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## Research Report

**Prefrontal white matter abnormalities in young adult with major depressive disorder: A diffusion tensor imaging study**Lingjiang Li<sup>a,\*</sup>, Ning Ma<sup>a,1</sup>, Zexuan Li<sup>a</sup>, Liwen Tan<sup>a</sup>, Jun Liu<sup>b</sup>, Gaolang Gong<sup>c</sup>, Ni Shu<sup>c</sup>, Zhong He<sup>b</sup>, Tianzi Jiang<sup>c,\*</sup>, Lin Xu<sup>d</sup><sup>a</sup>Mental Health Institute, The Second Xiangya Hospital of Central South University, Changsha, Hunan, China<sup>b</sup>Department of Radiology, The Second Xiangya Hospital of Central South University, Changsha, Hunan, China<sup>c</sup>National Laboratory of Pattern Recognition, Automation Institute, Chinese Academy of Sciences, Beijing, China<sup>d</sup>Laboratory of Learning and Memory, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming, Yunnan, China

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## ABSTRACT

Prefrontal impairments have been hypothesized to be most strongly associated with the cognitive and emotional dysfunction in depression. Recently, white matter microstructural abnormalities in prefrontal lobe have been reported in elderly patients with major depressive disorder (MDD) using diffusion tensor imaging (DTI). However, it is still unclear whether the same changes exist in younger patients. In the present study, we first utilized DTI to detect prefrontal white matter in young adults with MDD. Nineteen first-episode, untreated young adults with MDD and twenty age- and gender-matched healthy controls were recruited. DTI and localizing anatomic data were acquired. Then, the regions of interest (ROIs) were located in prefrontal white matter at 4 mm inferior, and 0, 4, 8, 12, 16 and 20 mm superior to the anterior commissure–posterior commissure (AC–PC) plane, respectively. Compared with healthy controls, patients with MDD showed significantly lower fractional anisotropy (FA) values in prefrontal white matter at bilateral 20 mm, right 16 mm and right 12 mm above the AC–PC. Furthermore, there was no significant correlation between the FA value of any ROI and illness course as well as severity of depression. Together with previous findings, the present results suggest that microstructural abnormalities in prefrontal white matter may occur early in the course of MDD and may be related to the neuropathology of depression throughout adulthood from young to elderly.

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**1. Introduction**

Existing evidence, such as that shown in morphometric and functional imaging studies, suggests prefrontal impairments in patients with major depressive disorder (MDD). On the one hand, magnetic resonance imaging (MRI) studies found re-

duced prefrontal lobe volume in depression (Kumar et al., 2000), including both its gray matter (Coffey et al., 1993; Drevets et al., 1997; Kumar et al., 1998) and white matter (Bell-McGinty et al., 2002). On the other hand, functional imaging studies demonstrated lower glucose metabolism and cerebral blood flow in prefrontal cortex in depressed patients (Baxter et al.,

\* Corresponding authors. L. Li is to be contacted at Mental Health Institute, The 2nd Xiangya Hospital of Central South University, No. 139 Renmin Zhong Road, Changsha 410011, Hunan, PR China. Fax: +86 731 5360086. T. Jiang, National Laboratory of Pattern Recognition, Automation Institute, Chinese Academy of Sciences, Beijing, China. Fax: +86 10 62551993.

E-mail addresses: [lj2920@163.com](mailto:lj2920@163.com) (L. Li), [jiangtz@nlpr.ia.ac.cn](mailto:jiangtz@nlpr.ia.ac.cn) (T. Jiang).

<sup>1</sup> Lingjiang Li and Ning Ma contributed equally to this work.

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1989; Mayberg et al., 1999; Nobler et al., 2000). Moreover and specifically, MRI (Coffey et al., 1993, 1990; Soares and Mann, 1997) and postmortem (Thomas et al., 2002) studies showed deep white matter hyperintensities at the level of prefrontal cortex in late-life depression.

