Extensive White Matter Abnormalities and Clinical Symptoms in Drug-Naive Patients With First-Episode Schizophrenia:
A Voxel-Based Diffusion Tensor Imaging Study

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ABSTRACT

Background: Increasing evidence shows that disruption of connectivity has been implicated as a central abnormality in schizophrenia, and the alterations in white matter may be the core basis for this disconnection. Diffusion tensor imaging (DTI) has shown white matter abnormalities in first-episode schizophrenia. However, few studies have examined the correlation between clinical symptoms and white matter abnormalities in drug-naive patients with first-episode schizophrenia.

Method: The white matter fractional anisotropy (FA) values of the whole-brain were determined by using voxel-based DTI in 39 drug-naive patients with first-episode schizophrenia (diagnosed according to *DSM-IV*) and 30 healthy controls matched for age and gender. The psychopathology of schizophrenia was assessed with the Positive and Negative Syndrome Scale (PANSS). The study was conducted from April 2009 to March 2010.

Results: The patients showed widespread FA reduction in several brain regions, including corpus callosum, brainstem, internal capsule, cingulate, and cerebellum in patients with first-episode schizophrenia when compared to healthy controls (all *P* values < .01 after adjusting for gender, age, and education). The correlation analysis showed a significant negative correlation between the FA value in the left cerebellum and positive symptoms ($r_{38} = -0.32$, $P < .05$) and a significant positive correlation between the FA values in the corpus callosum and both the PANSS general psychopathology subscore ($r_{38} = 0.39$, $P < .01$) and the PANSS total score ($r_{38} = 0.33$, $P < .05$).

Conclusions: Our results indicate that widespread disruption of white matter integrity occurs in an early stage of schizophrenic onset, suggesting an important role in pathogenesis and symptomatology of schizophrenia.

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Increasing evidence implicates disruption of connectivity as a central abnormality in schizophrenia[1,2] and shows that alterations in white matter may be the core basis for this disconnection.[3] Multiple lines of evidence now converge to implicate reduction in oligodendrocyte numbers, abnormal microstructure of myelin sheaths and/or axons, or disordered neuronal architecture as underlying pathophysiologic mechanism of white matter alterations in schizophrenia.[4–7] Thus, studying the white matter is crucial to understanding the neurobiologic substrate of schizophrenia because the abnormalities in white matter may play a fundamental role in the neurobehavioral manifestations of schizophrenia.[8] However, despite the fact that white matter deficits in schizophrenia have been widely reported, the results are inconsistent.[9–23]

Diffusion tensor imaging (DTI), a novel magnetic resonance imaging technique, can quantify the fiber orientation and the integrity of white matter pathways within neural networks. Diffusion tensor imaging measures water diffusion by using diffusion-weighted pulse sequences sensitive to microscopic random water motion.[24] Over the past few decades, an increasing number of DTI studies[6,7,9,10,25] have been used to investigate white matter alterations in schizophrenia. One of the commonly used DTI measures is fractional anisotropy (FA), a measure of directional dependence of diffusion of water, which is thought to reflect the anatomic features of neural fibers, such as fiber structural integrity, degree of myelination, fiber tract coherence, fiber diameter, and packing density in white matter.[26,27] A recent meta-analysis[28] of DTI studies in chronic schizophrenia has shown FA reductions at 112 coordinates in schizophrenia and no FA increases. Over all studies, significant reductions were present in the anterior corpus callosum, medial frontal/anterior cingulate cortex, right anterior limb of the internal capsule, and left temporal white matter, suggesting that networks of white matter tracts may be affected in schizophrenia, with the potential for "disconnection" of the gray matter regions, which they link.[28] However, the results are inconsistent due to confounders associated with the illness chronicity and prolonged exposure to antipsychotic medication as well as possible progressive white matter atrophy.[1,8]

The study of first-episode psychosis is particularly advantageous in understanding the neurobiology of schizophrenia, in part because of the opportunity to minimize the potential impact of confounds, such as illness duration, medication effects, and the psychiatric and medical comorbidities that are associated with

