

White matter integrity of the whole brain is disrupted in first-episode schizophrenia

Yihui Hao^a, Zhening Liu^a, Tianzi Jiang^c, Gaolang Gong^c, Haihong Liu^a, Lihua Tan^b, Fan Kuang^b, Lin Xu^{a,d}, Yanhong Yi^a and Zishu Zhang^b

^aThe Institute of Mental Health, ^bDepartment of Radiology, Second Xiangya Hospital, Central South University, Changsha, Hunan, ^cNational Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences, Beijing and ^dLaboratory of Learning and Memory, Kunming Institute of Zoology, Chinese Academy of Sciences, Kunming, Yunnan, PR China

Tel: +86 10 82614469; fax: +86 10 62551993; email: jiangtz@nlpr.ia.ac.cn

Sponsorship: The National Basic Research Program of China (2006CB500800) supported this work.

Received 17 October 2005; revised 8 November 2005; accepted 9 November 2005

Diffusion tensor imaging studies in schizophrenia have demonstrated lower diffusion anisotropy within white matter that provides information about brain white matter integrity. We have examined whether white matter is abnormal in first-episode schizophrenia by using diffusion tensor imaging. Twenty-one schizophrenic patients and healthy controls underwent diffusion tensor imaging scans that analyzed by using a rigorous voxel-based approach. We found that

fractional anisotropy in white matter of the patients was lower than that in controls at the cerebral peduncle, frontal regions, inferior temporal gyrus, medial parietal lobes, hippocampal gyrus, insula, right anterior cingulum bundle and right corona radiata. These results suggested that white matter integrity of the whole brain was disrupted in early illness onset of schizophrenia. *NeuroReport* 17:23–26 © 2006 Lippincott Williams & Wilkins.

Keywords: diffusion tensor imaging, first-episode schizophrenia, fractional anisotropy, white matter

Introduction

Growing evidences from diffusion tensor imaging (DTI) studies have supported the view that a disturbance in connectivity between different brain regions is responsible for the clinical symptoms and cognitive dysfunctions observed in schizophrenia [1]. Buchsbaum *et al.* [2] report a DTI study on the first time that white matter diffusion anisotropy was reduced in schizophrenic patients compared with that in normal controls. Since then, DTI study has attracted much attention because it may provide important new information about the anatomical connectivity of the brain.

Kanaan *et al.* [3] and Kubicki *et al.* [1] systematically reviewed DTI studies on schizophrenia. The most consistent finding is impairment of white matter integrity within the prefrontal and temporal lobes, and splenium of the corpus callosum, internal capsule, cingulum bundle, uncinate and arcuate fasciculus. Meanwhile, some reports suggest that white matter integrity in the whole brain is disrupted in chronic schizophrenia.

Not all of previous DTI studies report a reduced diffusion anisotropy in patients with schizophrenia [3]. This discrepancy may be because of different conditions including the data analysis. The two major methods in anisotropy analysis are region of interest (ROI) and whole brain voxel-based analysis. ROI has been used in a majority of previous

studies, but the placement of ROI is subjective and manual errors may occur while defining the anatomical area. In the case of schizophrenia, however, voxel-based analysis instead of ROI may be useful in detecting the abnormal regions in the whole brain. Furthermore, antipsychotic drugs may be related to the changes of anisotropy in the left frontal white matter and in the middle cerebellar peduncle [4]. These studies suggest that there is a need to carefully differentiate the effects of medication/unmedication and chronic/first-episodic patients [1,3].

To our knowledge, the participants in previous DTI studies were mainly medicated chronic schizophrenia patients. Only two studies involved the first-episode schizophrenic patients who showed no fractional anisotropy (FA) changes in the hippocampus and the corpus callosum by using the ROI approach [5,6]. Using voxel-based analysis, we have studied whether the white matter integrity is disrupted in the whole brain of first-episode schizophrenic patients.