Currently, diffusion tensor imaging (DTI), a new MRI technique, has also been used to study white matter and neural fiber tracts by measuring the movement of water molecules. Such studies in depression have reported microstructural white matter abnormalities in widespread prefrontal regions (Taylor et al., 2004; Nobuhara et al., 2004, 2006; Bae et al., 2006; Alexopoulos et al., 2002) and found prefrontal white matter alterations to be linked to neuropsychological function (Murphy et al., 2007). Moreover, Rusch et al. (2007) reported an association between a lifetime history of major depression and inferior frontal white matter integrity among women with borderline personality disorder. However, all these DTI studies recruited elderly patients, and no published DTI studies have detected the white matter integrity of prefrontal lobe in young adult depressed patients. Despite growing evidence supported prefrontal cortical abnormalities in younger as well as elderly depression (Botteron et al., 2002), postmortem study reported reduction of packing density and glial cells number in dorsolateral prefrontal cortex only in older rather than younger depressive patients (Miguel-Hidalgo et al., 2000). These complex findings cause a puzzle on what changes would be in white matter integrity of prefrontal lobe in young adult depression. However, it is worthy of clarifying such changes. Thus, we designed this study to determine if the prefrontal white matter microstructure of untreated young depressed adults is impaired in a pattern that is similar to the impairments found in older depressed adults.

## 2. Results

Patients with MDD exhibited lower fractional anisotropy (FA) values than did healthy controls in all regions of interest (ROIs)

**Table 1 – The regional white matter fractional anisotropy values of 19 patients with MDD and 20 healthy controls**

Region of interest	Patients (n=19)		Controls (n=20)		t (df=37)	p
	Mean	SD	Mean	SD		
Right AC-4	0.3011	0.0592	0.3165	0.0489	-0.891	0.379
Left AC-4	0.2937	0.0671	0.3155	0.0481	-1.172	0.249
Right AC0	0.3042	0.0691	0.3185	0.0517	-0.734	0.468
Left AC0	0.2974	0.0693	0.3295	0.0501	-1.666	0.104
Right AC+4	0.3189	0.0676	0.3210	0.0436	-0.113	0.910
Left AC+4	0.3111	0.0556	0.3295	0.0599	-0.995	0.326
Right AC+8	0.3121	0.0879	0.3360	0.0506	-1.047	0.302
Left AC+8	0.3132	0.0839	0.3320	0.0608	-0.806	0.425
Right AC+12	0.3105	0.0774	0.3615	0.0545	-2.389	0.022
Left AC+12	0.3211	0.0789	0.3605	0.0554	-1.815	0.078
Right AC+16	0.3105	0.0739	0.3565	0.0632	-2.092	0.043
Left AC+16	0.3195	0.1089	0.3460	0.0432	-1.009	0.319
Right AC+20	0.2963	0.0598	0.3570	0.0631	-3.079	0.004
Left AC+20	0.3037	0.0587	0.3505	0.0650	-2.356	0.024

AC, anterior commissure.

(Table 1). However, the significantly differences were in four regions, including bilateral 20 mm above the anterior commissure-posterior commissure (AC-PC) plane (AC+20) (left:  $t = -2.356$ ,  $p = 0.024$ ; right:  $t = -3.079$ ,  $p = 0.004$ ), right 16 and 12 mm above the AC-PC plane (AC+16:  $t = -2.092$ ,  $p = 0.043$ ; AC+12:  $t = -2.389$ ,  $p = 0.022$ ). Furthermore, there was no significant correlation between the FA value of any ROI and Hamilton Depression Rating Scale (HDRS) scores as well as illness course. We did not correct these results because we were more concerned about the risk of type II error.

## 3. Discussion

To our knowledge, this is the first study using ROI method to examine prefrontal white matter microstructure in young depressed adults. The young adults with MDD showed significant lower FA values in prefrontal white matter at bilateral 20 mm, right 16 and 12 mm above the AC-PC plane, which respectively locate at the level of superior and middle frontal gyri and contain fibers of the dorsolateral prefrontal circuit (Middleton and Strick, 2001). Our results support the findings of previous DTI studies in elderly depression, reporting white matter structural alterations in widespread prefrontal regions (Nobuhara et al., 2004, 2006; Taylor et al., 2004; Alexopoulos et al., 2002). Similar to our findings, one recent study with a much larger sample size reported that elderly depression exhibited lower FA values in the white matter of right and left superior frontal gyri and left middle frontal gyrus (Bae et al., 2006). In addition, our findings were quite congruent with smaller white matter volume in the right middle frontal gyrus in geriatric depression (Bell-McGinty et al., 2002). So, it seems that there are microstructural impairments of prefrontal white matter both in young and elderly depression. More interestingly, Bae et al. (2006) found that early-onset depression exhibited greater FA differences in prefrontal white matter compared with controls than did late-onset depression (cut-off at 50 years old). Furthermore, prefrontal lobe volume loss has been observed both in late-onset and in early-onset depression (Kumar et al., 1998). Thus, our present study and other lines of evidence strongly support that microstructural abnormalities in prefrontal white matter are related to depression throughout adulthood from young to elderly. At an integrated level, the dorsolateral prefrontal circuit originated in prefrontal cortex, projects to striatum and pallidum, then continues to thalamus, and finally returns to the cortex, functionally performing important effortful regulation of affective states and behaviors (Phillips et al., 2003) and modulating executive function (Tekin and Cummings, 2002). In this case, our findings, not only as a complement for previous ones, further explain certain pathogenesis on how the prefrontal-subcortical circuit plays an important role in emotion regulation in lifetime depression.