Clinical Points

- The white matter fractional anisotropy (FA) values of the whole brain were determined using voxel-based diffusion tensor imaging in 39 drug-naive patients with first-episode schizophrenia and 30 healthy controls.
- The patients showed widespread FA reduction in several brain regions compared to the controls.
- Correlation analysis showed significant associations between FA values in different brain regions and clinical symptoms of psychopathology.

chronicity of illness.[29] Compared to studies with chronic patients, however, relatively few attempts have been made to investigate patients with first-episode schizophrenia.[8] The results have also been inconsistent. For example, decreased FA has been reported in patients with first-episode schizophrenia.[30–37] However, some authors failed to replicate these findings[22,37,38] or even found increased FA.[31,33] Thus, the picture emerging is that FA alterations deserve further examination in patients with first-episode schizophrenia.

Several studies have examined the relationships between FA alteration and psychopathology in chronic schizophrenia, with mixed results. For example, low FA was found to be associated with negative symptoms in several tract regions[4,39,40]; however, positive symptoms were reported to be both positively[41–43] and negatively[44] correlated with FA in various brain regions. A more recent study[17] showed that the reduced FA value of the anterior part of the corpus callosum was negatively correlated with the avolition score on the Scale for the Assessment of Negative Symptoms in chronic schizophrenia. Data on the relationship between DTI measures and clinical variables in first-episode schizophrenia are sparse,[45] but several studies[29,46,47] found positive correlations between FA and positive symptoms. The discrepancies of the studies above could be due, in part, to the small sample size, limited brain regions investigated, different sample characteristics (naive vs medicated patients, patients in acute vs chronic or active phase vs remission), and other confounding factors in chronic patients (eg, illness chronicity, medication) in these previous studies.[17] In this voxel-based DTI study, we recruited a relatively larger sample than those used in previous studies of drug-naive patients with first-episode schizophrenia to examine whole-brain FA alteration. We also tried to establish correlations between FA alteration and clinical variables, especially the severity of psychotic symptoms in patients with first-episode schizophrenia, using the global subscale of the Positive and Negative Syndrome Scale (PANSS).[48]

METHOD

Subjects

Thirty-nine drug-naive Chinese Han patients (23 females) with a first episode were followed for 3 months as inpatients after admission to Beijing Hui-Long-Guan hospital in order to establish a *DSM-IV* diagnosis of schizophrenia using the Structured Clinical Interview for *DSM-IV* Axis I Disorders-Patient Edition (SCID-I/P).[49] The clinical subtypes were paranoid, 20 patients (51.3%); undifferentiated, 15 (38.5%); disorganized, 3 (7.7%); and other, 1 (2.6%). The patients had a mean ± SD age of 28.9 ± 10.2 years (range, 15–45), a mean duration of illness of 23.4 ± 19.1 months, and a mean education of 12.4 ± 3.1 years.

Thirty healthy volunteers (17 females) were recruited by advertisements at the local community. The controls had a mean ± SD age of 27.5 ± 7.9 years and a mean education of 12.3 ± 4.0 years. They were matched for gender, age, and education with the patients with first-episode schizophrenia. Current mental status and personal or family history of any mental disorder was assessed by a research psychiatrist. None of the controls presented a personal or family history of psychiatric disorder.

All subjects were Han Chinese from the Beijing area. Any subjects with medical illnesses or drug and alcohol abuse/dependence were excluded. The institutional review board of the Beijing Hui-Long-Guan Hospital approved the research protocol, and all subjects provided written informed consent. The study was conducted from April 2009 to March 2010.

Psychopathological Assessment in Patients

The patient's psychopathology was assessed with the PANSS on the day of the DTI test by 2 psychiatrists who were blind to the clinical status and treatment conditions. To ensure consistency and reliability of rating across the study, these 2 psychiatrists, who had worked at least 5 years in clinical practice, simultaneously attended a training session in the use of the PANSS before the start of the study. After training, a correlation coefficient greater than 0.8 was maintained for the PANSS total score by repeated assessments during the course of the study.

