right internal capsule. FA maps show sagittal, coronal, and axial views (from right to left). The background image is the standard MN152 brain template. Green voxels represent the FA white matter skeleton. Red-yellow voxels represent regions with lower FA in patients with MDD compared with healthy subjects.
enhancement option. Since age was not a covariate of the interest in these analyses, we regressed out the effect of age. Statistic results were corrected for multiple comparison with threshold-free cluster enhancement (TFCE) methods. Clusters with voxel-wise threshold of $P < 0.01$ as well as voxels $>50$ was considered statistically significant.

To examine whether clinical features of depression were related to the WM integrity in patients with MDD, linear regression analyses were performed. The FA values for each patient were extracted from the significant clusters of the comparison and then used for the regression analyses. Correlations between mean FA values within each significant cluster and patients’ age, years of education, illness duration, HRSD total score were analyzed. The threshold of $P < 0.05$ was considered to be significant for these analyses. We also used whole brain regression analyses on FA values and the clinical parameters. Statistic results were corrected for multiple comparisons with TFCE methods. Clusters with voxel-wise threshold of $P < 0.05$ as well as continuous voxels $>50$ was considered statistically significant.

3. Results

3.1. Subjects

Data from seven patients were excluded due to treatment non-response. Twenty-two patients with MDD and 19 healthy subjects completed the whole study. Demographic information, illness duration, and HRSD scores were shown in Table 1. MDD group and control group did not differ significantly in terms of age, gender and years of education.

3.2. Differences in FA values between patients with MDD and control subjects

As shown in Table 2 and Fig. 1, voxel-wise statistics revealed four brain WM tracts with lower FA values in patients with MDD compared with healthy subjects: the bilateral internal capsule, the genu of corpus callosum, the bilateral anterior corona radiata, and the right external capsule. In contrast, FA values were nowhere higher in patients compared with healthy subjects.

### 3.3. Correlations between FA values, depression severity, and related factors

Linear regression analyses showed no correlation between the decreased FA values in the above-mentioned four WM tracts and illness duration, or baseline HRSD total scores. There was also no correlation between the decreased FA values related to WM integrity of above-mentioned neuronal tracts and either the age or years of education of patients. Moreover, even in the whole brain regression analyses, no significant cluster was found.

4. Discussion

The primary finding in this study is that the MDD group exhibited significant lower FA values in the projection fibers (anterior corona radiate, internal capsule and the right external capsule), and the genu of corpus callosum. Because only first-episode, treatment-naive, short-illness-duration, and treatment-responsive young adults with MDD were enrolled, the current findings first provide information of altered WM integrity in this special subtype of patients.

When cut horizontally, the internal capsule can be classified into five main parts: the genu, the anterior limb, the posterior limb, the retrolenticular portion and the sublenticular portion. The genu of the internal capsule contains corticobulbar fibers, which originates in the motor cortex of the frontal lobe and runs between the cerebral cortex and the brainstem. The anterior limb of the internal capsule (ALIC) carries mostly the thalamocortical projection fibers, which predominately connect the medial dorsal thalamic nucleus to the frontal cortex [2]. The primary motor cortex sends its axons through the posterior limb of the internal capsule. The retrolenticular portion carries optic tracts including the geniculo-cortical radiations. While the sublenticular portion are tracts involved in the auditory pathway from medial geniculate nucleus to the primary auditory cortex. The lower FA in the internal capsule may reflect the abnormalities of the WM tracts in cortical–subcortical neural circuits. Of these circuits, the frontal–subcortical neural circuits contain the frontal cortex, striatum, globus pallidus, thalamus, and five subcortical circuits [23,24]. Dysfunctions of each subcortical circuit may lead to different clinical signs and symptoms. For example, impairment of emotional stability, executive function and

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Demographic information and disease severity in treatment response patients and healthy subjects.</th>
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<tbody>
<tr>
<td>Demographic data</td>
<td>MDD patients (n = 22)</td>
</tr>
<tr>
<td>Gender (male/female)</td>
<td>12/10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>28.09 ± 9.91</td>
</tr>
<tr>
<td>Years of education (years)</td>
<td>12.23 ± 2.52</td>
</tr>
<tr>
<td>HRSD score</td>
<td>25.89 ± 6.26</td>
</tr>
<tr>
<td>Illness duration (months)</td>
<td>2.95 ± 1.73</td>
</tr>
</tbody>
</table>

MDD, major depressive disorder; HRSD, Hamilton Rating Scale for Depression.
* The P value for gender distribution was obtained by Chi-square test.
* The P values were obtained by two samples t-tests.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Areas of lower FA in young adults with treatment-response MDD compared with healthy subjects.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Areas of lower FA patients vs controls (MDD-HS)</td>
<td>X</td>
</tr>
<tr>
<td>Anterior corona radiate (L)</td>
<td>−14</td>
</tr>
<tr>
<td>Anterior corona radiate (R)</td>
<td>16</td>
</tr>
<tr>
<td>External capsule (L)</td>
<td>24</td>
</tr>
<tr>
<td>External capsule (R)</td>
<td>6</td>
</tr>
<tr>
<td>Internal capsule (L)</td>
<td>−9</td>
</tr>
<tr>
<td>Internal capsule (R)</td>
<td>19</td>
</tr>
</tbody>
</table>

