White Matter Abnormalities in Schizophrenia and Schizotypal Personality Disorder

Marc S. Lener1, Edmund Wong2, Cheuk Y. Tang2, William Byne1,3,4, Kim E. Goldstein1, Nicholas J. Blair1,5, M. Mehmet Haznedar1,4, Antonia S. New1,3, Eran Chemerinski1,4, King-Wai Chu1,5, Liza S. Rimsky1, Larry J. Siever1,3,4, Harold W. Koenigsberg1,4, and Erin A. Hazlett*1,3,5

1Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY; 2Translational and Molecular Imaging Institute, Department of Radiology, Icahn School of Medicine at Mount Sinai, New York, NY; 3Mental Illness Research, Education, and Clinical Center (MIRECC VISN 3), James J. Peters Veterans Affairs Medical Center, Bronx, NY; 4Department of Outpatient Psychiatry, James J. Peters Veterans Affairs Medical Center, Bronx, NY; 5Research and Development, James J. Peters Veterans Affairs Medical Center, Bronx, NY

*To whom correspondence should be addressed; Mental Illness Research, Education, and Clinical Center, James J. Peters VA Medical Center, 130 West Kingsbridge Road, Room 6A-44, Bronx, NY, US; tel: 718-584-9000 x3701, fax: 718-364-3576, e-mail: erin.hazlett@mssm.edu

Prior diffusion tensor imaging (DTI) studies examining schizotypal personality disorder (SPD) and schizophrenia, separately have shown that compared with healthy controls (HCs), patients show frontotemporal white matter (WM) abnormalities. This is the first DTI study to directly compare WM tract coherence with tractography and fractional anisotropy (FA) across the schizophrenia spectrum in a large sample of demographically matched HCs (n = 55), medication-naive SPD patients (n = 49), and unmedicated/never-medicated schizophrenia patients (n = 22) to determine whether (a) fronto-striatal-temporal WM tract abnormalities in schizophrenia are similar to, or distinct from those observed in SPD; and (b) WM tract abnormalities are associated with clinical symptom severity indicating a common underlying pathology across the spectrum. Compared with both the HC and SPD groups, schizophrenia patients showed WM abnormalities, as indexed by lower FA in the temporal lobe (inferior longitudinal fasciculus) and cingulum regions. SPD patients showed lower FA in the corpus callosum genu compared with the HC group, but this regional abnormality was more widespread in schizophrenia patients. Across the schizophrenia spectrum, greater WM disruptions were associated with greater symptom severity. Overall, fronto-striatal-temporal WM dysconnectivity is attenuated in SPD compared with schizophrenia patients and may mitigate the emergence of psychosis.

Key words: DTI/MRI/schizotypal personality disorder/schizophrenia/psychosis/white matter/genu/cingulum/inferior longitudinal fasciculus

Introduction

A dimensional approach to investigating the underlying pathophysiology of mental disorders has been promoted by the National Institute of Mental Health (NIMH) as a part of the Research Domain Criteria (RDoC) initiative, as well as leading psychiatry investigators1 cognizant that mental illness exists within a broad spectrum of disorders that may share core phenomenological and pathophysiological characteristics. Prior to the development of the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-5), a cluster model of psychosis was proposed for selected psychotic and related disorders that demonstrated strong evidence of overlap between schizophrenia and schizotypal personality disorder (SPD).2 At present, the schizophrenia spectrum is conceptualized as a continuum of disorders ranging in severity from schizophrenia, characterized by frank psychosis, to SPD, the prototypical schizophrenia-related personality disorder, characterized by less severe, schizophrenia-like symptoms.3 SPD is related to schizophrenia in terms of shared genetics, biological markers, and phenomenological characteristics.4 However, when compared with schizophrenia symptomatology, individuals with SPD experience less severe psychotic-like symptoms, including suspiciousness, magical thinking, ideas of reference, as well as perceptual distortions such as illusions.