Materials and methods

Participants

Twenty-one first-episodic patients (12 men, 9 women) and 21 normal controls (10 men, 11 women) were involved in this study. The patients were recruited from the Institute of

Mental Health, Second Xiangya Hospital of Central South University, China, from February 2005 to July 2005. Psychiatrists administered a clinical interview using the Positive and Negative Syndrome Scale (PANSS) [7]. The total score of PANSS was between 43 and 113 (72.16 ± 21.92). All patients met the following inclusion criteria: (1) DSM-IV criteria for schizophrenia; (2) duration of illness must be less than 2 years and the maximum allowed exposure to antipsychiatric treatment is 2 weeks in the year preceding study entry or 6 weeks lifetime exposure [8]; (3) age between 18 and 45 years; (4) absence of neurological or significant physical disorders; (5) absence of dependence on alcohol or illicit drugs; (6) no history of receiving electroconvulsive therapy (ECT). Normal controls were recruited from the community and had no history of psychiatric disorder. They also met the inclusion criteria (3), (4), (5) and (6). Approval was obtained from the ethical committee of the hospital. Informed consents were obtained from all participants.

The ages of the patients were between 18 and 42 years (23.71 ± 5.47 years) and length of illness was between 6 and 24 months (10.33 ± 6.22 months). The education level was between 9 and 16 years (13.14 ± 2.12 years). All the patients were receiving antipsychotic medication during the time of imaging. Four patients were receiving typical antipsychotics (sulpiride), and 17 patients were receiving atypical antipsychotics (clozapine, risperidone, olanzapine, seroquel, and aripiprazole). All medication doses were converted to chlorpromazine equivalence (364.06 ± 143.75 mg/day). The ages of control individuals were between 19 and 33 years (25.05 ± 4.58 years). The education level of the controls was between 7 and 18 years (15.14 ± 2.57 years). All participants were right-handed. No significant differences in age, as well as sex, were observed between the patient group and the control group ($P > 0.05$).

Imaging acquisition

Magnetic resonance imaging was performed on 1.5-T magnetic resonance scanner (GE signal 1.5T Twinspeed, Milwaukee, Wisconsin, USA). The standard head coil was used for radio frequency transmission and reception of the nuclear magnetic resonance signal. Head motion was minimized with restraining foam pads provided by the manufacturer.

Diffusion weighted imaging was acquired with single-shot echo planar imaging sequence in alignment with the anterior-posterior commissure plane. The diffusion sensitizing gradients were applied along 13 non-collinear directions ($b=1000$ s/mm²), together with an acquisition without diffusion weighting ($b=0$). Thirty contiguous axial slices were acquired with a slice thickness of 4 mm and no gap. The acquisition parameters were as follows: TR=12000 ms; TE=105 ms; matrix=128 × 128; FOV=24 × 24 cm; NEX=5.

Image processing

The diffusion tensor matrix was calculated according to the Stejskal and Tanner equation [9]. Three pairs of eigenvalues (λ_1 , λ_2 , λ_3) and eigenvectors can be obtained by diagonalization of the tensor matrix. The principal direction at each point was given by the eigenvector that corresponds to the largest eigenvalue, and FAs [10] were calculated according

to the following formula:

$$FA = \frac{\sqrt{3[(\lambda_1 - \langle \lambda \rangle)^2 + (\lambda_2 - \langle \lambda \rangle)^2 + (\lambda_3 - \langle \lambda \rangle)^2]}}{\sqrt{2(\lambda_1^2 + \lambda_2^2 + \lambda_3^2)}},$$

$$\langle \lambda \rangle = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}.$$

For each participant, the $b=0$ image was first normalized to the standard Montreal Neurological Institute (MNI) space using statistical parameters maps (SPM2) (Wellcome Department of Cognitive Neurology, London, UK), and then the transformation matrix was applied to the FA map in order to normalize the FA map to the standard MNI space. All images were re-sampled with a final voxel size of $2 \times 2 \times 2$ mm³. Further, each FA map was spatially smoothed by an 8-mm full-width at half the maximum Gaussian kernel in order to decrease spatial noise and compensate for the inexact nature of normalization.

Statistical analysis

Intergroup comparisons (controls vs. patients) were carried out using a two-sample *t*-test analysis in a voxel-by-voxel manner. Voxels with $Z > 3.47$ ($P < 0.001$ uncorrected for multiple comparisons) and clusters of size > 30 voxels were considered as significant differences between the patients and controls. For visualization of the regions showing significantly different FA values between the two groups, the significant clusters were superimposed onto SPM2's spatially normalized template brain.

