White Matter Integrity Deficit in Treatment-naïve Adult Patients with Major Depressive Disorder

从未接受治疗抑郁症患者之脑白质完整性缺损

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Abstract

Objectives: The fronto-limbic system plays critical roles in cognitive functions, including emotion. This is supported by recent reports in the studies of major depressive disorder using diffusion tensor imaging of the brain. This study examined white matter integrity and correlations to cognitive function in treatment-naïve adult patients with major depressive disorder.

Methods: Fractional anisotropy values, derived from diffusion tensor imaging, were compared in 18 treatment-naïve adult patients with major depressive disorder and 18 well-matched healthy controls by voxel-based analysis. Correlation of fractional anisotropy with performance of cognitive tests was also analysed.

Results: Lower fractional anisotropy values in the bilateral medial frontal gyri, right subgyral frontal and temporal lobes, and left middle frontal and cingulate gyri were observed in patients than in controls. However, no correlation between mean fractional anisotropy values and cognitive scores was found.

Conclusion: These findings support the notion that deficit of white matter integrity in the fronto-limbic system may be the neural substrate of major depressive disorder.

Key words: Anisotropy; Cognition; Depressive disorder, major; Diffusion tensor imaging; Limbic system

Introduction

It is well documented that the fronto-limbic system is composed of the frontal cortex, cingulate, and medial temporal cortex, which play critical roles in cognitive functions, such as memory, decision-making, inference, executive control, attention, language, and emotion. Major depressive disorder (MDD) is a mood disorder characterised by depressed mood and loss of interest or pleasure. Recently, 2 studies using diffusion tensor imaging (DTI) found that...
adult patients with MDD had a deficiency in white matter integrity in their fronto-limbic systems. Nine other studies reported similar findings when the same protocol was used in elderly patients with depression. Two of these reports found significant correlations between white matter integrity deficit in the fronto-limbic system and cognitive performance of Trail Making Test or Stroop Color-Word Test. However, to date there have been few studies reporting significant correlations between fractional anisotropy (FA), a measure often used in diffusion imaging in which it is thought to reflect fibre density, axonal diameter, and myelination in white matter in abnormal white matter brain regions and cognitive functioning in treatment-naïve adult patients with MDD. It is hypothesised that white matter FA changes may be associated with severity of cognitive impairment in patients with MDD. This study examined white matter integrity in treatment-naïve adult patients with MDD using DTI. A correlation analysis between mean white matter FA values in the abnormal brain regions with cognitive performance of Trail Making, Wisconsin Card Sorting, Stroop Color-Word, and Verbal Fluency tests was performed.

Methods

Participants

Eighteen treatment-naïve adult patients with MDD were recruited from the inpatient and outpatient departments at the Second Xiangya Hospital of Central South University, Changsha, Hunan, China. Eighteen healthy controls were enrolled. All patients met the inclusion criteria of current major depressive episode as assessed by 2 experienced psychiatrists using the Structural Clinical Interview for the Fourth edition of the Diagnostic and Statistical Manual of Mental Disorders; first episode without any medication; aged between 18 and 45 years; were right-handed Han Chinese; and had a Hamilton Rating Scale for Depression (HAMD) score of ≥ 17. Patients and healthy controls were excluded if they had a history of neurological diseases or other serious physical diseases; history of electroconvulsive therapy; history of substance (drugs, alcohol, other psychoactive substance) abuse; and contra-indications for therapy; history of substance (drugs, alcohol, other psychoactive substance) abuse; and contra-indications for treatment-naïve adult patients with MDD. It is hypothesised that white matter FA changes may be associated with severity of cognitive impairment in patients with MDD. This study examined white matter integrity in treatment-naïve adult patients with MDD using DTI. A correlation analysis between mean white matter FA values in the abnormal brain regions with cognitive performance of Trail Making, Wisconsin Card Sorting, Stroop Color-Word, and Verbal Fluency tests was performed.

Verbal Fluency tests were performed by an experienced

Making, Wisconsin Card Sorting, Stroop Color-Word, and

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Neuropsychological assessments, including the Trail Making, Wisconsin Card Sorting, Stroop Color-Word, and Verbal Fluency tests, were performed by an experienced psychiatrist for all patients with MDD. The study was approved by the Hospital Ethics Committee. Written informed consent was obtained from all participants.

Imaging Acquisition

Scans were performed on a 1.5-Tesla GE Signa Twinspeed MRI scanner (General Electric Medical System, Milwaukee WI, US) equipped with high-speed gradients. A birdcage head coil was used for radiofrequency transmission and reception of nuclear magnetic resonance signal. Participants were placed in the supine position in the scanner, and their head was snugly fixed with foam pads provided by the manufacturer to minimise head motion. Their bilateral external auditory meatuses were plugged with earplugs to minimise the noise influence. Diffusion-weighted images were acquired with a single-shot echo planar imaging sequence aligned to the straight axial plane. Diffusion sensitising gradients were applied along 13 non-collinear directions (b = 1000 s/mm²). Images with no diffusion weighting (b0 images) were acquired. Thirty contiguous axial slices were acquired with the following parameters: repetition time, 12,000 ms; echo time, 107 ms; acquisition matrix, 128 x 128; field of view, 24 x 24 cm; number of excitations, 5; slice thickness, 4 mm, and no gap.

