IMPORTANCE Accumulating evidence supports the hypothesis that cerebral white matter abnormalities are involved in the pathophysiology of schizophrenia; however, findings from in vivo neuroimaging studies have been inconsistent. Besides confounding factors, including age, illness duration, and medication effects, an additional cause for the inconsistent results may be heterogeneity in the nature of white matter alterations associated with the disorder.

OBJECTIVE To investigate whether different patterns of white matter abnormalities exist in a large cohort of medication-naive patients with first-episode schizophrenia and the relationship between such patterns and clinical parameters.

DESIGN, SETTING, AND PARTICIPANTS A cross-sectional diffusion tensor imaging study of 113 medication-naive patients with first-episode schizophrenia and 110 demographically matched healthy control individuals. The study was conducted in the mental health center of West China Hospital, Sichuan University, Chengdu, China, from January 2006 to June 2014.

MAIN OUTCOMES AND MEASURES The patterns of white matter abnormalities revealed by tract-specific analysis in conjunction with hierarchical clustering.

RESULTS With diffusion features extracted from 18 fiber tracts, cluster analysis revealed 2 patterns of abnormalities. One pattern (42.5% of patient sample) showed widespread white matter abnormalities compared with matched healthy control individuals, while another pattern (57.5% of patient sample) only showed circumscribed regional white matter abnormalities, mainly in the left superior longitudinal fasciculus. Patients in these subgroups did not differ in demographic features; however, negative symptoms were more severe in patients with widespread white matter abnormalities.

CONCLUSIONS AND RELEVANCE Two distinct patterns of white matter abnormalities exist at the early phase of schizophrenia, with those having global abnormalities experiencing more severe negative symptoms. The finding that distinct subgroups of patients with schizophrenia have different forms of white matter pathology may reflect qualitatively distinct genetic influences or neurodevelopmental alterations and thus represents a promising strategy for resolving neurobiological heterogeneity in the schizophrenia syndrome.
S

chizophrenia has long been hypothesized as a syn-
drome involving insufficient or ineffective communi-
cation between brain regions.\(^1\) As cerebral white mat-
ter comprises densely packed, mostly myelinated axons that
interconnect gray matter regions, pathology in white matter
has been proposed to be a contributing factor in the patho-
physiology of schizophrenia.\(^2\) This hypothesis has been sup-
ported by postmortem and genetic studies, which have dem-
onstrated abnormalities in myelination,\(^3\),\(^4\) oligodendrocytes,\(^5\)
and axons\(^6\) in patients with schizophrenia.

Using diffusion tensor imaging (DTI), magnetic reso-
nance imaging studies targeting regions of interest (ROIs)
and using voxel-based morphometry and tract-based spatial
statistics\(^7\) have reported decreased fractional anisotropy
(FA), a putative index that reflects white matter integrity, in
patients with schizophrenia. However, the location and
range of deficits varied considerably across studies. For
instance, most ROI-based studies found FA reduction in the
uncinate,\(^8\) cingulum,\(^9\) fornix,\(^10,\)\(^11\) corpus callosum,\(^12\) and
inferior longitudinal fasciculus (ILF),\(^13\) whereas negative
results in the targeted ROIs have also been reported.\(^14,\)\(^15,\)\(^16\)
Results from voxel-based morphometry studies have like-
wise shown different regional patterns of FA reductions in
patients with schizophrenia.\(^17\) Thus far, tract-based spatial
statistic results have shown localized FA reduction within the
superior longitudinal fasciculus (SLF),\(^18,\)\(^19\) or widespread
white matter abnormalities across the whole brain\(^20,\)\(^21\) in
first-episode patients, and in patients with chronic disease,
deficits have been seen in the corpus callosum, ILF, inferior
fronto-occipital fasciculus (IOF), and SLF.\(^22,\)\(^23\)

It is widely accepted that schizophrenia is a heteroge-
nous illness clinically, neurobiologically and genetically.\(^24\)
Thus, a possible explanation for the inconsistent findings is
the existence of different underlying pathophysiology that
lead to different patterns of white matter abnormalities
among subtypes of patients with schizophrenia.\(^25\) The
potential for such heterogeneity is suggested by some early
studies that have reported discrete or more generalized
white matter pathology. For example, Kitis et al\(^26\) reported
FA reduction in the left uncinate and Rowland et al\(^27\) found
lower FA localized to the right superior longitudinal
fasciculus and middle frontal white matter in deficit
syndrome schizophrenia, while Voineskos et al\(^28\) reported
more diffuse alterations in patients with deficit schizophrenia.
Symptom features have also been linked to white mat-
ter pathology as Guo et al\(^29\) reported right lateralized white
matter abnormalities only in paranoid schizophrenia. How-
ever, symptom-based subtyping strategies have been criti-
cized for their instability over time and the inability to
ensure that patients in any clinical subtype share similar
neural system pathology.\(^30\) Thus, an alternative approach
resolving schizophrenia heterogeneity using neurobiologi-
cal parameters, such as diffusion properties of white matter
tracts, may represent an advantageous strategy for identifying
subgroups or subtypes of the illness.

