Alterations of white matter integrity in adults with major depressive disorder: a magnetic resonance imaging study

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Objective: The purpose of our study was to investigate alterations of white matter integrity in adults with major depressive disorder (MDD) using magnetic resonance imaging (MRI). **Methods:** We performed diffusion tensor imaging with a 3T MRI scanner on 45 patients with major depression and 45 healthy controls matched for age, sex and education. Using a voxel-based analysis, we measured the fractional anisotropy (FA), and we investigated the differences between the patient and control groups. We examined the correlations between the microstructure abnormalities of white matter and symptom severity, age of illness onset and cumulative illness duration, respectively. **Results:** We found a significant decrease in FA in the left hemisphere, including the anterior limb of the internal capsule and the inferior parietal portion of the superior longitudinal fasciculus, in patients with MDD compared with healthy controls. Diffusion tensor imaging measures in the left anterior limb of the internal capsule were negatively related to the severity of depressive symptoms, even after we controlled for age and sex. **Conclusion:** Our findings provide new evidence of microstructural changes of white matter in non–late-onset adult depression. Our results complement those observed in late-life depression and support the hypothesis that the disruption of cortical–subcortical circuit integrity may be involved in the etiology of major depressive disorder.

Objectif : L'étude visait à enquêter sur des altérations de l'intégrité de la matière blanche chez les adultes atteints d'un trouble dépressif majeur (TDM) en utilisant l'imagerie par résonance magnétique (IRM). **Méthodes :** Nous avons procédé à une imagerie du tenseur de diffusion au moyen d'un appareil IRM 3T sur 45 patients atteints de dépression majeure et 45 participants témoins en bonne santé appariés selon l'âge, le sexe et l'éducation. Nous avons effectué une analyse voxel par voxel pour mesurer l'anisotropie fractionnelle (AF) et nous avons étudié les différences entre les patients et les participants témoins. Nous avons examiné les liens entre les anomalies microstructurelles de la matière blanche et la gravité des symptômes, l'âge à l'apparition de la maladie et la durée cumulative de celle-ci respectivement. **Résultats :** Nous avons constaté une diminution importante de l'AF dans l'hémisphère gauche, y compris le segment antérieur de la capsule interne et le lobule pariétal inférieur du faisceau longitudinal supérieur chez les patients examinés par TDM comparativement aux participants témoins en bonne santé. On a établi un lien négatif entre les mesures d'imagerie du tenseur de diffusion dans le segment antérieur gauche de la capsule interne et la gravité des symptômes de dépression, même après avoir tenu compte de l'âge et du sexe. **Conclusion :** Nos constatations produisent de nouvelles preuves de changements microstructurels de la matière blanche dans les cas de dépression d'apparition non tardive chez l'adulte. Nos résultats complètent ceux qu'on a observés dans les cas de dépression de fin de vie et appuient l'hypothèse selon laquelle la perturbation de l'intégrité du circuit cortical–sous-cortical joue un rôle dans l'étiologie du trouble dépressif majeur.

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Introduction

Major depressive disorder (MDD), the most common psychiatric disorder and the most important precursor of suicide, will be the second cause of global disease burden by the year 2020, according to the World Health Organization. Therefore MDD is a pressing public health problem.

Although the etiology and the pathophysiology of MDD are not fully understood, increasing evidence is challenging the concept that MDD is a "functional" disorder.[1] In vivo, structural and functional imaging studies have confirmed that abnormalities of some specific regions of the brain (e.g., the frontal cortex,[2,3] cingulate cortex,[2,4] basal ganglia,[5–7] hippocampus[4,8] and parietal lobe[3,9,10]) are involved in the etiology of MDD. Postmortem studies of people with MDD have also revealed abnormalities in the frontal cortex[11] and basal ganglia.[12] In the last 2 decades, it has been suggested that cortical–subcortical neuronal circuits play an important role in the pathogenesis of MDD, especially the frontal–striatal–thalamic neuronal circuits.[6,13,14] The limbic–thalamic–cortical networks have also been reported to be crucial in the etiology of MDD.[6,8,9]