Imaging Acquisition

All patients were scanned at admission, and they remained unmedicated until the scanning. Magnetic resonance imaging examinations were performed on a 3.0 Tesla scanner (General Electric) equipped with an 8-channel brain-phased array coil at the Department of Radiology, Peking University First Hospital, Beijing, China. The DTI scan was performed with single-shot echo-planar imaging sequence with the following scan parameters: repetition time = 13,525 milliseconds, echo time = 77.3 milliseconds, field of view = 256 × 256 mm^2, matrix = 128 × 128, 50 slices, thickness = 2.4 mm, skip = 2.4 mm, b-factor = 1,000 seconds/mm^2, 19 gradient directions, and 2 averages. The $b = 0$ images were scanned 3 times. The subjects were instructed to remain motionless and to keep their eyes closed, and foam pads were applied to minimize head motion. However, images with robust motion artifacts were removed from the analysis.

Analysis of Images

Voxel-based analysis of the DTI data was carried out using the Functional Magnetic Resonance Imaging of the

Table 1. Demographics of Patients With First-Episode Schizophrenia and Healthy Controls[a]

	Control (n = 30)			Schizophrenia (n = 39)			*t*	*P*
Variable	Mean	SD	Range	Mean	SD	Range	Test	Value
Age, y	27.47	7.89	18–45	28.87	10.22	15–45	−0.62	.54
Gender								
Male	n = 13			n = 16				
Female	n = 17			n = 23				
Education, y	12.30	4.03	9–20	12.44	3.09	6–19	−0.16	.87
PANSS								
Total				88.77	22.15	64–142		
Positive				25.38	6.88	15–40		
Negative				20.56	8.68	7–42		
General				42.51	11.87	28–72		

[a]There was no significant difference between patient and normal control groups in age, gender, and education (all *P* values > .05).
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Brain (FMRIB) software library (http://www.fmrib.ox.ac.uk/). First, FA images were created by fitting a tensor model to the raw diffusion data using the FMRIB's Diffusion Toolbox. Next, brain extraction was undertaken by using the brain extraction tool.[50] These steps were referred to as the preprocessing stages. For the next step, all subjects' FA data were then aligned into a common space using the FMRIB's nonlinear image registration tool, which uses a b-spline representation of the registration warp field.[51] Next, the normalized FA image of each subject was resampled to $2 \times 2 \times 2$ mm^3 Montreal Neurological Institute space. This resulted in a standard space version of each FA image. Then, a mean FA image was calculated and thinned to generate a mean FA skeleton that represents the centers of all tracts common to the group. A threshold FA value of 0.2 was set.[6,7] The maximum FA value observed in a direction perpendicular to each tract was assigned to each skeleton voxel. Each subject's aligned FA data were then projected onto this skeleton, and the resulting data were fed into voxel-wise, cross-subject statistics.[6] Finally, spatial smoothing was performed with a 6-mm full-width half-maximum Gaussian kernel.

Statistical Analysis

Group-level analyses were carried out to examine brain regions with significant detectable white matter abnormalities in schizophrenia. The voxel-wise FA values were compared between the patient and control subjects using a parametric 2-sample *t* test of Statistical Parametric Mapping 8 (SPM8) software (Wellcome Department of Imaging Neuroscience; London, United Kingdom), with gender, age, and education as covariates. Contrasts were used to detect FA changes between patients and controls, and results were thresholded at false discovery rate (FDR)–corrected $P < .05$ (see Figure 1 and Table 2). The FDR is the proportion of false positives (incorrect rejections of the null hypothesis) among those tests for which the null hypothesis is rejected.[52] The FDR method is more appropriate to apply to neuroimaging data than the more conservative Bonferroni approach when group differences are likely to be present in multiple pixels.[30,52]

Partial correlation analysis was used to examine the relationships between FA and clinical symptoms in patients with schizophrenia, while adjusting for various potentially confounding variables of gender, age, sex, and education as covariates. Only those mean FA values extracted from the regions with significant group differences were calculated. We applied Bonferroni corrections to adjust for multiple testing. Since we used the 4 components of PANSS (positive, negative, general psychopathology, and total score) and we found decreased FA in 5 brain regions, a *P* value of .0025 (.05/20) was considered significant.