Results

In a voxel-by-voxel contrast, several regions showed significantly lower FA values in the patients than in the controls (uncorrected $P < 0.001$, cluster size > 30 voxels). The coordinates and *Z* scores of peak voxels for these regions are briefly listed in Table 1. The white matter areas that showed lower FA values are the bilateral cerebral peduncle (Fig. 1A), bilateral hippocampal gyrus (Fig. 1B), right corona radiata (Fig. 1C), bilateral precuneus (Fig. 1D), right (Fig. 1E) and left (Fig. 1F) cuneus, left fronto-orbital area (Fig. 1G) and right middle frontal lobe (Fig. 1H), left (Fig. 1I) and right (Fig. 1J) inferior temporal gyrus, right superior cerebellar peduncle (Fig. 1K), bilateral insular (Fig. 1L), right anterior cingulum (Fig. 1M). No FA value was significantly higher in the patients than those in controls.

Discussion

The present DTI studies have strongly suggested that the reduced FA is not regional but distributed in the whole brain of a schizophrenic patient, extending from the frontal to occipital brain regions. These findings of DTI studies in first-episode schizophrenia are consistent with previous reports on chronic schizophrenia.

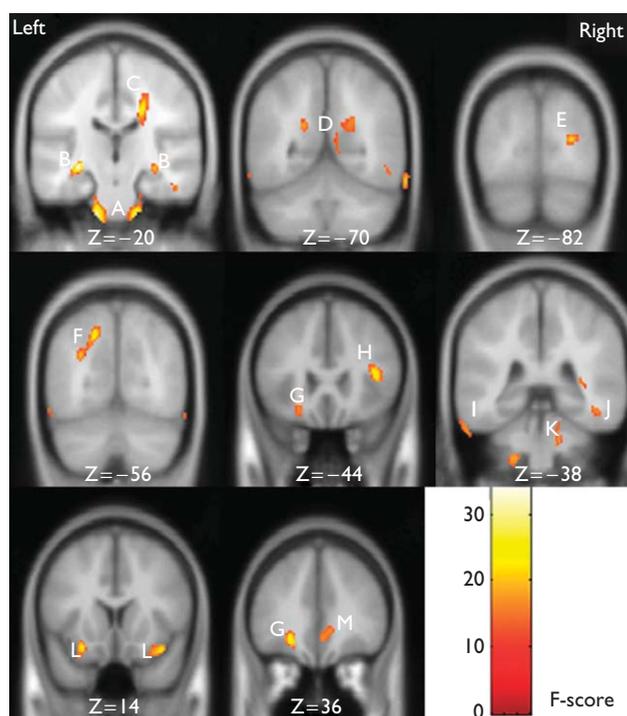
DTI studies have documented that the integrity of the cingulum bundle is disrupted in patients with schizophrenia compared with normal controls [11–13]. Wang *et al.* [14] and Ardekani *et al.* [15] report a reduced FA in the bilateral anterior cingulum bundle in schizophrenia patients. In the present study, we detected a significant reduction of FA value in the right anterior cingulum bundle of first-episode schizophrenic patients compared with that of normal

Table 1 Regions with reduced fractional anisotropy values in schizophrenia patients compared with those in normal controls (uncorrected $P < 0.001$)

Description of extent of cluster	L/R	Cluster size ^a	Z score	MNI coordinates of most significant voxel (x, y, z)
Cerebral peduncle	L/R	668/668	4.53/4.43	-14, -20, -42/16, -20, -42
Frontoorbital area, white matter	L	319	4.37	-22, 36, -10
Middle frontal gyrus, white matter	R	68	4.07	38, 24, 12
Inferior temporal gyrus, white matter	L/R	416/368	4.63/4.27	-60, -44, -24/50, -50, -10
Precuneus, white matter	L/R	207/32	4.14/3.47	-18, -70, 42/22, -60, 44
Cuneus, white matter	L/R	46/59	3.77/3.95	-18, -56, 24/26, -82, 12
Hippocampus	L/R	270/63	4.70/3.92	-30, -22, -8/30, -20, -10
Insular	L/R	412/70	4.74/4.67	-28, 14, -14/38, 14, -16
Anterior cingulum	R	108	3.63	10, 36, -4
Corona radiata	R	257	4.29	22, -22, 36
Superior cerebella peduncle	R	31	3.60	14, -38, -34

^aCluster size is in the unit of voxel.

L/R; left/right; MNI, Montreal Neurological Institute.