In addition, minimizing the influence of potential con-
founding factors is particularly important in addressing
questions of biological heterogeneity. Most previous DTI
studies included chronic and medicated patients, and it is
conceivable that long-term antipsychotic medication or sec-
ondary factors related to course of illness effects may con-
tribute to abnormalities observed in DTI.\(^31\) Thus, studying
medication-naive first-episode patients is particularly attrac-
tive for investigating heterogeneity in the clinical neurobiol-
ogy of schizophrenia.

The current study aimed to characterize diffusion prop-
erties of major white matter tracts in a relatively large sample
of patients with medication-naive first-episode schizophre-
nia relative to matched healthy control individuals in order to
use cluster analysis to identify subgroups of patients based on
the pattern of white matter alterations in diffusion properties
across fiber tracts and to identify clinical differences be-
tween identified subgroups of patients.

Methods

Participants

In this study conducted from January 2006 to June 2014, par-
ticipants included 113 right-handed patients with first-
episode schizophrenia (56 men; 57 women; mean age, 23.8
years; age range, 16-46) and 110 matched healthy control in-
dividuals (58 men; 52 women; mean age, 23.4; age range, 18-
41) (see the eAppendix in the Supplement for a detailed
description of the demographics). Diagnosis of patients was
determined using the Structured Clinical Interview for DSM-
IV, and clinical symptoms were assessed using the Positive and
Negative Syndrome Scale (PANSS).

This study was approved by the ethics committee of
Sichuan University, Chengdu, Sichuan, China; written
informed consent was obtained from each participant.

Magnetic Resonance Imaging Acquisition

All magnetic resonance imaging scans were performed using a
GE Signa EXCITE 3.0-T scanner (GE Healthcare). Diffusion
tensor imaging (20 diffusion-encoding directions) and high-
resolution Ti data were acquired from each participant (see the
eAppendix in the Supplement for detailed scanning param-
eters).

DTI Processing and Automatic Tracts Identification

Whole-data processing steps are illustrated in eFigure 1 in the
Supplement (see the eAppendix in the Supplement for a de-
tailed description). For routine DTI processing, head motion,
and eddy current correction, brain extraction and tensor model
fitting were all performed using FSL software (FMRIB Software
Library, FMRIB).\(^32\)

We used automated fiber quantification\(^33\) software to
identify 18 white matter tracts in each participant’s brain.
The identification procedure included 3 primary steps:
(1) whole-brain deterministic fiber tractography, (2) waypoint
ROI-based tract segmentation, and (3) probability map-based
fiber refinement (see the eAppendix in the Supplement for a
detailed description of the automated fiber quantification
processing). The identified 18 tracts were bilateral anterior
thalamic radiation, corticospinal tract (CST), cingulum cingu-
late, cingulum hippocampus, IFOF, ILF, SLF, uncinate, genu, and splenium of the corpus callosum (eFigure 2 in the Supplement).

**Feature Extraction, Cluster Analysis, and Cluster Validation**

After tract identification, the diffusion measurement along the tract core, defined as the tract profile, was extracted from each fiber tract. In addition to FA, the tract profile of mean diffusivity (MD), a summative measure that describes average total diffusivity in a given voxel, was also evaluated. The resulting tract profiles were visually inspected to exclude patients with obvious calculation error in fiber reconstruction or identification and then smoothed using 10-point moving average to reduce local dramatic variation caused by imaging noise. The integration of FA and MD values along the full length of tract profiles were defined as the features of a tract (Figure 1). In this way, each tract had 2 features and each participant would have 36 features to depict their global white matter status (see the eAppendix in the Supplement for a detailed description about feature extraction).

Agglomerative hierarchical clustering was performed on patients with schizophrenia using the 36 white matter features extracted above. The optimal cluster number was determined using Silhouette, Dunn, and connectivity indices, which reflect the compactness, separation, and connectedness of the generated clusters. The stability of the cluster solution was also tested using a subsampling technique (see the eAppendix in the Supplement for a detailed description of the cluster analysis and cluster validation).