Table 2. Regions Showing Significant Fractional Anisotropy Difference Between Schizophrenia and Control Subjects[a]

		MNI Coordinate of Peak Voxel				
Region	Hemisphere	*x*	*y*	*z*	*t* Test	Cluster Size (voxel)
Cerebellum	Left	−26	−56	−28	3.59	125
Brainstem	Right	14	−26	−22	4.14	138
Cingulate	Left	−22	34	−2	3.62	139
Internal capsule	Right	18	2	0	4.13	327
Corpus callosum	Right	4	20	16	4.14	209

[a]Results were thresholded at false discovery rate–corrected $P < .05$. All *P* values < .01 after adjusting for gender, age, and education.
Abbreviation: MNI = Montreal Neurological Institute.

RESULTS

Demographic and Symptom Data

Table 1 shows the demographic data of the subjects in the present study. All the participants were right-handed. There were no significant differences between patient and normal control groups on age, gender, and education. No significant correlations were found between the FA values and these demographic variables in the patient and control groups or in the combined group (all *P* values > .05).

Mean scores on the PANSS were 25.4 ± 6.9 (positive subscale), 20.6 ± 8.7 (negative subscale), 42.5 ± 11.9 (general psychopathology subscale), and 88.8 ± 22.2 (total PANSS score).

Group Differences in FA Values

Compared with the controls, the patients showed widespread areas of reduced FA, including corpus callosum, brainstem, internal capsule, cingulate, and cerebellum (all adjusted *P* values < .01) (Table 2 and Figure 1). In addition, the patients did not show significantly higher FA values in any regions than the controls.

Relationship Between FA Values and Psychopathology in Schizophrenia

The correlation analysis showed a significantly negative correlation between the FA value in the left cerebellum and positive symptoms ($r_{38} = -0.32$, $P < .05$; Figure 2A), which remained significant even after adjusting for gender, age, education, and illness duration as covariates ($P < .05$). Interestingly, a significantly positive correlation between the FA values in corpus callosum and the PANSS general psychopathology subscore ($r_{38} = 0.39$, $P < .01$; Figure 2B) and the PANSS total score ($r_{38} = 0.33$, $P < .05$; Figure 2C) were observed after adjusting for gender, age, education,

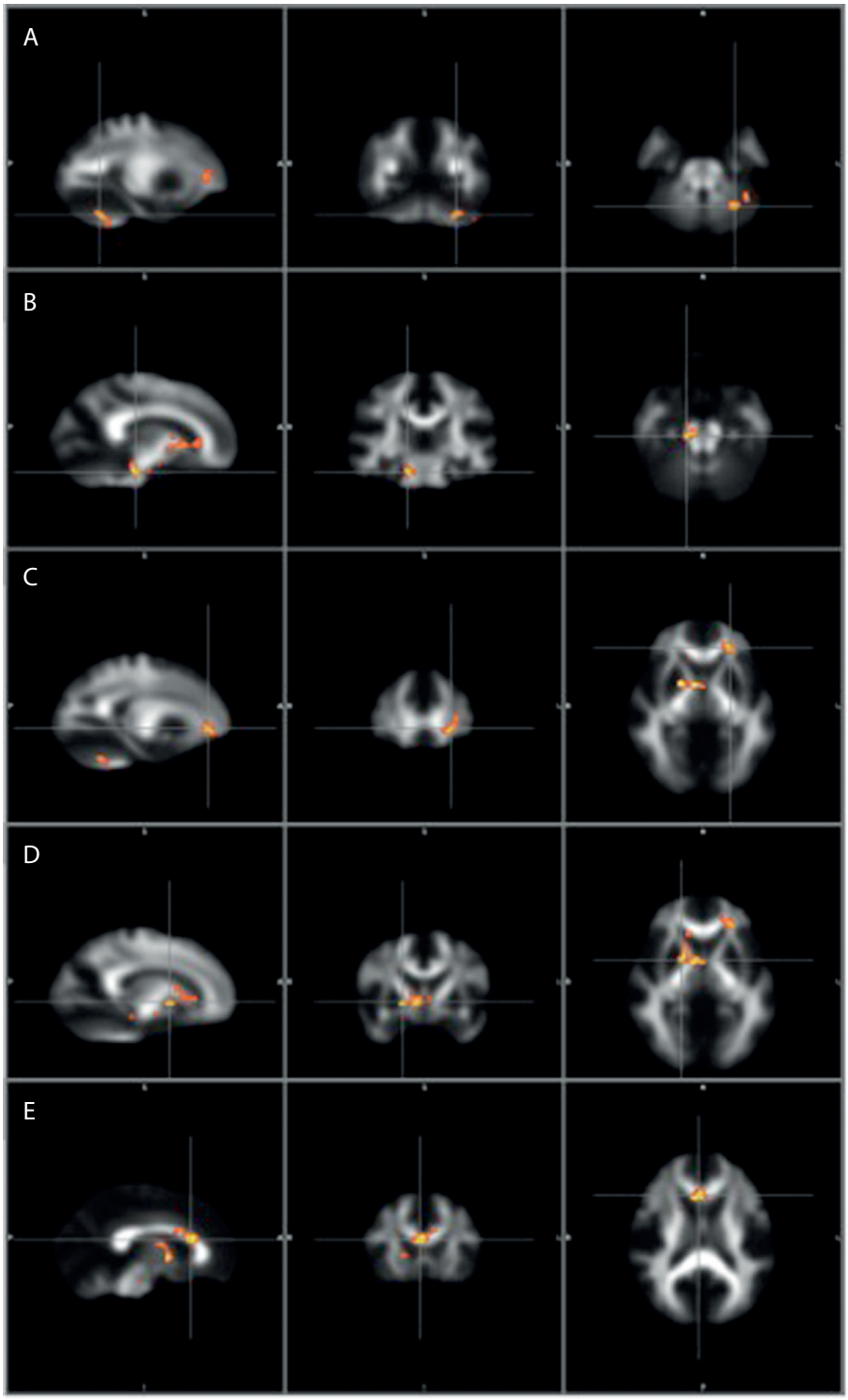
and illness duration. However, these significant results did not pass Bonferroni corrections (*P* value should be < .0025).