Our group has presented a model of the pathophysiology of schizophrenia spectrum disorders4 which posits that shared deficits reflect a common neurodevelopmentally based cortical pathology (eg, prefrontal cortical hypodopaminergia), as well as white matter (WM) pathway connectivity abnormalities between cortical regions of interest, particularly fronto-temporal lobe and subcortical regions. This model also proposes that, in contrast to schizophrenia patients, SPD patients may have factors that protect them from developing frank psychosis, such as greater prefrontal reserves (by way of compensation through recruitment of frontal-mediated
neural circuits), which, in turn, leads to milder cognitive and social impairments.4–6

Fractional anisotropy (FA)—a diffusion tensor imaging (DTI) measure of directional diffusion of water—is a proxy of WM integrity. In general, a reduction of FA is thought to reflect disrupted WM connectivity related to abnormalities in fiber density, axonal diameter, trajectories, and/or myelination. DTI studies of separate groups of schizophrenia and SPD patients have consistently demonstrated FA disturbances in temporal lobe WM and the tracts connecting temporal and frontal lobe regions.7–11 In a meta-analysis of 40 DTI studies in schizophrenia, 34 demonstrated positive findings, the majority of which were in prefrontal and temporal lobe regions.9 A DTI meta-analysis of 15 studies suggested that abnormalities in 2 large WM networks are important in the pathology of schizophrenia.10 The first network interconnects the frontal lobe with the thalamus and cingulate, and includes the corpus callosum (CC) genu, cingulum bundle (CB), left anterior thalamic radiation, left corticobulbar tract, and the left inferior fronto-occipital fasciculus. The second network interconnects the frontal lobe with the insula, hippocampus–amygdala, and occipital lobe, and includes the CC splenium, the fornix/stria terminalis, left inferior longitudinal fasciculus (ILF), and left inferior fronto-occipital fasciculus.10 In subsequent schizophrenia DTI studies, FA reductions have been reported in the anterior limb of the internal capsule (ALIC), arcuate fasciculus, anterior commissure, CB, uncinate fasciculus, and fornix.12–15

Despite only a few DTI studies in SPD, abnormalities in temporal lobe WM tracts have consistently been reported, while frontal lobe findings have been more mixed.16 Consistent with this review and our frontal lobe sparing concept in SPD,4 we reported lower FA in left temporal lobe WM in SPD patients compared with healthy controls (HCs),17 resembling observations in schizophrenia, while HC-SPD differences in frontal lobe WM regions were not significant. While our prior SPD work reported no significant FA reductions in the ALIC, fewer dorsal ALIC-dorsolateral prefrontal cortex (DLPFC) tracts were observed in SPD patients compared with HCs and this abnormality was associated with greater symptom severity.18 Lower FA in the uncinate fasciculus has also been reported in SPD,8 an abnormality that has been associated with greater symptom severity, including ideas of reference, suspiciousness, and interpersonal deficits.7 Taken together, DTI abnormalities in SPD resemble those reported in schizophrenia, but appear to be less marked.

Compared with HCs, patients at high risk for psychosis show lower FA in the superior longitudinal fasciculus and this abnormality has also been associated with clinical deterioration in social and cognitive functioning.19 Similar to chronic schizophrenia patients, first-episode patients exhibit reduced FA in the left uncinate fasciculus,20 as well as reductions in the CC, posterior limb of the internal capsule, external capsule, fornix, superior- and inferior fronto-occipital fasciculus, and CB.21 Trend level FA decreases were also reported in the ILF of first-episode patients, whereas in chronic schizophrenia patients, significant FA decreases were observed,22 suggesting a progressive deterioration in WM integrity. In a study of schizophrenia patients, unaffected relatives, and HCs, the relatives had FA values that fell between patients and controls within the arcuate fasciculus and CB.23 This finding suggests that having frontal-temporal WM abnormalities may increase the risk for psychosis and, among those patients who progress to frank psychosis, progression of WM changes may precede the onset of psychosis and progress during the early course of illness. Taken together, region-specific WM abnormalities have been reported in separate samples of SPD and schizophrenia patients and are associated with severity of illness and/or likelihood to develop frank psychosis.

