White matter abnormalities in medication-naïve adult patients with major depressive disorder: Tract-based spatial statistical analysis

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Abstract

OBJECTIVE: While increasing evidence suggests that major depressive disorder (MDD) is coincident with the altered white matter microstructure in many brain regions including the prefrontal cortex, parietal lobe, ventral tegmental area and limbic system, it remains controversial in the nature of white matter structural changes and in its relationship with depression syndrome. We believe that the age of patients and the antidepressant treatment to them would contribute to that controversy. Here in this study we explored the microstructural changes of the entire brain white matter of the adult patients with first-episode, antidepressant drug-naïve MDD.

DESIGN: We performed the diffusion tensor imaging (DTI) among a relatively large sample size of patients and age-matched control individuals (forty-one MDD patients and forty-one control subjects) and used recently developed tract-based spatial statistics to analyze the difference of mean fractional anisotropy (FA) between patients and control individuals.

RESULTS: We surprisingly found that MDD patients exhibited a significantly greater mean FA, which is used to elucidate the structural organization of the neural fibers, than control subjects in the whiter matter of the left superior longitudinal fasciculus. However, this change in the white matter of MDD patient did not correlate with depressive clinical features (HMAD, illness duration and initial age) in the present study.

CONCLUSION: Our data suggest that a potential compensatory regeneration of nerve fibers occurs in the early course of MDD development. Advanced understanding of the potential nerve fiber regeneration in the early course of MDD and its associated mechanisms will possibly shed light on a better strategy for MDD prevention and treatment.
INTRODUCTION

Major depressive disorder (MDD) (also known as clinical depression) is a mental disorder characterized by a feeling of sadness and helplessness, a pervasive and persistent low mood that is accompanied by low self-esteem and by a loss of interest or pleasure in normally enjoyable activities. In recent years, depressive disorders are leading causes of disability worldwide according to the World Health Organization report (http://www.who.int/mental_health/management/depression/definition/en/index1.html). Although the big picture of the depression pathogenesis remains elusive, several hypotheses propose that biological, psychological and social factors can all play a crucial role in causing depression. More importantly, non-invasive neuroimaging studies in clinic settings have significantly advanced our knowledge of the brain structural and functional changes associated with MDD (Drevets 2000). In addition to the structural changes in the prefrontal cortex, cingulate gyrus, basal ganglia, hippocampus and thalamus have been investigated (Drevets et al. 2008), cerebral white matter (WM), consisting of axonal bundles that connect brain cortex regions and create proximal and distal neural networks for facilitating complex behaviors and mood, has also attracted much attention given that WM can mediate functional connections between multiple neural systems (Le Bihan 2003).

Diffusion tensor imaging (DTI) is a noninvasive method that measures the microstructural alteration of major neuronal fiber pathways in vivo by measuring the diffusion of water in neural tissues. Numerous studies using DTI in depressive patients have found diffusion fractional anisotropy (FA; A common measurement for elucidating the structural organization of the neural fibers in WM) abnormalities in certain brain regions, suggesting that WM structural anomalies exist in depression (Taylor et al. 2001; Yang et al. 2007). To date, the majority of the DTI studies suggest a loss of coherence in WM bundles among MDD patients. For example, several DTI studies have found frontal and temporal reduced FA in depression (Nobuhara et al. 2006; Wu et al. 2011). In addition, the relationship between the observed loss of white matter coherence and the mental state of MDD patients has been explored by a measurement based on the Hamilton Depression Rating Scale (HAMD) (Dalby et al. 2010). However, the outcome of these investigations has revealed an absence of correlation between the reduced FA value and the depressive state that was evaluated by the HAMD test (Li et al. 2007).

Although it is common to observe a reduced FA value in the MDD patient brain by analyzing DTI images with the methods of region-of-interest (ROI) (Yang et al. 2007) analysis or voxel-based analysis (VBA) (Zou et al. 2008), a few studies (Blood et al. 2010) report a significantly greater FA value in the right ventral tegmental area in depressive patients. This discrepancy may result from the analysis sensitivity and the individual’s age given that both young (McKinnon et al. 2009) and late-life MDD patients were subjected to these investigations. To eliminate the artificial errors and minimize the effects of misalignment, Smith and colleagues (Smith et al. 2006) proposed a tract-based spatial statistics (TBSS) approach that conducts statistical analysis along individual white matter skeletons in the entire brain.

In the present study, using a TBSS analyzed-DTI study approach, we investigated the white matter integrity in medication-naïve adult MDD patient brain, especially focused on the regions that connect emotion-related limbic and cortical areas. To our surprise, we found that MDD patients exhibited a significantly greater mean FA value than control subjects in the white matter of the left superior longitudinal fasciculus. In addition, by performing a HAMD test, we examined whether the observed WM changes was correlated with the mental state of the MDD patients. Although the observed white matter change in left superior longitudinal fasciculus failed to be correlated with depressive mental state in the present study, our data suggest a potential compensatory regeneration of nerve fibers may occur in the early course of MDD pathogenesis.