DISCUSSION

In the present DTI study, a fully automated voxel-based method was used to examine the whole-brain white matter FA alteration in drug-naive patients with first-episode schizophrenia, as well as its relationship to clinical phenotypes. Our results demonstrate widespread FA reduction in the 5 brain regions corpus callosum, brainstem, internal capsule, cingulate, and cerebellum at the early stages of schizophrenia compared to healthy controls. Moreover, lower FA in the left cerebellum was negatively associated with positive symptoms, and lower FA in corpus callosum was positively associated with both the PANSS general psychopathology subscore and the PANSS total score. These findings indicate that the FA abnormalities are present even at the early stage of first-episode schizophrenia, which supports the dysconnection hypothesis of schizophrenia,[2] suggesting that dysconnectivity, as the primary pathophysiology of schizophrenia, might contribute to the clinical symptoms of the illness. However, it is worth mentioning that these significant associations between decreased FA in these brain regions (left cerebellum and corpus callosum) and clinical symptoms did not pass Bonferroni correction due to multiple testing. We speculate that this small effect size of FA abnormalities on psychopathology is probably a matter of location of the white matter impairment rather than a matter of the intensity of the impairment.

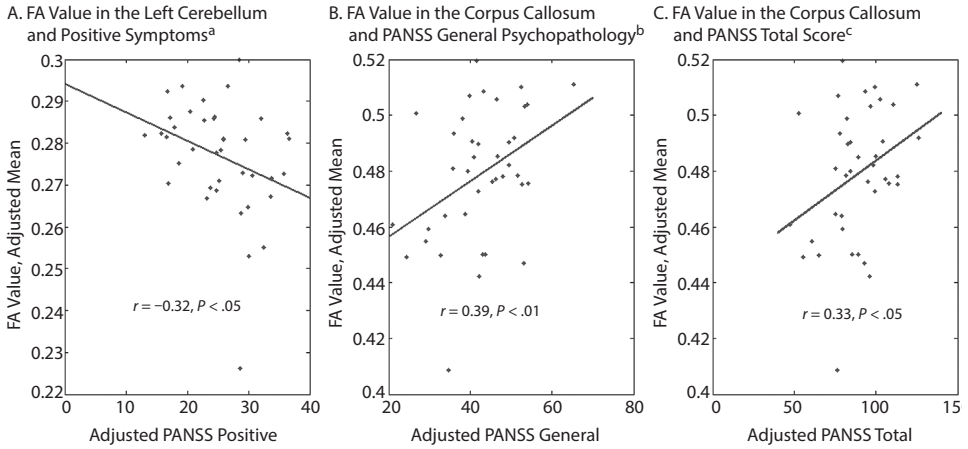
In the present study, the result of widespread FA reduction in several brain regions in patients with first-episode schizophrenia compared with that of healthy controls is concordant with most of the studies evaluating FA values in chronic patients with schizophrenia,[28] as well as in first-episode schizophrenia,[30–36] suggesting that the widespread disruption of white matter integrity might contribute to the pathophysiology of schizophrenia. However, some other studies failed to find any difference in FA values between patients with first-episode schizophrenia and healthy controls,[23,37,38] or even increased FA values in schizophrenia.[31,33] Several factors may be responsible for the discrepancy, such as differences in DTI techniques, including scanner differences in field strengths, head coils, and sequence parameters; different filter selection; differences in FA analysis