Paying close attention to the abnormalities of neuroanatomical circuits, white matter, which connects regions of the brain anatomically and functionally, has been considered to play an important part in the pathophysiology of MDD. Structural imaging studies have reported a significant increase of white matter hyperintensities, which suggests that a change in water content in the frontal[15,16] and parietal[16] lobes occurs in patients with major depression, mostly in late-life depression. Some studies have reported significant bilateral reduction of white matter volume in the anterior cingulate cortex, the gyrus rectus[2] and the hippocampus[8] in patients with MDD. A magnetic resonance spectroscopy (MRS) study involving patients with metastatic breast cancer showed that chemotherapy-induced reductions in the levels of glutamate/glutamine observed in the white matter of the centre semiovale region were associated with combined suicidal ideation and depressive symptoms.[17] Other MRS studies of MDD revealed higher levels of myo-inositol/creatine and choline/creatine in frontal white matter.[18] Some studies suggested that cognitive impairment was correlated with lesions in white matter of patients with major depression.[7,19]

Diffusion tensor imaging (DTI) is a magnetic resonance imaging (MRI) technique that measures the diffusion of water molecule in tissues; DTI is particularly useful for examining organized areas of the brain such as white matter and neural fibre tracts.[20] It yields an index of principle directionality of diffusion termed fractional anisotropy (FA).[21] In white matter, the principle direction of water diffusion is along the myelinated tracts, so DTI is a quantitative method to evaluate the integrity of white matter connectivity in vivo. The 2 major methods employed to analyze DTI data are manual measurements of regions of interest (ROIs) and voxel-based analysis. A conspicuous limitation of the manual ROI method is its lack of standard guidelines for the delineation of specific regions of the brain that can not avoid artificial errors completely. However, voxel-based analysis has no such shortage and can detect the abnormal regions throughout the brain. Both approaches have been widely used in neuroimaging studies of psychiatric diseases such as schizophrenia,[22] bipolar disorder[23] and depression.[24–27]

Previous DTI studies of depressed patients using the ROI method mostly concentrated on late-life depression or geriatric depression. They found consistently decreased FA values in the white matter of the frontal cortex[24–27] and the anterior cingulate cortex (ACC),[25] suggesting the disruption of the structural integrity of white matter in geriatric patients with depression. Some studies of late-life depression mentioned that FA values of the inferior frontal lobe were negatively related to the severity of depression[24] and that lower FA values lateral to the ACC were associated with a low rate of remission.[27] However, fewer studies have focused on white matter abnormalities (e.g., white matter hyperintensities;[28] the reduction of the white matter volume in the frontal lobe;[29] and decreased FA values in the right middle frontal gyrus, the left lateral occipitotemporal gyrus, the subgyral and angular gyri of the right parietal lobe[30]) in younger patients with MDD. These studies had small samples and relatively low field strength MRI systems.

In the present study, we performed a voxel-based analysis using DTI with a 3.0 Tesla (3T) MRI scanner to explore the relation between the integrity of white matter and the pathophysiology of MDD in adults. We hypothesized that, in this group of patients with non–late-onset MDD, microstructural abnormalities of white matter that otherwise appeared normal could be detected and that these alterations would be correlated with depressive symptoms.

Methods

Participants

We recruited patients with diagnosed MDD from the Mental Health Center, West China Hospital of Sichuan University. We also advertised to recruit healthy controls from the 5 city districts of Chengdu, China. We matched participants in both groups for age, sex and education. An experienced psychiatrist (X.S.) performed a psychiatric examination for all patients to diagnose MDD. We assessed the severity of depressive symptoms using the 17-item Hamilton Depression Rating Scale (HDRS).[31] The patients were depressed and taking antidepressant medications at the time of the exam.

To enrol in our study, participants met the following inclusion criteria. Participants fulfilled the *Diagnostic and statistical manual of mental disorders*, fourth edition (DSM-IV)[32] criteria for MDD, were aged 18–55 years, experienced their first episode of depression when they were younger than 50, had experienced a first episode of depression or had responded to previous treatment with antidepressants, and had a total HDRS score greater than 18. We excluded people who had primary neurologic diseases such as dementia or stroke; had other major psychiatric disorders, including schizophrenia, bipolar affective disorder, personality disorder and substance abuse or dependence; had severe or acute medical conditions; had gravidity; or had metal indwelling devices, precluding MRI.