**Fig. 1** Transverse slices through regions with reduced fractional anisotropy values in white matter in schizophrenic patients compared with those in controls. (A) Bilateral cerebral peduncle, (B) bilateral hippocampus, (C) right corona radiata, (D) bilateral precuneus, (E) right cuneus, (F) left cuneus, (G) left frontoorbital area, (H) right middle frontal lobe, (I) left inferior temporal gyrus, (J) right inferior temporal, (K) superior cerebellar peduncle, (L) bilateral insular, (M) right anterior cingulum.

controls. The anterior cingulum bundle is central to limbic circuitry [16] and its dysfunction links to attention deficits in schizophrenia. The most common interpretation for reduced FA is that it reflects lower white matter 'integrity'. Reduced FA in white matter is consistent with the idea that schizophrenia involves the disruption of cortical regions, which is supported by studies in other modalities. Consistent with our finding of the anterior cingulum bundle, a previous report has found that cingulotomy patients with small bilateral lesions in the anterior cingulate gyrus show deficits of attention and executive dysfunction, which are prominent features of schizophrenia [17].

Significant reduction in diffusion anisotropy has been found in the white matter of the frontal, temporal and parietal areas in schizophrenic patients [16,18,19]. Similarly, in the present study, we observed that the FA was significantly reduced in the white matter areas of the frontal lobes, inferior temporal gyrus and parietal lobes in both hemispheres in schizophrenic patients compared with that of controls. Large-scale disruption of white matter integrity in our present study further illuminated that those changes in patients with schizophrenia should be sought at the supra-regional rather than regional level. Both structural and functional abnormalities of frontoparietal and frontotemporal networks have been described in schizophrenia [20,21], which may constitute a basis for the impairment of cognitive functions, such as selective attention, language processing and the execution of working memory. Deficits in these cognitive functions are believed to be a cardinal feature of the pathophysiology of schizophrenia [22].

The fact that there are similar findings in first-episode and chronic schizophrenia suggested that white matter diffusion abnormalities are present at early illness onset. The present findings of reduced FA in the bilateral hippocampus are not consistent with a previous report by Begre *et al.* [5], who has examined FA of the hippocampus by using ROI analysis in seven first-episode schizophrenic patients and normal controls. This discrepancy may be relevant to a different approach of data analysis or other conditions.

Most DTI studies in schizophrenia find positive results, although there are many negative results compared with controls. A positive result was obtained for some regions by some groups but this result was not obtained by other groups in the same region. A long history of antipsychotics medication and the length of illness are possible confounding factors in the studies of DTI. Therefore, all the patients we recruited were first-episode schizophrenic patients whose exposure to medication was limited and length of illness was short. Taken together, the similar distribution regions of the reduced FA between patients with chronic or first-episode schizophrenia and normal controls suggested that white matter integrity of the whole brain may not be caused by the effect of antipsychotics and the length of illness. Consistent with this notion, Foong *et al.* [23], Kubicki *et al.* [11,13], and Minami *et al.* [18] find that the FA is not correlated with the medication dose or length of illness of schizophrenia.

The cut-off for P -value (uncorrected) and cluster size was relatively strict, experientially in the present studies. The interpretation for these results, however, requires some cautions. For example, type II error might cause some abnormal regions under the significant level. Furthermore, our current method (i.e. voxel-based morphometry) cannot determine the particular regions that may be involved in schizophrenia, while this can be done by the ROI-based method. Further work should be carried out with regard to these matters.

Conclusion

We have demonstrated reductions in white matter integrity in first episode schizophrenic patients compared with that in controls. The regional distribution of these differences is similar to those reported previously in chronic schizophrenia. Assessing differences in white matter integrity across the whole brain, we suggest that white matter integrity disruption in schizophrenia may occur in early illness onset and may not be relevant to the effects of antipsychotic drugs.

Acknowledgement

The authors thank Dr Meng Liang (National Laboratory of Pattern Recognition, Institute of Automation, Chinese Academy of Sciences) for his assistance in data processing.