Figure 1. Comparison of Fractional Anisotropy (FA) in 5 Brain Regions Between Patients With Schizophrenia and Healthy Control Subjects[a]



[a]Compared with the controls, the patients showed widespread areas of reduced FA values, including cerebellum (A), brainstem (B), cingulate (C), internal capsule (D), and corpus callosum (E). Results were thresholded at false discovery rate–corrected *P* < .05.

Figure 2. Correlation Between Clinical Symptoms and Fractional Anisotropy (FA) in Different Brain Regions



[a]After adjusting for gender, age, education, and illness duration, the partial correlation analysis showed a significantly negative correlation between the FA value and the PANSS positive symptoms in the left cerebellum ($r_{38} = -0.32$, $P < .05$).
[b]After adjusting for gender, age, education, and illness duration, the partial correlation analysis showed a significantly positive correlation between the FA values and the PANSS general psychopathology subscore ($r_{38} = 0.39$, $P < .01$) in the corpus callosum
[c]After adjusting for gender, age, education, and illness duration, the partial correlation analysis showed a significantly positive correlation between the FA values and the PANSS total score ($r_{38} = 0.33$, $P < .05$) in the corpus callosum.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

(voxel-based approach vs probabilistic tractography algorithm vs tract based spatial statistics); sampling of patients in different stages of disease progression (acute vs chronic or active phase vs remission); different illness courses; the subtypes of schizophrenic patients recruited; or the biological/ethnic heterogeneity.

The decreased FA values in several brain regions in the present study are consistent with the hypothesis of disrupted connectivity between brain regions of schizophrenia, suggesting that the abnormalities in white matter may play a fundamental role in the neurobehavioral manifestations of schizophrenia[8] and may account for the global nature of the clinical, cognitive, and social symptoms that are a hallmark of the illness.[1,22] While a considerable heterogeneity has been observed in the results of DTI studies, our current results, together with those in most of the previous studies, provide strong support for white matter abnormalities in the pathophysiology of schizophrenia, even at the early stage of the illness. Our results of the lower FA in the 5 brain regions corpus callosum, brainstem, internal capsule, cingulate, and cerebellum also suggest that the white matter abnormalities are especially notable for pathways involving interhemispheric connections and frontal and limbic white matter.[22] However, it is noteworthy that the neuropathological mechanisms responsible for lower FA in patients with schizophrenia remain not yet completely understood. Since FA is influenced by factors affecting neuronal fiber diameter, density, and myelination as well as tract coherence and extracellular diffusion,[25,33] lower FA has been postulated to reflect abnormalities in myelination, oligodendrocytes, neuronal loss, disruption of the integrity of the cell membrane, or alterations in fiber orientation.[22] However, this remains to be elucidated in further investigation.