We screened eligible controls through a diagnostic interview: the Structured Clinical Interview for DSM-IV Axis I Disorders, nonpatient edition (SCID-NP).[33] A trained rater examined these participants to rule out current or past DSM-IV axis I disorders among them and their first-degree relatives.

All participants were right-handed and provided written informed consent after receiving a detailed explanation of the study. The ethical committee of West China Hospital of Sichuan University approved this study.

MRI acquisition

For all participants, we performed MRI examinations at the Department of Radiology in West China Hospital using a 3T MRI scanner (Signa; GE Medical Systems) with a standard 8-channel phase array head coil. We provided ear plugs for each participant to reduce noise interference during the scan. We used foam cushions offered by the manufacturer to increase the comfort of participants and decrease head motion.

Before the acquisition of each image, we applied a strict quality assurance scan to ensure the stability of the signal. We obtained the diffusion images using a single-shot spin-echo echo planar imaging (SE-EPI) sequence. We applied the diffusion sensitizing gradients simultaneously along 15 noncolinear directions ($b = 1000 \, s/mm^2$) as well as an acquisition without diffusion weighting ($b = 0$). We acquired 42 contiguous slices with a 3-mm slice thickness and no gaps. The other acquisition parameters were: repetition time (TR) = 10 000 ms, echo time (TE) = 70.8 ms, number of excitations (NEX) = 2, a 128×128 matrix and field of view (FOV) = 24×24 cm. The total acquisition time was 5 minutes and 40 seconds. An experienced neuroradiologist (Q.C.), who was blinded to the group of participants, reviewed all the scans to exclude obviously gross abnormalities.

Statistical analysis

We processed all diffusion images using a free software DTI studio (Department of Radiology, Johns Hopkins University School of Medicine, Baltimore, MD; available at http://cmrm.med.jhmi.edu/) to generate the FA maps on a pixel-by-pixel basis. We determined 3 eigenvalues ($\lambda_i = 1, 2, 3$) and eigenvectors ($\varepsilon_i = 1, 2, 3$) for each voxel. The principle direction of each point was given by the eigenvector that corresponded to the largest eigenvalue.[21]

We then performed a voxel-based analysis under statistical parameters maps (SPM2; Wellcome Department of Cognitive Neurology, Institute of Neurology, University College London, UK; available at www.fil.ion.ucl.ac.uk/spm/software/). We normalized all of the $b = 0$ images to the standard Montreal Neurological Institute (MNI) space to estimate the normalization parameters using the EPI template supplied by SPM2, and the original voxel size of $1.875 \times 1.875 \times 3$ mm^3 was interpolated to a final voxel size of $1 \times 1 \times 1$ mm^3. We then applied these parameters to the FA maps to normalize them to the MNI space. We spatially smoothed the normalized FA maps with a 6-mm full width at half maximum isotropic Gaussian kernel to improve the signal-to-noise ratio.

We performed analysis of variance (ANOVA) in depressed patients, subdivided by medication type, to investigate the possible effect of medication type on FA values. We considered clusters to be statistically significant at $p < 0.001$ (uncorrected). We then performed a voxel-based analysis using a 2-sample t test between patients and healthy controls. We selected a relative threshold of 0.8 to include almost all white matter and exclude grey matter and cerebrospinal fluid (CSF). We considered spatially contiguous clusters with 2-tailed p values lower than 0.001 (uncorrected) and 0.05 at voxel level after false discovery rate (FDR) correction to be significant differences between the patients and the controls. We overlapped the white matter regions of the brain representing significantly different FA values between the 2 groups on the mean normalized and smoothed FA maps. We transformed the coordinates into the Talairach space.

We manually drew the volumes of interest (VOIs) on the basis of the significantly different clusters between both groups in the 2-sample t test. We then extracted the mean FA values of the VOIs. We used SPSS 11.5 for Windows (SPSS Inc.) for the successive analysis. We applied a partial correlation model controlling for age and sex to test the correlation between the decreased FA values and HDRS scores, age at the onset of illness and cumulative illness duration, respectively. All the tests were 2-tailed, and we considered the results to be significant at a threshold of $p < 0.05$.