**Statistical Analysis**

Demographic characteristics, including age, sex distribution, and years of education, were compared between healthy control individuals and patient subgroups identified by the cluster analysis using 1-way analysis of variance or χ² test. Clinical symptom scores (PANSS positive and negative scores) and illness duration were similarly compared between patient subgroups using 2-tailed t test (2 subgroups) or analysis of variance (>2 subgroups). All statistical test results were considered significant if corrected P values were less than .05.

Fractional anisotropy and MD profiles were compared between healthy control individuals and patient subgroups in a pointwise manner. The tract profiles from a participant were arranged in a single matrix. All these matrices were fed into permutation-based statistical analysis with 10,000 permutations using the FSL Randomize program, with age and illness duration as covariates. The statistical results were subject to familywise error correction for multiple comparisons following threshold-free cluster enhancement and thresholded at P < .05 (see eFigure 3 in the Supplement for the flowchart of pointwise comparison).

Additional exploratory analysis of the correlation between diffusion properties and PANSS positive/negative symptoms scores were performed within whole patient group and within each subgroup using partial Pearson correlation, with age as a covariate.

**Results**

**Hierarchical Clustering**

The result of hierarchical clustering is shown as a combination of dendrogram and heat map illustration in Figure 2. According to the definition of used validating indices, the maximum is preferred for both the Silhouette and Dunn indices to determine the optimal number of clusters, while the minimum is preferred for the connectivity index. Our cluster result achieved the maximum for the Silhouette index (0.51) and Dunn index (19.25) and the minimum for connectivity (2.93) when the cluster number was equal to 2 (eFigure 4 in the Supplement). The stability test also suggested the 2-cluster solution is most stable (eFigure 5 in the Supplement). Thus, the optimal cluster number that best
represents the data structure was determined to 2. Subsequent analysis mainly focused on these 2 subgroups (subgroup 1 and subgroup 2 indicated in Figure 2). Forty-eight patients (42.5%) were placed in subgroup 1 and 65 patients (57.5%) were placed in subgroup 2. From visual inspection of the dendrogram, the patients in subgroup 1 showed rela-

Each column represents a patient and each row represents a diffusion property of a fiber tract. Two main subgroups (denoted by subgroup 1 and subgroup 2) were identified. FA indicates fractional anisotropy; IFOF, inferior fronto-occipital fasciculus; ILF, inferior longitudinal fasciculus; L, left; MD, mean diffusivity; R, right; SLF, superior longitudinal fasciculus.

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Abbreviation: NA, not applicable.

of the right SLF (lum hippocampus and right ILF, and the frontallobe portion bilateral CST, the temporal lobe portion of the bilateral cingulate of the left thalamic radiation, the inferior portion of the inother segments in the posterior portion of the left thalamic radiation, the inferior portion of the left anterior thalamic radiation, the inferior portion of the left CST, occipitallobe portion of the splenium of the corpus callosum, both ends of the left cingulum cingulate and left uncinate, the temporal lobeportion of the right uncinate, and the intermediate component of the bilateral IFOF. Subgroup 2 showed regional FA reduction mainly in the left SLF and other small segments in the posteriorportion of the left thalamic radiation, the inferior portion of the bilateral CST, the temporal lobe portion of the bilateral cingulum hippocampus and right ILF, and the frontal lobe portion of the right SLF (Figure 3).

Pointwise comparison of MD profiles between healthy control individuals and subgroup 1 showed extensive elevation in the entire bilateral cingulum hippocampus, bilateral ILF, bilateral IFOF, bilateral SLF, bilateral uncinate, genu of the corpus callosum, the left CST, both ends of the splenium of the corpus callosum and most of the bilateral thalamic radiation, bilateral cingulum cingulate, and the right CST. Subgroup 2 showed regional MD elevation in the inferior portion of the CST and posterior portion of the cingulum cingulate (Figure 4). A summary on average FA and MD of each identified fiber tract from healthy control individuals and patient subgroups was appended in the Supplement (eTables 1 and 2).