MATERIALS AND METHODS

Participants

The human subjects recruited for this study were approved by the Medical Ethics Committee of the Shanxi Medical University. All MDD patients and the control subjects were made aware of the objectives of the study and signed informed consent documents prior to being enrolled in the research.

Forty-one right-handed, medication-naïve patients with current MDD (male/female [M/F]: 21/20, mean age: 32.35 years, standard deviation [SD]:6.52, mean years of education: 13.29 years, SD: 4.11) were recruited from outpatient and inpatient units in the Department of Psychiatry, First Hospital of Shanxi Medical University. The MDD patients must meet all the following criteria to be recruited: 1) Eighteen to fifty years of age; 2) right-handed; 3) meeting diagnosis of current MDD based on Diagnostic and Statistical Manual-IV criteria; 4) having a total score of Hamilton Depression Rating Scale (HAMD17)>17 and a total score of Hamilton Anxiety Scale (HAMA) <14. Diagnoses of MDD were based on the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P) and consensus of at least two psychiatrists.

Forty-one right-handed, age and gender-matched control subjects (M/F: 21/20, mean age: 32.58 years, SD: 5.32, mean years of education: 14.55 years, SD: 3.12) were recruited from the nearby community with matching the following criteria: 1) inconformity axis I MDD diagnosis in DSM-IV; 2) having a total score of HAMD <7 and a total score of HAMA<7.

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All patients and control subjects have no history of head injury, systemic medical illness, other primary psychiatric diagnosis, substance abuse, pregnancy, claustrophobia, serious physical illness, treatment with antidepressants, previous electroconvulsive therapy, suicidal tendencies and self-injury, family history of mental disorders, and the usual MRI contraindications.

Data acquisition and preprocessing
Magnetic resonance images were acquired at the People’s Hospital of Shanxi Province (3-T Siemens, Magnetom Trio, A Tim System). Subjects were placed in a supine position with eyes closed and in an awakened state, wearing headphones to reduce background noise. The subjects were restrained on foam pads to minimize head motion. A standard head coil was used for radio frequency transmission and reception of the magnetic resonance signal. Whole-brain 3D T1-weighted images were acquired using a sagittal 3-dimensional FLASH with the following parameters: repetition time (TR), 2300 milliseconds; echo time (TE), 2.95 milliseconds; resolution, 256×256; 160 continuous slices; acquisition time, 9 minutes 14 seconds. Diffusion tensor data were acquired using a coronal diffusion-weighted single-shot spin-echo planar imaging sequence, 12 diffusion gradient directions, diffusion sensitive factor b=1000 s/mm²; TR, 6000 milliseconds; echo time (TE), 90 milliseconds; flip angle, 90°; field of view, 240×240; 45 continuous slices, 3-mm-thick sections; sections gaps, 0; matrix-size, 128×128 voxels; acquisition time, 4 minutes 14 seconds.

Data analysis
Diffusion-weighted images were analyzed using the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL; http://www.fmrib.ox.ac.uk/fsl). Briefly, fat saturation was first used to remove scalp signal to avoid disrupting neural signal owing to chemical shift or ghosting artifacts, and the effects of gradient coil eddy currents were adjusted. Then, whole-brain voxel-wise analysis of FA data was performed by aligning each subject’s FA image into a higher-resolution FA standard space (Montreal Neurological Institute [MNI] according to a nonlinear registration algorithm implemented in TBSS). Next, FA maps were averaged to generate a mean FA image after image registration. The gained mean FA image was minimized to produce a template skeleton that embodies the center of all tracts. The FA skeleton was set at threshold to FA>0.2 to exclude peripheral tracts. Each subject’s aligned FA data were projected onto this template skeleton. The final data were then estimated using voxel-wise between-subject statistics (Randomise [a TBSS statistical tool] http://www.fmrib.ox.ac.uk/fsl/randomise/index.html) and were analyzed by cluster size with Threshold-Free Cluster Enhancement (TFCE).

A paired two-tailed t-test was used to compare group difference in mean FA between MDD patients and control subjects. The correlation of the FA value with the mental state of depression (HAMD), the illness course, or age of onset of the depression disorder was examined by a two-tailed Spearman’s correlation analysis. p<0.05 was considered statistically significant.

RESULTS
Participants
The current MDD patient and control groups were matched by age, gender ratio and years of education. Of all the depressive subjects, the average initial age was 32.35±6.52 years. The average illness course was 6.05±3.21 months, and the average HAMD score was 23.78±6.11.

TBSS-base FA difference between MDD patients and control subjects
In the present study, we analyzed our DTI images using the TBSS approach. Across the regions that connect emotion-related limbic and cortical areas we focused on, we found that MDD patients exhibited a significantly greater mean FA value than control subjects in the white matter of the left superior longitudinal fasciculus (MNI x, y, z coordinates, −27, −22, 21; t=4.88; p<0.001) (Figure 1), which was inconsistent with the previous study (cite TZ Jiang’s paper, PLoS ONE 7(5): e37561. doi:10.1371/journal.pone.0037561). Given that we had a larger sample size and set a higher threshold for TBSS analysis compared to the previous research, we believe our data represent the WM changes in this specific brain region, which suggests a potential compensatory regeneration of nerve fibers may occur in the early course of MDD pathogenesis.