Image Processing

Diffusion-weighted images were pre-processed with the soft DtiStudio software, version 2.40 (Johns Hopkins University [MD], US). Diffusion tensor matrix was calculated according to the Stejskal and Tanner equation. Three pairs of eigenvalues (λ₁, λ₂, λ₃) and eigenvectors (ε₁, ε₂, ε₃) can be obtained by diagonalisation of the tensor matrix. The largest eigenvalue (λ₁) corresponds to the principal eigenvector (ε₁), which demonstrates the main diffusion direction within the voxel. The FA value was calculated according to the following formula:

After image pre-processing on DtiStudio software, the original DTI images were transformed into parametric images of b0 and FA. For each participant, the b0 image and FA image were first normalised to standard Montreal Neurological Institute space by implementing the Statistical Parametric Mapping software package (SPM2, Wellcome Department of Cognitive Neurology, London, UK) on MATLAB 6.5 (Mathworks, Inc., Natick [MA], US). All images were re-sampled with a final voxel size of 2 x 2 x 2 mm³. Each normalised FA map was spatially smoothed with an 8-mm full-width half-maximum Gaussian kernel to decrease spatial noise and to compensate for the inexact nature of normalisation. No correction for eddy current distortions was applied.

Statistical Analyses

Voxel-based Analysis

The Voxel-based analysis strategy used in this study was the same as that used in previous DTI studies. Comparisons of normalised and smoothed FA images between the 2 groups were performed using 2-sample t test in a voxel-by-voxel manner. Clusters with p < 0.001 (uncorrected) between groups and size > 30 voxels (i.e. k > 30) were identified and superimposed onto the SPM2’s spatially normalised template brain for easy visualisation.

Fractional Anisotropy Value Analysis

Mean FA values of identified clusters were calculated for
each participant using a self-developed program.23 The two-sample t test implemented on the Statistical Package for the Social Sciences version 11.5 (SPSS, Inc., Chicago [IL], US) was used to confirm the statistical significance of the identified clusters. Correlation analysis was conducted between mean FA values in each of the identified clusters and cognitive performances. The data were presented as means (standard deviations) [SDs]. The significance level was set at p < 0.05.

Results

There were 9 women and 9 men with a mean (SD) age of 27.4 (6.4) years, and a mean (SD) duration of education of 11.8 (3.2) years. The mean (SD) illness duration was 15.1 (3.9) months, and the mean (SD) 17-item HAMD score was 24.2 (4.3). In the control group, there were 9 women and 9 men, with a mean (SD) age of 27.0 (6.8) years and a mean (SD) duration of education of 11.9 (2.7) years. The 2 groups were well matched for sex, age, ethnicity, and education (p > 0.05).

White matter integrity deficits indicated by lower FA values in the bilateral medial frontal gyri, right subgyral frontal and temporal lobes, and left middle frontal and cingulate gyri were found (Fig). The mean FA values of each of the clusters showed a significant difference between the MDD patients and the controls (p < 0.001) [Table]. The FA values had no correlation with performance of cognitive tests.

Discussion

The major finding of this study was that treatment-naïve adult patients with MDD showed white matter integrity deficit in the fronto-limbic system compared with the healthy controls. Although the locations of some clusters were somewhat different, the main findings in the frontal, temporal, and cingulate areas are basically consistent with previous reports of treatment-naïve adult patients with MDD5,6 and elderly people with depression.7-12,14,15 Characteristics of illness duration and sample size, and methodological differences including image data acquisition and pre-processing may have contributed to these slight differences. However, all the findings suggest that disruption of white matter integrity is a common feature in MDD patients, with different extent and content for each individual. Microstructural changes in the white matter of the fronto-limbic system may result in disconnection of

![Figure. Coronal images showing the identified white matter regions where fractional anisotropy values were significantly reduced in adult patients with major depression relative to well-matched healthy controls (p < 0.001, uncorrected). The colour bar represents the range of t values. The findings are displayed on a T1 template. (a) Right medial frontal gyrus (76 voxels; MNI coordinate for the maximal point of difference: x = 18 mm, y = 42 mm, z = 24 mm). (b) Right subgyral frontal lobe (95 voxels; x = 32 mm, y = 40 mm, z = 10 mm). (c) Right subgyral temporal lobe (30 voxels; x = 52 mm, y = –36 mm, z = –12 mm). (d) Left medial frontal gyrus (31 voxels; x = –14 mm, y = 56 mm, z = 10 mm). (e) Left middle frontal gyrus (67 voxels; x = –30 mm, y = 44 mm, z = –4 mm). (f) Left cingulate gyrus (42 voxels; x = –14 mm, y = –10 mm, z = 44 mm). Abbreviations: L = left; R = right; MNI = Montreal Neurological Institute.](image-url)
cortical and subcortical regions. Accordingly, patients with MDD may exhibit a series of related syndromes, including disorder of mood regulation and executive dysfunctioning. Thus, white matter deficits of the fronto-limbic system, as a common feature, may contribute to the pathogenesis of major depression.

The other findings suggest no correlation between white matter integrity deficits expressed as FA values and scores of cognitive function tests, although 2 previous studies\(^3,15\) of geriatric depression reported significant correlations between FA or FA values and scores of the Trail Making Test or Stroop Color-Word Test. This could be attributed to the age difference or other possible non-linear correlation. Another possibility could be that many factors contribute to the pathogenesis of MDD, and thus one of the cognitive tests may not correlate to FA values.

There were some certain limitations to this study. For example, the sample size was small, and cognitive assessment was relatively limited. Despite these limitations, the major finding is robust and independent of age, sex, and medication. However, future studies are needed to examine fibre tract changes in the specific regions of the fronto-limbic system using fibre tractography based on DTI. In addition, this study was a cross-sectional research. To further understand the relationship between FA value and cognitive performance, follow-up study with a larger sample is needed in the future.

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