To our knowledge, no study to date has examined DTI in a schizophrenia spectrum sample that includes both SPD and schizophrenia patients. Given the NIMH RDoC initiative and new DSM-5 includes SPD as a schizophrenia spectrum disorder, this dimensional investigation is an important next step. The aim of the present study was to examine WM tract coherence with tractography, as well as FA across the schizophrenia spectrum and determine whether FA abnormalities in key WM tracts implicated in schizophrenia are similar to, or distinct from those observed in SPD. The study’s aim was to focus on FA in particular WM tracts thought to play an important role in the pathophysiology of schizophrenia spectrum disorders and visible with our magnetic resonance imaging (MRI) scanner capabilities. This included the: CC genu (frontal lobe WM tract), ALIC (frontal-striatal-thalamic tract), ILF (temporal lobe), and the CB (frontal-temporal). A HC group was examined to provide a benchmark for normal FA values and we hypothesized that, compared with HCs, the schizophrenia patients would evince lower FA in WM tracts involving frontal, frontal-striatal-thalamic, and temporal lobe regions, while the SPD patients would be intermediate between the HC and schizophrenia groups and show sparing, particularly in frontal lobe WM tracts. Similar to prior DTI work,7 exploratory correlations between clinical symptom severity and WM integrity (measured as FA) were conducted only for the tracts that showed significant between-group FA differences.

Methods

Sample Characteristics

Forty-nine medication-naive individuals with SPD, 22 schizophrenia patients off all psychoactive medication, and 55 age- and gender-matched HCs were studied (Table 1). Participants received a medical screening and diagnostic interviews were conducted by a clinical psychologist trained in the assessment of Axis I and personality disorders. For all participants, Axis
### Table 1. Demographics for Healthy Control (HC), Schizotypal Personality Disorder (SPD), and Schizophrenia (SZ) Groups

<table>
<thead>
<tr>
<th></th>
<th>Healthy Controls (n = 55)</th>
<th>SPD Patients (n = 49)</th>
<th>SZ Patients (n = 22)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years):</strong></td>
<td>33.4 (9.3; 20–57)</td>
<td>36.5 (10.0; 20–55)</td>
<td>33.2 (9.6; 21–51)</td>
<td>HC vs SPD: P = .11</td>
</tr>
<tr>
<td><strong>Gender:</strong></td>
<td>27 Men</td>
<td>33 Men</td>
<td>16 Men</td>
<td>HC vs SPD: P = .06</td>
</tr>
<tr>
<td></td>
<td>28 Women</td>
<td>16 Women</td>
<td>6 Women</td>
<td>HC vs SZ: P = .93</td>
</tr>
<tr>
<td><strong>Education:</strong></td>
<td>5.2 (2.5; 1–9)</td>
<td>4.7 (2.0; 1–8)</td>
<td>4.1 (1.8; 2–7)</td>
<td>SPD vs SZ: P = .20</td>
</tr>
<tr>
<td></td>
<td>3 L</td>
<td>4 L</td>
<td>2 L</td>
<td>SPD vs SZ: P = .66</td>
</tr>
<tr>
<td></td>
<td>1 Ambidextrous</td>
<td>2 Ambidextrous</td>
<td>1 Ambidextrous</td>
<td>SPD vs SZ: P = .25</td>
</tr>
<tr>
<td><strong>Duration of illness (years):</strong></td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>HC vs SPD: P = .07</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HC vs SZ: P = .94</td>
</tr>
<tr>
<td><strong>Total BPRS score:</strong></td>
<td></td>
<td></td>
<td></td>
<td>SPD vs SZ: P = .96</td>
</tr>
<tr>
<td></td>
<td></td>
<td>32.5 (4.3; range: 24.0–38.0)</td>
<td>32.5 (4.3; range: 24.0–38.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Positive symptom factor score:</strong></td>
<td>12.6 (1.9; range: 7.0–15.0)</td>
<td>12.6 (1.9; range: 7.0–15.0)</td>
<td>12.6 (1.9; range: 7.0–15.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Negative symptom factor score:</strong></td>
<td>6.5 (2.7; range: 4.0–11.0)</td>
<td>6.5 (2.7; range: 4.0–11.0)</td>
<td>6.5 (2.7; range: 4.0–11.0)</td>
<td></td>
</tr>
<tr>
<td><strong>SPD total symptom severity:</strong></td>
<td>7.1 (1.1; range: 5.0–9.0)</td>
<td>7.1 (1.1; range: 5.0–9.0)</td>
<td>7.1 (1.1; range: 5.0–9.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Interpersonal factor score:</strong></td>
<td>3.2 (0.9; range: 1.5–5.0)</td>
<td>3.2 (0.9; range: 1.5–5.0)</td>
<td>3.2 (0.9; range: 1.5–5.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Paranoid factor score:</strong></td>
<td>2.2 (0.7; range: 1.0–3.0)</td>
<td>2.2 (0.7; range: 1.0–3.0)</td>
<td>2.2 (0.7; range: 1.0–3.0)</td>
<td></td>
</tr>
<tr>
<td><strong>Cognitive factor score:</strong></td>
<td>1.8 (0.6; range: 0.0–3.0)</td>
<td>1.8 (0.6; range: 0.0–3.0)</td>
<td>1.8 (0.6; range: 0.0–3.0)</td>
<td></td>
</tr>
</tbody>
</table>