Consistent with the findings by Bae et al. (2006), we found no statistically significant correlation between DTI measures of any region and depressive severity as well as the illness duration, which was contrast to recent report (Nobuhara et al., 2006). This may be due to the relatively small sample size and narrow HDRS scores range in the present study. In addition, differences in mean age of subjects, age of depression onset, illness duration and drug administration, could contribute to

the inconsistency. However, according to Bae et al. (2006), these findings suggest that prefrontal white matter abnormalities may increase the risk of developing depression but have no association with depression severity and illness duration.

There are several limitations to this study, including the small sample size, large range of illness course (from 3 to 24 months), the absence of apparent diffusion coefficient (ADC) and type I error (uncorrected). In order not to reduce the power of the study further, we allowed the type II error rate to increase. Moreover, our results demonstrated that the standard deviations are somewhat high, and in general standard deviations seem to be higher among patients than among controls. One reason may be the head motion. Another reason may be the heterogeneity of patients caused by stressful live events occurring before depression onset in some cases, variant degree of anxiety somewhat common in depression, etc. In spite of these limitations, our findings suggest that prefrontal white matter pathology may occur early in the course of MDD. However, more work in larger sample of younger depressed subjects with better homogeneity should be needed to further explore such suggestion, the relationship between these abnormalities and response to treatment, the risk of relapse.

## 4. Experimental procedure

### 4.1. Participants

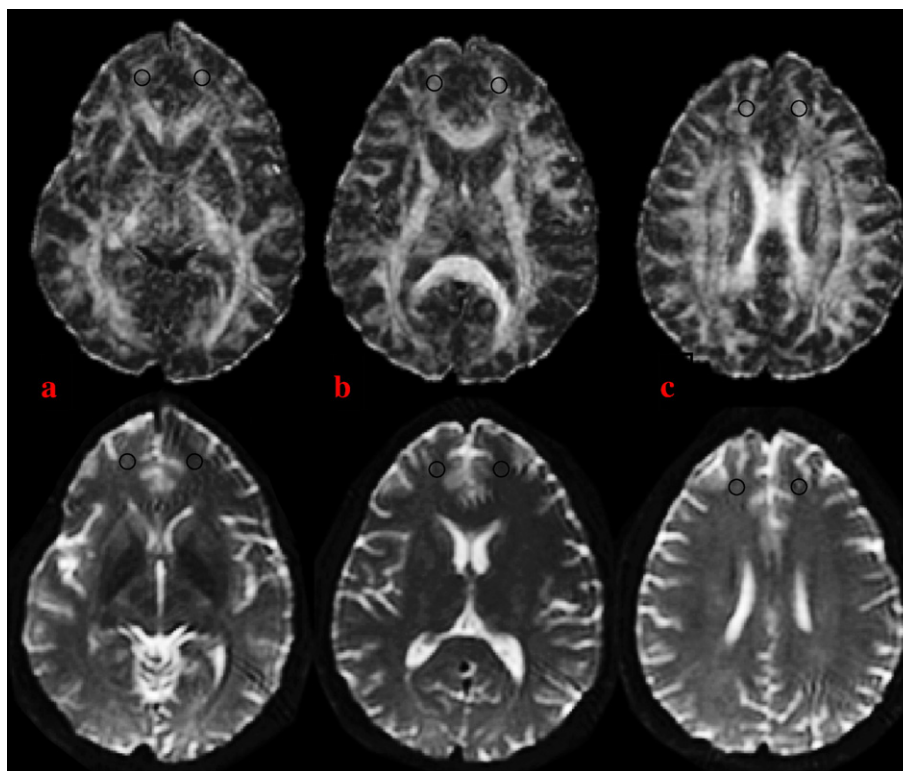
Participants in this study included 19 right-handed MDD patients (15 females; aged 20–41 [mean=28.1, SD=7.4] years)