P values are corrected for multiple comparisons (corrected for multiple comparisons at contiguous voxels with at least 50 voxels and cluster level P < 0.01). MDD, major depressive disorder; HS, healthy subjects.
motivation observed in patients with MDD, may be due to dysfunctions of the orbitofrontal circuit, the dorsolateral prefrontal circuit, and the anterior cingulate circuit, respectively [20,23,24]. Since the frontal–subcortical neural circuits consisted of massive bundles of fibers converging in the internal capsule [2], reduced WM integrity in the internal capsule could therefore conceivably damage long-range communication among a great number of frontal cortex and subcortical areas. Growing literatures supports the notion that dysfunction of the frontal–subcortical circuits may underlie the pathogenesis of MDD [1,16,20,23,24]. Our findings of lower FA values in the internal capsule, together with previous studies [13,23,24], further support the hypothesis that damage of the WM tracts integrity in the frontal–subcortical circuits might be associated with the pathogenesis of treatment-responsive MDD.

Corpus callosum has an important role in the interaction between the two hemispheres, such as the integration of high-level cognitive, linguistic and perceptual processing. Decreased FA in corpus callosum might result in abnormalities of these functions. Lower FA in the corpus callosum has been seen in geriatric depression [22] and the melancholic subtype of MDD [13]. Using TBSS approach, Kieseppa et al. [12] found suggestive decreased FA in the posterior body of corpus callosum. Consistent with previous studies, the current study indicates that the lower FA in the genu of the corpus callosum might contribute to the functional alterations in the inter-hemispheric system of emotional regulation in treatment-responsive depression.

The corona radiata is related to the corticospinal tract, the corticopontine tract, and the corticobulbar tract. The corticospinal tract mainly contains motor axons that travel between the cerebral cortex and the spinal cord. The corticopontine tract is a WM sheet which projects from the cerebral cortex to the pontine nuclei and the corticobulbar tract carries signals to motor neurons of the cranial nerve nuclei [14]. Altered WM integrity of the corona radiata gives rise to a set of motor signs and symptoms. Decreased FA in the left posterior corona radiata has previously been reported in melancholic MDD [13]. However, no FA alterations in the corona radiata were detected by the other two studies [12,23]. The inconsistencies may result from different inclusion criteria, such as the patients’ age, illness duration, the severity of depression, medication, and the clinical subtypes. By recruiting merely the first-episode, treatment-naive, and treatment-responsive young adults, our results strongly suggest the involvement of the bilateral anterior corona radiata in the pathogenesis of the treatment-responsive patients with MDD.

The external capsule is a pathway for cholinergic fibers from the basal forebrain to the cerebral cortex. The basal forebrain, the major cholinergic output of the CNS, includes a group of structures, such as the nucleus basalis, diagonal band of Broca, and medial septal nuclei. These structures are important in the production of acetylcholine, and play a key role in learning and sleep. Like the findings in the corona radiata, decreased FA was found in the bilateral external capsule in the melancholic patients with MDD [13], and the other two studies failed to reveal such results [12,23]. In line with the previous study [13], lower FA in the right external capsule might partly contribute to learning impairments and sleep disturbance seen in the treatment-responsive patients with MDD in the present study.

Since clinical characteristics such as illness duration and the symptoms have been reported to be related to abnormal FA in MDD [3,21], the finding of no correlation between the decreased FA values in the currently detected neuronal traits and demographics and illness characteristics in the present study was somewhat unexpected. Although this finding could be confounded by the small sample size, it is also possible that the alterations of FA in these regions may be a trait marker for treatment-responsive patients regardless of the severity of symptoms and other related factors.

5. Study limitations

The heterogeneous pharmacological profiles firstly limited the present study. The same patient may show treatment nonresponse to one antidepressant and treatment response to the other. Thus it is possible that some treatment-responsive patients might be excluded from the study as treatment nonresponsive patients. This heterogeneous pharmacological profile might limit the translational value of our results.

The current study is further limited by not including patients who were treatment-nonresponsive. Hence we could not justify the effects of responsiveness from depression, treatment, and/or both. Future large sample size studies including patients with treatment-nonresponsive MDD, and treatment-responsive MDD, and healthy subjects are warranted to support or refute our results.

6. Conclusions

In summary, our findings first suggest that the abnormalities of the WM tracts, major in the projection fibers and corpus callosum, may play a role in the pathogenesis of treatment-responsive MDD.

Contributors

Dr. J. Zhao designed the study along with Dr. H. Chen, Drs. Z. Liu, Z. Xue, and R. Wu collected the original imaging data. Drs. W. Guo, F. Liu, C. Ma and C. Xiao managed and analyzed the imaging data, and Drs. W. Guo and K. Gao wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

No conflict of interest declared.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neulet.2012.06.027.

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