Results

We enrolled 45 patients with diagnosed MDD (15 men, 30 women) aged 18–52 (mean 33.2, standard deviation [SD] 8.9) years and 45 healthy controls (15 men, 30 women) aged 18–53 (mean 31.0, SD 10.3) years. The mean number (and SD) of years of education was 13.4 (3.6) years for patients and 12.9 (3.4) years for controls. The groups were well matched in age ($t_{88} = 1.09$, $p = 0.28$) and years of education ($t_{88} = 0.60$, $p = 0.55$). The cumulative duration of illness for patients was 1–84 (mean 20.0, SD 18.4) months. Among patients, the onset of illness occurred at an average age of 31.6 (SD 8.9) years. The mean HDRS score was 23.8 (SD 3.3). Of the 45 patients, 7 were treated with tricyclic antidepressants, 23 with selective serotonin reuptake inhibitors (SSRI) and 15 with selective serotonin noradrenaline reuptake inhibitors (SNRI). No patient had received eletroconvulsive treatment (ECT).

The ANOVA model revealed no differences in FA values among the groups of depressed patients subdivided by type of medication. In a voxel-by-voxel contrast, we observed a significant reduction of white matter FA values among patients with MDD compared with healthy controls in 2 regions of the left hemisphere: the white matter in the anterior limb of the left internal capsule (ALIC) (Fig. 1 and Table 1) and the inferior parietal portion of the left superior longitudinal fasciculus (SLF) (Fig. 1 and Table 1). We observed no significant increases in FA values in depressed patients compared with healthy controls.

Lower FA values in the left ALIC were significantly correlated with higher HDRS scores ($r_{41} = -0.33$, $p = 0.032$), when controlled for age and sex. We observed no statistically sig-

nificant correlation between white matter FA values in the inferior parietal portion of the left SLF and HDRS scores ($r_{41} = -0.11$, $p = 0.483$). After we controlled for age and sex, the age at onset of illness did not correlate significantly with FA values in the left ALIC ($r_{41} = -0.10$, $p = 0.512$) or in the left SLF ($r_{41} = 0.11$, $p = 0.483$), nor did the cumulative duration of illness ($r_{41} = 0.10$, $p = 0.511$; $r_{41} = -0.11$, $p = 0.484$).

Discussion

We observed decreased white matter FA values in the left ALIC and the inferior parietal portion of the left SLF in adult patients with MDD, and there was a statistically negative correlation between the FA values in the left ALIC and HDRS scores representing symptom severity of MDD, regardless of differences in age and sex. To our knowledge, this is the first DTI study using a high field-strength MRI system and voxel-based analysis to determine white matter abnormalities in a large group of adults with depression. A previous DTI study involving adults with depression had a small sample.[30]

Our findings provide new evidence of microstructural abnormalities in white matter with an otherwise normal appearance in adult patients with MDD. Using voxel-based analysis, we have provided evidence of white matter changes
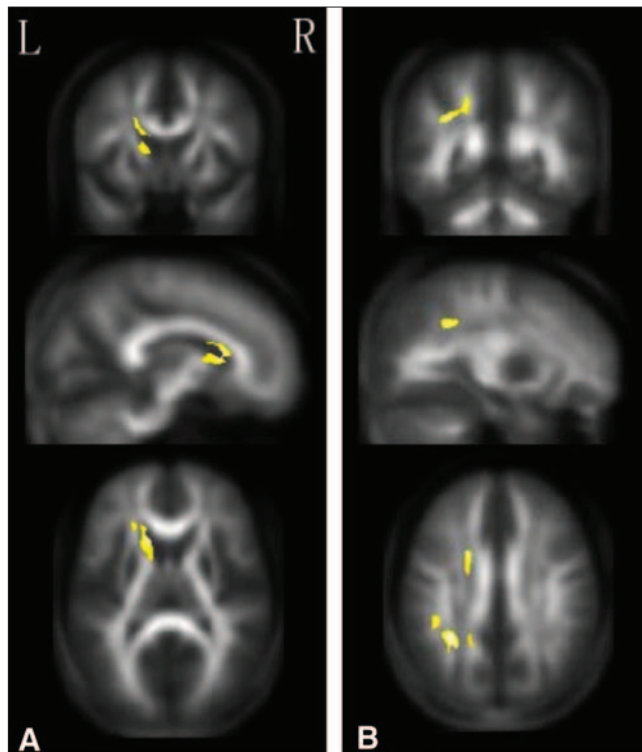