Recently, some studies examining the relationship between DTI data and the PANSS in schizophrenia have had inconsistent results. While negative symptoms were correlated with low FA in several tract regions,[4,39,40] positive symptoms such as auditory hallucinations were reported to be both positively[41–43] and negatively[44] correlated with FA in various brain regions. Recently, Moriya et al[38] reported a positive correlation of FA values with positive symptom scores in the white matter adjacent to the right lateral ventricle and reported a negative correlation between the FA values in same brain region and negative symptom scores. A more recent study[17] showed that the reduced FA in the anterior part of the corpus callosum was negatively associated with negative symptoms in chronic schizophrenia. Interestingly, a recent study[47] investigating the association between FA and psychopathological symptoms in first-episode patients with schizophrenia showed that positive symptoms correlated positively with FA scores in the right frontal lobe, left anterior cingulate gyrus, left superior temporal gyrus, right middle temporal gyrus, right middle cingulate gyrus, and left cuneus. However, Liu et al[6] did not find a significant association between the FA value and severity of clinical symptoms in never-medicated chronic schizophrenia. Our current results show that lower FA in the left cerebellum was negatively associated with positive symptoms, and lower FA in corpus callosum was positively associated with both the PANSS general psychopathology subscore and the PANSS total score. Taken together, these results suggest that disruption in the

brain connectivity in different brain regions may account for different core symptoms of schizophrenia early in the course of illness. Thus, dysconnectivity and the subsequent psychopathological symptoms appear to be intrinsic to the disorder and present at illness onset. However, it is still unclear why these discrepancies for the association between FA values and clinical symptoms were present, which could be partly due to the small sample size, limited brain regions investigated, different sample characteristics, and other confounding factors (eg, ethnic background, age at onset, or illness duration) in these previous studies. Therefore, future studies with greater numbers of patients with first-episode schizophrenia in different ethnic populations are needed to validate on these findings.

Several limitations of this study should be noted. First, our sample size was still relatively small because of recruitment difficulties of drug-naive patients with first-episode schizophrenia. A replication trial in an independent sample is needed with a potentially larger sample size and from different ethnic populations in order to test for a false-positive association. Second, the cross-sectional design we used prevented asserting valid conclusions due to the disease process. That is, it was impossible to tell with certainty whether the clinical symptoms were present as a consequence of the regional disconnectivities of the brain in schizophrenia. A future longitudinal study could quite likely better reveal a fundamental role of the white matter abnormalities in the neurobehavioral manifestations of schizophrenia. Third, it is still not clear whether fiber coherency and fiber crossing are correlated with decreased or increased FA. Also, we do not know whether the widespread FA reduction in the 5 brain regions corpus callosum, brainstem, internal capsule, cingulate, and cerebellum reflects a decrease in number of axons, decreased axonal diameter, or thinner myelination sheaths.[4] Fourth, although a voxel-based approach has an advantage in terms of objectivity and no intentional measurements, it could potentially be contaminated with registration or normalization errors.[38] Fifth, we had only 1 acquisition at $b = 0$ seconds/mm^2 and 19 directions. It is better to acquire 3–6 low-b image sets and 30 directions in clinical DTI studies to improve the accuracy of the tensor measurement.[53] Sixth, one of the main methodological limitations is that the data have been analyzed using voxel-based morphometry, which is not the most current approach for DTI.[53,54] Tract-based spatial statistics[55] can produce more rigorous results and will be utilized in our ongoing diffusion tensor magnetic resonance imaging study in a large sample of patients with first-episode schizophrenia.

In summary, with fewer confounders, including illness chronicity, antipsychotic medication, and possible progressive white matter atrophy, our findings indicate that patients with first-episode schizophrenia have lower FA values, especially in the 5 brain regions corpus callosum, brainstem, internal capsule, cingulate, and cerebellum at the early stages of illness compared to healthy controls, suggesting the dysconnectivity model of schizophrenia.[2,56] Moreover, lower FA in the left cerebellum was negatively associated with positive symptoms, and lower FA in corpus callosum was positively associated with both the PANSS general psychopathology subscore and the PANSS total score, suggesting that white matter deficits may be associated with the clinical symptoms of patients with first-episode schizophrenia.[8,21] While we speculated that disruption in the brain connectivity may be the neuropathological mechanisms for the symptomatology of schizophrenia, the underlying mechanisms are still unknown, and we were able to show only an association between positive symptoms and general psychopathology in left cerebellum or corpus callosum rather than other brain regions. Therefore, these findings remain preliminary because of the limited sample size and require replication in larger samples in different ethnicities.

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