Correlation Analysis

In whole patient group partial correlation analysis between PANSS positive/negative and FA/MD of each fiber tract, we found moderate negative correlations between negative symptom score and the average FA of the following tracts: left anterior thalamic radiation (r = −0.36; P < .001), left CST (r = −0.33; P = .005), genu of the corpus callosum (r = −0.42; P < .001), right IFOF (r = −0.41; P < .001), right IFOF (r = −0.32; P = .002), left ILF (r = −0.43; P < .001), and right ILF (r = −0.45; P < .001). Positive correlations were also found between negative symptom score and average MD of the following fiber tracts: left anterior thalamic radiation (r = 0.39; P < .001), right anterior thalamic radiation (r = 0.34; P < .001), left CST (r = 0.41; P < .001), right CST (r = 0.36; P = .001), genu of the corpus callosum (r = 0.32; P = .002), left IFOF (r = 0.36; P < .001), left ILF (r = 0.34; P < .001), and left uncinate (r = 0.34; P = .001). No significant correlation was found between positive symptom score and average FA/MD value of any tract in the whole patient group. In addition, no significant correlation was found between diffusion properties (FA or MD) of fiber tracts and positive or negative symptom scores within either subgroup.

Discussion

Although most researchers agree that white matter abnormalities exist in schizophrenia, whether these abnormalities are localized to specific tracts or spread throughout the brain remains controversial.40 Issues including medication history, varying illness duration, and small sample size have been considered likely to cause these inconsistent findings. Another alternative is that there are neurobiologically distinct subgroups of patients with schizophrenia with discrete forms of white matter pathology. Using a neuroimaging data-driven method, the current study, supporting that second possibil-

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Table. Demographic and Clinical Characteristics for Subgroups of Patients and Matched Healthy Control Individuals

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean (SD)</th>
<th>Healthy Control</th>
<th>Subgroup 1</th>
<th>Subgroup 2</th>
<th>Statistical Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>24.67 (7.57)</td>
<td>23.62 (8.98)</td>
<td>24.35 (6.65)</td>
<td>F = 0.30</td>
<td>df = 2, 220</td>
</tr>
<tr>
<td>Sex, No.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>25</td>
<td>31</td>
<td>58</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>23</td>
<td>34</td>
<td>52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Education, y</td>
<td>11.92 (2.60)</td>
<td>11.78 (3.66)</td>
<td>12.10 (3.30)</td>
<td>F = 0.19</td>
<td>df = 2, 220</td>
</tr>
<tr>
<td>Illness duration, y</td>
<td>0.91 (0.56)</td>
<td>0.72 (0.66)</td>
<td>NA</td>
<td>t = 1.56</td>
<td>df = 111</td>
</tr>
<tr>
<td>Symptoms*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>24.63 (7.41)</td>
<td>24.31 (6.31)</td>
<td>NA</td>
<td>t = 0.25</td>
<td>df = 111</td>
</tr>
<tr>
<td>Negative</td>
<td>22.81 (7.56)</td>
<td>17.09 (7.87)</td>
<td>NA</td>
<td>t = 3.88</td>
<td>df = 111</td>
</tr>
</tbody>
</table>

Abbreviation: NA, not applicable.

* Positive and negative symptom scores from the Positive and Negative Syndrome Scale.
**Patterns of White Matter Abnormalities in First-Episode Schizophrenia**

**Figure 3. The Pointwise Comparison of Fractional Anisotropy (FA) Profile Between Healthy Control Individuals and Patient Subgroups**

The plots of FA profiles of 18 identified fiber tracts from healthy control individuals and patient subgroups (green for healthy control individuals, blue for subgroup 1, and red for subgroup 2) in mean (SD) (solid lines for means and shaded areas for SDs). The blue bars under the FA profile indicate the regions of significant difference between subgroup 1 and healthy control individuals; the red bars under the FA profile indicate the regions of significant difference between subgroup 2 and healthy control individuals. The x-axis represents the location between the beginning and termination waypoint regions of interest. L indicates left; R, right.

In the subgroup with milder and more localized white matter alterations, the SLF, which is the major white matter connecting prefrontal and parietal cortices, was most affected. According to the macrocircuit theory, specific white matter tracts...
Figure 4. The Pointwise Comparison of Mean Diffusivity (MD) Profile Between Healthy Control Individuals and Patient Subgroups

The plots of MD profiles of 18 identified fiber tracts from healthy control individuals and patient subgroups (green for healthy control individuals, blue for subgroup 1, and red for subgroup 2) in mean (SD) (solid lines for means, shaded areas for SDs). The blue bar under the MD profile indicates the regions of significant difference between subgroup 1 and healthy control individuals; the red bar under the MD profile indicates the regions of significant difference between subgroup 2 and healthy control individuals. The x-axis represents the location between the beginning and termination waypoint regions of interest. L indicates left; R, right.