**Note:** Standard deviations and ranges are shown in parentheses. t Tests were conducted for between-group comparisons and P values are reported. Participants were screened for severe medical or neurological illness and head injury by comprehensive medical history and laboratory tests taken by a physician. For all participants, exclusionary criteria included: history of significant head trauma, neurological disease, organic mental syndromes, significant medical illness, history of substance dependence, substance abuse disorder within the previous 6 months, any psychoactive medication in the last 2 weeks (6 weeks for fluoxetine), or a positive urine toxicology screen for drugs of abuse on the day of the MRI. SPD patients were also excluded if they met criteria for a past or present psychotic disorder or bipolar I disorder. HC participants had no history of an Axis I or personality disorder or a first-degree relative with an Axis I disorder. MRI, magnetic resonance imaging.

*Education = highest degree earned: where 1 = some high school, no diploma; 2 = General Education Degree (GED); 3 = high school diploma; 4 = technical training; 5 = some college, no degree; 6 = associate's degree; 7 = bachelor's degree; 8 = master's degree; 9 = MD/PhD/JD/PharmD.*

*For the schizophrenia group, clinical symptom severity was assessed with the Brief Psychiatric Rating Scale (BPRS) on the day of the MRI scan and 2 patients did not have a complete BPRS so, their data are not included.*

*For the SPD group, clinical symptom severity was assessed using methodology published in earlier papers (eg, 6, 17). Briefly, each of the DSM-IV criteria for SPD were rated on a 4-point scale (0 = absent, 0.5 = somewhat present, 1.0 = definitely present/prototypic, 2.0 = severe, pervasive during the Structured Interview for Personality Disorders (SID-P). As required for a DSM-IV diagnosis of SPD, these patients met at least 5 of the 9 SPD criteria with a rating ≥1.0. To quantify the level of overall clinical symptom severity, we added up these 9 individual symptom ratings for a total severity score. Next, we calculated 3 different factor scores based on prior work (eg, 6, 17). First, an interpersonal/negative symptom factor score for SPD was calculated by totaling the scores for 4 of the SPD symptom criteria: odd thinking and speech (item 4 of the DSM-IV criteria), inappropriate or constricted affect (item 6), odd behavior (item 7), and social isolation (item 8). Second, a paranoid factor score was calculated by totaling the scores for ideas of reference (item 1), suspiciousness (item 5), and social anxiety (item 9). Lastly, a cognitive/perceptual factor score was calculated by totaling the scores for odd beliefs and magical thinking (item 2) and unusual perceptual experiences/illusions (item 3).*

I diagnoses were determined with the Structured Clinical Interview for DSM-IV Disorders and for HC and SPD participants, personality disorder diagnoses and severity of SPD symptoms were determined with the Structured Interview for DSM-IV Personality Disorders (SIDP-IV). In our group, the intraclass correlation for the SPD diagnosis is kappa = 0.73. All HC and SPD participants were recruited through advertisements in local newspapers/online postings. Schizophrenia patients were recruited through referrals from the psychiatry emergency room and outpatient clinics at the Mount Sinai Hospital. None of the SPD patients had been hospitalized previously or taken antipsychotic medication. The schizophrenia patients were off psychoactive medications at the time of their scan for a minimum of 2 weeks as in our other studies, or were never medicated (n = 5). Participants provided written informed consent approved by the Institutional Review Board. Functional MRI (fMRI) data from a subset of the participants in the present DTI study were previously reported, as follows: (HC and SPD patients) and (HC and schizophrenia patients; Koenigsberg HW, unpublished data).