References

- Kubicki M, McCarley R, Westin CF, Park HJ, Maier S, Kikinis R, *et al.* A review of diffusion tensor imaging studies in schizophrenia. *J Psychiatr Res* 2005 (in press).
- Buchsbaum MS, Tang CY, Peled S, Gudbjartsson H, Lu D, Hazlett EA, *et al.* MRI white matter diffusion anisotropy and PET metabolic rate in schizophrenia. *Neuroreport* 1998; **9**:425–430.
- Kanaan RA, Kim JS, Kaufmann WE, Pearson GD, Barker GJ, McGuire PK. Diffusion tensor imaging in schizophrenia. *Biol Psychiatry* 2005 (in press).
- Okugawa G, Nobuhara K, Minami T, Tamagaki C, Takase K, Sugimoto T, *et al.* Subtle disruption of the middle cerebellar peduncles in patients with schizophrenia. *Neuropsychobiology* 2004; **50**:119–123.
- Begre S, Federspiel A, Kiefer C, Schroth G, Dierks T, Strik WK. Reduced hippocampal anisotropy related to anteriorization of alpha EEG in schizophrenia. *Neuroreport* 2003; **14**:739–742.
- Price G, Bagary MS, Cercignani M, Altmann DR, Ron MA. The corpus callosum in first episode schizophrenia: a diffusion tensor imaging study. *J Neurol Neurosurg Psychiatry* 2005; **76**:585–587.
- Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull* 1987; **13**:261–276.
- Fleischhacker WW, Keet IP, Kahn RS. The European First Episode Schizophrenia Trial (EUFEST): rationale and design of the trial. *Schizophr Res* 2005; **78**:147–156.
- Stejskal EO, Tanner JE. Spin diffusion measurements: spin echoes in the presence of a time-dependent field gradient. *J Chem Phys* 1965; **42**: 288–292.
- Basser P, Pierpaoli C. Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *J Magn Reson* 1996; **111**(B):209–219.
- Kubicki M, Westin CF, Nestor PG, Wible CG, Frumin M, Maier SE, *et al.* Cingulate fasciculus integrity disruption in schizophrenia: a magnetic resonance diffusion tensor imaging study. *Biol Psychiatry* 2003; **54**: 1171–1180.
- Sun Z, Wang F, Cui L, Breeze J, Du X, Wang X, *et al.* Abnormal anterior cingulum in patients with schizophrenia: a diffusion tensor imaging study. *Neuroreport* 2003; **14**:1833–1836.
- Kubicki M, Park H, Westin CF, Nestor PG, Mulkern RV, Maier SE, *et al.* DTI and MTR abnormalities in schizophrenia: analysis of white matter integrity. *Neuroimage* 2005; **26**:1109–1118.
- Wang F, Sun Z, Cui L, Du X, Wang X, Zhang H, *et al.* Anterior cingulum abnormalities in male patients with schizophrenia determined through diffusion tensor imaging. *Am J Psychiatry* 2004; **161**:573–575.
- Ardekani BA, Nierenberg J, Hoptman MJ, Javitt DC, Lim KO. MRI study of white matter diffusion anisotropy in schizophrenia. *Neuroreport* 2003; **14**:2025–2029.
- Tamminga CA, Vogel M, Gao X, Lahti AC, Holcomb HH. The limbic cortex in schizophrenia: focus on the anterior cingulate. *Brain Res Brain Res Rev* 2000; **31**:364–370.
- Benes FM. Neurobiological investigations in cingulate cortex of schizophrenic brain. *Schizophr Bull* 1993; **19**:537–549.
- Minami T, Nobuhara K, Okugawa G, Takase K, Yoshida T, Sawada S, *et al.* Diffusion tensor magnetic resonance imaging of disruption of regional white matter in schizophrenia. *Neuropsychobiology* 2003; **47**:141–145.
- Kumra S, Ashtari M, McMeniman M, Vogel J, Augustin R, Becker DE, *et al.* Reduced frontal white matter integrity in early-onset schizophrenia: a preliminary study. *Biol Psychiatry* 2004; **55**:1138–1145.
- Schlaepfer TE, Harris GJ, Tien AY, Peng LW, Lee S, Federman EB, *et al.* Decreased regional cortical gray matter volume in schizophrenia. *Am J Psychiatry* 1994; **151**:842–848.
- Honey GD, Bullmore ET, Sharma T. De-coupling of cognitive performance and cerebral functional response during working memory in schizophrenia. *Schizophr Res* 2002; **53**:45–56.
- Goldman-Rakic PS. Working memory dysfunction in schizophrenia. *Neuropsychiatry Clin Neurosci* 1994; **6**:348–357.
- Foong J, Maier M, Clark CA, Barker GJ, Miller DH, Ron MA. Neuropathological abnormalities of the corpus callosum in schizophrenia. *J Neurol Neurosurg Psychiatry* 2000; **68**:242–244.