Correlations analysis
Using a two-tailed Spearman’s correlation analysis, we analyzed the correlation between FA value of the left superior longitudinal fasciculus and HAMD, duration of illness or age of depression onset. No significant correlations were found between the FA value and the MDD patients’ HAMD score (p>0.05; Figure 2A), illness duration (p>0.90; Figure 2B), or age at illness onset (p>0.05; Figure 2C). These results were consistent with previous imaging reports (Drevets 2000; Yang et al. 2007; Zhu et al. 2011), and suggested that the white matter alteration in the left superior longitudinal fasciculus might occur prior to depressive disorder genesis.

DISCUSSION
In our study, we provided evidence that white matter alteration occurred in the left superior longitudinal fasciculus in adult MDD patients, which concurred with previous imaging reports (Dalby et al. 2010; Zhu et al. 2011; Zuo et al. 2012). However, our TBSS-based DTI studies among a relatively large sample size of
patient pool revealed an increased mean FA value in the left superior longitudinal fasciculus of medication-naive adult patients with MDD. Given that FA value is believed to be an indicator for the structural organization of the neural fibers in white matter, the increased FA value in MDD patients suggested a potential compensatory regeneration of nerve fibers that might occur in the early course of MDD development. Advanced understanding of the potential nerve fiber regeneration in the early course of MDD and its associated mechanisms will possibly shed light on a better strategy for MDD prevention and treatment.

The superior longitudinal fasciculus trajectory starts mainly from the forehead dorsolateral cerebrum hemisphere to the parietal lobe of the ipsilateral cerebral hemisphere, which constitutes the forehead dorsolateral cortex-parietal neural circuit (Schmahmann et al. 2007). It has been reported that the forehead dorsolateral cortex and its related neural circuits was thought to play a role in emotional dysregulation in affective disorders (Tekin & Cummings 2002). We did observe a change in the left superior longitudinal fasciculus white matter (WM) area, which suggested that this observed WM alteration might be involved in the depressive disorders. In our current study, we found a greater FA value in the left superior longitudinal fasciculus among patients with MDD compared to that was found in control subjects. This is inconsistent with
previous studies (Alexopoulos et al. 2002; Nobuhara et al. 2006; Murphy et al. 2007) in which a reduced FA value was reported not only in the left superior longitudinal fasciculus region (Zuo et al. 2012) but also in other cortical regions among subjects with later-onset depression. This discrepancy may be due to the differences in the age of subjects, age at onset of depression (Bhagat & Beaulieu 2004), illness duration, depression severity, drug administration (Nugent et al. 2006), subjects with hypertension (Pantoni 2002), subjects with early life stress (Mervaa et al. 2000), methods of imaging, data processing, and data analysis.

In the adult brain, stress, depression, and other insults may cause axonal damage, but simultaneously, the neurotrophic factors or other molecular players may facilitate neuronal repair, regeneration and reconstruction of the synapses as well to endorse a functional compensation. A previous study (Houenou et al. 2007) observed more reconstructed fibers in the left uncinate fasciculus of subjects with bipolar disorder compared to that was found in controls. It is also (Blood et al. 2010) found that the FA value was increased in the right ventral tegmental white matter in MDD subjects, which was coincident with a decrease of glial density and an increase of the ratio of axons to cell bodies. In our study, we observed a greater FA in subjects with MDD compared to that of in controls. While the underlined mechanisms remains unclear, it is possible that a compensatory reconstruction of nerve fibers exists in the early course of depression.

In addition, we found no significant correlation between the increased FA values in the left superior longitudinal fasciculus and recorded clinical features of depression, such as severity (as expressed in HAM-D scores), duration of illness, and age of illness onset. These results were consistent with previous imaging reports (Ma et al. 2007; Yang et al. 2007; Zou et al. 2008), and suggested that the white matter alteration in the left superior longitudinal fasciculus might occur prior to depressive disorder genesis.

We have to note that there are some limitations in the present study. Since TBSS is a method used to analyze the entire brain, it may yield more false positive findings compared to ROI analysis. Another limitation is the lack of follow-up of the subjects with MDD, which obstructed us to exclude subjects with bipolar disorder without following-up. Finally, the subjects using tobacco and/or alcohol were not eliminated in our analyses.

**CONCLUSION**

In summary, the observed greater FA value in the left superior longitudinal fasciculus in MDD patients may reflect the WM abnormality in the forehead dorsolateral cortex neural circuit, which is associated with mood regulation among depression patients. To maintain a relatively normal brain function, nerve fiber reconstruction may occur early for the functional compensation within the course of depressive disorder. Understanding of the potential nerve fiber regeneration in the early course of MDD and its associated mechanisms will possibly shade light on a better strategy for MDD prevention and treatment.

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