### Measures of Symptom Severity

To examine the clinical correlates of FA abnormalities in schizophrenia, we calculated overall clinical symptom...
severity with the total 18-item Brief Psychiatric Rating Scale (BPRS) score, as well as the positive and negative symptom factor scores. For each of the SPD patients, we calculated the following symptom severity scores from the SIDP-IV: (a) each of the 9 DSM-IV symptom criteria for SPD were rated on a 4-point scale (0 = absent, 0.5 = somewhat present, 1.0 = definitely present/prototypic, and 2.0 = severe/pervasive) and the total was calculated as an overall symptom severity score. As required for a DSM-IV diagnosis of SPD, these patients met at least 5 of the 9 SPD criteria with a rating ≥1.0: (b) based on our prior morphometric and FA work in SPD, we calculated 3 symptom factor scores: interpersonal/negative, cognitive/perceptual, and paranoid (table 1).

**Diffusion Tensor Imaging**
All participants were scanned on a Siemens Allegra 3T head-dedicated scanner at Mount Sinai Hospital for acquisition of axial structural and diffusion tensor images. A pulsed-gradient spin-echo sequence with echo planar imaging pulse sequence acquisition was used. A b-factor of 1250 was chosen based on tests performed to find the optimal balance for signal-to-noise ratio and diffusion weighting. Twelve gradient directions with $b = 1250$ s/mm$^2$ were used (repetition time $[TR] = 4100$ ms, echo time $[TE] = 80$ ms, field of view $[FOV] = 21$ cm, matrix $128 \times 128$, 28 slices, thickness = 3 mm, skip = 1 mm). High-resolution 3D-MP-RAGE images were also obtained ($TR = 2500$ ms, $TE = 4.4$ ms, $FOV = 21$ cm, matrix size = $256 \times 256$, 208 slices with thickness = 0.82 mm).

**Image Processing and Statistical Analysis**
DTI tractography was implemented in Matlab v2013 (The Mathworks) and used the brute force, streamline algorithm with multiple anatomical criteria for each tract increasing the validity of the tractography. Streamline termination criteria for FA was $<0.10$ and for intervoxel deflection was ($>45^\circ$). To minimize intersubject variance and maximize reproducibility, all anatomical tracking criteria were defined on a study-specific template (ie, mean FA image of all subjects in the current study) that was created with the tract-based spatial statistics package (TBSS) of FSL (FSL, Oxford, www.fmrib.ox.ac.uk/fsl). Tracking criteria were converted from template coordinates to each subject's DTI image using the transformation determined by the TBSS routine. The anatomical definitions for tracking the genu and splenium of the CC, bilateral ILF, and bilateral CB were guided by prior work describing how to identify these tracts. Tract-specific FA was entered into a mixed-model MANOVA. We report the multivariate (Wilks Lambda) $F$ from Statistica to adjust probabilities for repeated-measure effects with more than 2 levels. Fisher’s Least Significant Difference post-hoc tests were used to follow-up significant interaction effects with diagnostic group. The between-group factor was diagnostic group: HC vs SPD vs schizophrenia. The repeated measures included: WM tract (CB, ILF, and ALIC) and hemisphere. In addition to tractography methods, voxel-wise analysis was performed using the TBSS routines implemented in FSL (FSL, Oxford, www.fmrib.ox.ac.uk/fsl) to compare FA between groups on the WM skeleton image (multiple-comparison correction was used and the $P$ value was set to 0.05). Additional details on the tractography methods can be found in our prior publication.

Clinical correlations with FA were evaluated with Pearson’s $r$ for only those WM tracts that showed significant between-group differences. Similar to prior DTI work, correlations were evaluated on an exploratory basis, with $P < .05$ as the cut-off for reporting statistical significance, rather than by using a correction for multiple comparisons.