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are disrupted either as a cause or a consequence of a disorder in the gray matter regions they connect. Morphological studies in schizophrenia have observed significant cortical thinning in the prefrontal cortex and superior parietal lobe. Given the observations that regional neuronal activity can regulate oligodendrocyte precursor cell proliferation, oligodendrogenesis, and myelin remodeling to affect white matter microstructure, the regional abnormality in the SLF might be secondary to the cortical abnormality related to functional alteration or genetic factors. It is also worth noting that the SLF is a late-maturing tract, thus potentially more vulnerable to later neurodevelopmental disturbances during adolescence to early adulthood or neurotoxic effects that take place around the onset of the first psychotic symptoms.

It was also noteworthy that patients with widespread and more prominent white matter abnormalities exhibited greater severity in negative symptoms than those with regional deficits. In fact, negative symptoms (ie, anhedonia, amotivation, and social dysfunciton) were found to be related to specific white matter deficits in previous studies, notably with alterations in the corpus callosum, uncinate, SLF, and ILF. Consistent with previous reports, the current study also found moderate correlations between the severity of negative symptoms and diffusion measurements of certain tracts, including the anterior thalamic radiation, CST, genu of the corpus callosum, ILF, IFOF, SLF, and uncinate at the whole patient group level. However, the absence of significant correlation between severity in negative symptoms and diffusion measurements in the subgroup level suggests that the white matter deficit may not be the direct cause of negative symptoms; instead, they may both be downstream phenomena of the same upstream pathogenesis. This hypothesis is partially supported by neurochemical studies that have proven that proinflammatory cytokines can markedly induce anhedonic behavior and social impairments as neuroinflammation is a possible pathogenesis for schizophrenia.

From a broader perspective, our data-driven approach using measures of brain pathology rather than clinical phe-
nomenclature to classify patients may represent a significant advance in the evolution of diagnostic practices in psychiatry to benefit from and use advances from clinical neuroscience. We recognize that our specific observations using DTI data for grouping patients on the basis of the form of their white matter pathology require validation and further exploration of their origins and relevance for the crucial clinical questions about identifying prodromal states and predicting treatment outcomes and illness course. Also, defining the number of subgroups in a patient population remains a statistical challenge, with different approaches yielding somewhat different solutions. Yet, our demonstration of the subtypes of patients classified by their neuroimaging measures in the present study is one step forward in the use of such measures to subgroup and eventually help diagnose illness and plan treatments for patients with psychotic disorders. This is consistent with the broad aims of the Research Domain Criteria project from the National Institute of Mental Health and the Bipolar and Schizophrenia Network for Intermediate Phenotypes consortium, which have collaborated.

Several issues should be considered with regard to interpreting the current findings. First, because we were limited by the number of diffusion directions acquired, the fiber tractography was based on a tensor model, which cannot solve the crossing-fiber problem in some voxels. Furthermore, to avoid anatomical variations from superficial regions, only the portions between 2 waypoint ROIs before tracts arborize to the innervate cortex were used in the analyses. Measuring superficial areas using higher-resolution techniques available now, but that were less established when we began to recruit the study samples, may provide more useful information relevant to the macrocircuit hypothesis in future work.

Although the patient sample used in this study was relatively large and free from medication exposure and course of illness effects, it may be insufficient to fully capture the neurobiological heterogeneity of schizophrenia as seen in white matter tract disturbances. With a larger patient sample, smaller patient subgroups might be detected in cluster analyses or the subgroups defined might be parsed into smaller groups. Thus, replication studies, especially with larger sample sizes to validate and perhaps improve on our identification of 2 subgroups, are needed to extend the findings from the current study.

Conclusions

Using a purely data-driven analysis scheme, the current study identified 2 subgroups of patients with schizophrenia defined by different patterns of white matter abnormalities. The group with more severe and widespread white matter pathology had more severe negative symptoms, suggesting a clinical relevance to the neurobiologically based subgrouping. The findings suggest that patterns of white matter abnormalities may provide a promising biomarker for subtype patients with schizophrenia for studies of illness mechanism and as a quantitative phenotype for genetic research.

REFERENCES

1. Friston KJ. The disconnection hypothesis. Schizophr Res. 1998;30(2):115-125.
11. Takei K, Yamase H, Abe O, et al. Disrupted integrity of the fornix is associated with impaired...
memory organization in schizophrenia. Schizophr Res. 2008;103(1-3):52-61.