Fig. 1: White matter regions with significantly reduced fractional anisotropy values in 45 adult patients with major depressive disorder compared with 45 healthy controls. The coloured regions indicate the white matter in (**A**) the left anterior limb of the internal capsule and (**B**) the left superior longitudinal fasciculus. Results were considered to be statistically significant at $p < 0.05$ at voxel level after false discovery rate correction.

in the left ALIC. According to the theory of neuronal circuits, the alterations of the left ALIC might reflect the disconnection of cortical and subcortical regions. The frontal–striatal–thalamic neuronal pathway contains the frontal cortex, the striatum, the globus pallidus and the thalamus and includes 5 circuits: the motor circuit, the oculomotor circuit, the dorsolateral prefrontal circuit, the lateral orbitofrontal circuit and the anterior cingulate circuit. Dysfunctions of each circuit may lead to different syndromes. For example, dysfunctions of the dorsolateral prefrontal circuit, the orbitofrontal circuit and the anterior cingulate circuit may lead to damage of executive function, emotional lability and motivation, which can commonly be seen in patients with MDD.[13] Sackeim[34] also reported that the dorsolateral prefrontal circuit and the lateral orbitofrontal circuit are prominently associated with MDD. Hence there is a close relation between neuronal circuit damage and the pathophysiology of MDD. Since the frontal–striatal–thalamic neuronal circuits consisted of massive bundles of fibres converging in the ALIC,[35] our finding of reduced FA values in the left ALIC supported the theory that damage of the frontothalamic pathway might be associated with MDD.

Most previous DTI studies of late-life MDD using the ROI method did not choose the ALIC as an ROI, so they were unable to report corresponding FA values in this region of the brain. Only 1 study included the bilateral ALIC as an ROI, and it failed to reveal significant differences of FA values between patients with late-life MDD and healthy controls.[25] Conversely, we observed significantly reduced FA values in the left ALIC. These discrepancies may be explained by the different age at onset of illness among participants in our study or by our use of voxel-based analysis rather than the ROI method. However, white matter in the frontal cortex, the ACC and the ALIC belongs to the frontothalamic circuits so our findings, together with those of previous DTI studies, provide further evidence of microstructural alterations of the neural circuits in the white matter of patients with depression and prove the important role of the structural integrity of white matter in the etiology of MDD.

Only 1 small-scale DTI study[30] of adult patients with MDD, which involved mostly women, used voxel-based analysis; it did not demonstrate a significant difference in FA values in the ALIC. However, significant clusters found in that study did not survive after FDR correction,[30] whereas our results remained statistically significant after FDR correction. The main reason for this difference was probably the different

Table 1: Centre of clusters showing a significant decrease in fractional anisotropy values in adult patients with major depressive disorder compared with healthy controls

Tract*	Cluster size	t score	p value†	Talairach x	y	z
Anterior limb of internal capsule	1603	4.95	0.037	−13	18	10
Superior longitudinal fasciculus	1777	5.05	0.037	−33	−47	29

*Left hemisphere.
†Corrected for false discovery rate.

sample size and sex ratio in the samples. In addition, more advanced technologies such as high field strength, more nonlinear directions and thinner slice thickness may also contribute to such difference.

We also found that FA values decreased in the parietal portion of the left SLF. This finding is congruent with those of previous functional neuroimaging studies of decreased cerebral blood flow in the left parietal lobe in adolescents with MDD.[36] Freedman[10] reported that parietal lobe integrity was disrupted in patients with MDD because they manifested poorly in tactile learning problems. Our findings, together with those of Freedman, further support the hypothesis that the damage of white matter integrity may be relevant to functional deficit in the corresponding cortex.