and 20 matched right-handed healthy controls (16 females; aged 19–42 [mean=26.7, SD=6.9] years). The education years were similar between patients and healthy controls (mean age, MDD=11.5 years, SD=3.5; control=12.7 years, SD=2.8,  $p>0.05$ ). All patients were recruited from outpatients at department of psychiatry, the Second Xiangya Hospital, Central South University, China, who were diagnosed by Structured Clinical Interview for DSM-IV (SCID). These patients had scores ranged from 22 to 32 (mean=28.0, SD=3.6) on the 17-item HDRS at the time of study. All patients were first-episode and had never received psychopharmacological medication in their lives, with mean age of illness onset of 26.8 (SD=7.5) years and mean illness duration of 3 to 24 (mean=10.7, SD=7.3) months.

Shared exclusion criteria for both patients and healthy controls included any history of loss of consciousness, DSM-IV diagnosis of substance abuse or dependence, mental retardation and/or serious medical (including hypertension, diabetes etc.) or neurological illness. Additional exclusion criteria for patients included any lifetime psychiatric disorder other than MDD. Additional exclusion criteria for healthy controls included any personal history of psychiatric illness or any family history of major psychiatric or neurological diseases in their first degree relatives. The study was approved by the Ethics Committee of the Second Xiangya Hospital of Central South University, China. All subjects participated voluntarily and signed written informed consent.

### 4.2. Image acquisition and processing

Diffusion tensor imaging was performed on a 1.5-Tesla GE scanner (Twin-speed, Milwaukee) using a standard head



**Fig. 1** – Map with the representative ROIs at (a) 4 mm below the anterior commissure, (b) 8 and (c) 20 mm above the anterior commissure for the FA (the top row) and  $b=0$  (the bottom row) images.



radiofrequency coil. In order to control artifacts of DTI, we placed cushions around the subjects' head to minimize head movement and kept the constant temperature and humidity and homogeneous magnetic field before each scan. Single-shot echo planar (EPI) diffusion-weighted imaging was aligned with the AC-PC plane using following parameters: repetition time/echo time (TR/TE), 12,000/105 ms; acquisition matrix, 128×128; field of view (FOV), 24×24 cm; NEX, 5; slice thickness, 4 mm; no gap, 30 contiguous axial slices. The diffusion sensitizing gradients were applied along 13 non-collinear directions ( $b=1000$  s/mm<sup>2</sup>), together with an acquisition without diffusion weighting ( $b=0$ ).

Three pairs of eigenvalues ( $\lambda_1, \lambda_2, \lambda_3$ ) and eigenvectors were derived by diagonalization of the diffusion tensor matrix. And then the FA value was calculated (Basser and Pierpaoli, 1996).

Circular ROIs chosen encompassed 8 voxels in diameter and were separately positioned bilaterally in frontal white matter of seven consecutive slices, starting from the next slice to the most caudal slice displaying genu of corpus callosum on the AC-PC plane. All ROIs were 56.6 mm<sup>2</sup> size and were drawn in white matter on both FA and  $b=0$  maps. Fig. 1 illustrates representative ROIs at 4 mm below the AC-PC plane (AC-4), 8 and 20 mm above the AC-PC plane (AC+8 and AC+20) for FA and  $b=0$  images. Mean FA values were determined for all ROIs.

The inter-rater reliability was established by having two raters to independently draw ROIs at each slice. The intra-class correlation coefficients between the two raters were all over 0.83.

#### 4.3. Statistic analysis

Inter-group (patients vs. controls) differences in mean FA value for each region were examined with independent t-test. Spearman's rank correlation coefficient ( $r_s$ ) was used to test the correlation between the mean FA value of each region and HDRS scores as well as illness duration.  $p$ -value (two-tailed) lower than 0.05 was considered statistically significant.

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