It is known that the SLF is a major bidirectional association tract connecting large parts of the frontal cortex with the parietal, occipital and temporal lobes. For the frontal cortex, fibres of SLF especially terminate in or originate from the dorsal and ventral premotor and prefrontal cortices, including Brodmann areas 6, 8, 9 and 46, according to a new study of the association fibre pathways in the human brain.[37] All these areas are known as parts of the dorsolateral prefrontal cortex (DLPFC). The SLF is part of the frontal–subcortical circuits that participate in the modulation of the DLPFC function. Hypofunctions of the DLPFC in patients with MDD have been well explored.[38] The decreased FA values that we observed in the left SLF at the inferior parietal portion focus on the disruption of the white matter integrity in frontal–subcortical circuits connecting with DLPFC and provide further evidence of dysfunctions of DLPFC circuits as a core feature of pathology in MDD. This finding also suggests that the local damage of white matter integrity may further affect the function of distant anatomically connected cortices.

Still, previous DTI studies of patients with late-life MDD did not include the parietal lobe as an ROI, so their results did not contain data on FA values in this area. Ma and colleagues[30] found that there were white matter abnormalities in the subgyral and angular gyri of the right parietal lobe in adult patients with MDD, whereas our results revealed a significant reduction of FA values in the left inferior parietal portion of the SLF. The varied sample sizes and sex ratios may explain the different results. Ma's findings were not significant after FDR correction; our results remained significant after FDR correction for multiple comparisons. Furthermore, our results were also consistent with the hypothesis that lesions in the left hemisphere are commonly associated with depression.[14]

We found the left ALIC FA values negatively correlated with HDRS scores, even when controlled for age and sex. Similarly, one study using the circular ROI method reported that FA values in the inferior frontal lobe (orbitofrontal circuits) were negatively related to severity of late-life depression.[24] As mentioned, tracts of the fronto–subcortical circuits converge in the ALIC.[35] Dysfunctions of these circuits may result in many kinds of symptoms that are common among patients with MDD.[13] Our findings support the theory that there are positive correlations between damage to white matter integrity and the severity of depressive symptoms. Owing to the mean age of

participants, different scanning parameters and a different method of analysis, another study that used the oval ROI method failed to demonstrate the relation between FA values and the severity of depressive symptoms in patients with late-life MDD.[25]

We found no correlation between FA values in the left ALIC and age at the onset of illness; this finding is consistent with the results of a large-scale study involving patients with late-life depression that reported no relation between DTI measures in the bilateral internal capsule and age at onset of illness.[25] We found no relation between FA values in the left SLF and age at onset of illness. One study suggested that age was associated with alterations in DTI measures in frontal white matter, the posterior limb of the internal capsule and the genu of the corpus callosum.[39] We speculate that in the left ALIC and the left parietal portion of the SLF, age at onset of illness is not the main reason for different FA values.

Shergill and colleagues[22] proposed that the cumulative duration of illness may affect FA values in patients with schizophrenia; however, no correlation between duration of illness and FA values in patients with MDD has been reported. We found no relation between DTI measures and cumulative duration of illness in adult patients with MDD. Whether alterations of FA values are associated with genetic factors requires further investigation.

A number of factors increased the reliability of our results. Although we used voxel-based analysis, we were able to control type I errors in part by setting a more rigorous entry magnitude and using FDR correction. Our sample was large (45 patients and 45 controls), and we used a 3.0 T MRI scanner, which has a higher resolution than 1.5 T MRI systems used in previous DTI studies. Despite patients in our study taking antidepressant medication, we observed no differences in FA values among groups of depressed patients subdivided by type of medication after we performed ANOVA. Finally, we had more noncolinear acquisition directions and thinner slice thickness.

The principal limitation of our study is the large range in ages among participants and the cumulative duration of illness. Furthermore, because it was not a follow-up study, we were unable to precisely explore the dynamic changes of FA values, the relation between those changes and participants' response to treatment, and duration of illness.

Conclusion

In summary, we have demonstrated alterations in white matter integrity in the left ALIC and in the inferior parietal portion of the left SLF in adult patients with MDD. These findings provide new evidence of microstructral changes in the white matter of adults with non–late-onset depression. These data complement the abnormalities of white matter observed in late-life depression and suggest that the disruption of cortical–subcortical circuit integrity is involved in the etiology of MDD. Prospective studies in medication-naive patients that use advanced techniques such as DTI fibre tracking are required to explore the precise relation between FA values and the severity of depression, age at onset of ill-

ness, response to treatment, risk of relapse and genetic factors.

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