**Results**

**TBSS Analysis**
As can be seen in figure 1, the TBSS analysis showed an overall spectrum pattern for FA abnormalities with schizophrenia patients exhibiting marked decreases in the CC genu and ALIC compared with the HC group. Additionally, the schizophrenia patients showed less marked but significantly lower FA in the posterior limb of the internal capsule and medial temporal region (ILF) compared with HCs. In contrast, the SPD patients only showed decreased FA compared with HCs in the CC genu. There were no significant SPD-schizophrenia differences for the TBSS analysis.

**Tract-Specific Fractional Anisotropy Analysis**
FA in the ILF showed a spectrum pattern with HC > SPD > schizophrenia that was more robust in the left hemisphere (HC > schizophrenia, $P < .01$; SPD > schizophrenia, $P < .02$). In the CB, there were no HC-SPD differences, but the schizophrenia patients had significantly lower left hemisphere FA compared with both the HC and SPD groups (HC > schizophrenia, SPD > schizophrenia, both $P < .01$), diagnostic group $\times$ tract $\times$ hemisphere interaction, $F[4,244] = 3.09$, $P < .02$ (figure 2). Although a spectrum pattern for FA in the ALIC emerged, there were no statistically significant between-group differences.

Averaged across WM tracts (CB, ILF, and ALIC), the schizophrenia patients showed lower FA in the left hemisphere (HC > schizophrenia, SPD > schizophrenia, both $P < .01$) compared with both HCs and SPD patients, $F[2,123] = 5.79$, $P < .01$ (figure 3). Both of these interaction effects remained significant with an ANCOVA controlling for gender and handedness.
Correlations were conducted between symptom severity scores and FA values for the tracts that showed significant between-group differences, including CC genu, left ALIC, left ILF, and left CB. Analyses were conducted separately for the SPD and schizophrenia groups.

In the schizophrenia group, greater overall symptom severity was associated with lower FA in the CC genu.
(r[18] = −.53, P < .02; figure 4, top), left ILF (r[17] = −.47, P < .05; figure-4, middle), and at a trend level, the left ALIC (r[18] = −.42, P < .07). The correlation coefficient for the left cingulum did not reach significance (P > .26). Greater positive symptom severity was associated with lower FA in the genu (r[18] = −.48, P < .04) and left ILF (r[17] = −.47, P < .05). None of the correlations with negative symptoms reached significance or trend levels.

In the SPD group, greater overall symptom severity was also associated with lower FA in the CC genu (r[47] = −.36, P < .02; figure 4, bottom) and at trend levels in the left ILF and left cingulum (both r values = −.25, P values < 0.09). The correlation for the left ALIC was not significant (P > .73). Greater interpersonal-related symptom severity was associated with lower FA in the genu (r[47] = −.44, P < .002) and the left cingulum (r[47] = −.31, P < .04), and at a trend level in the left ILF (r[47] = −.27, P < .07). None of the correlations with paranoid or cognitive impairment factors were significant.

**Discussion**

The main finding of this study is that schizophrenia patients exhibit reduced FA in specific frontal, frontal-striatal, and temporal lobe WM tracts, while SPD patients demonstrate FA values in these same WM regions that are intermediate between the HC and schizophrenia groups. To our knowledge, this is the first DTI study to directly compare SPD and schizophrenia patients and reveal a pattern consistent with the concept that WM abnormalities reflect a spectrum pattern with SPD patients showing less severe WM disturbances compared with schizophrenia patients.

Of the tracts examined, which included the CC genu, ALIC, ILF, and CB, the SPD patients only differed significantly from HCs in the genu while HC-schizophrenia differences were more marked and widespread. These results are consistent with a large number of DTI studies in schizophrenia reporting regional WM changes, eg, [10,11]. Decreased FA within the CC genu has been well replicated in schizophrenia patients, [10,11] nonpsychotic offspring of schizophrenia patients, [15] and at-risk individuals who developed schizophrenia as compared with a high-risk comparison group who did not develop psychosis. [36] FA in the CC has not previously been examined in SPD, although we have reported attenuated CC shape abnormalities in SPD compared with schizophrenia. [37] Thus, this pattern of FA findings in SPD is consistent with our hypothesis that they have relative sparing of frontal pathways implicated in schizophrenia. It also highlights the possibility that corticocortical and transcallosal altered connectivity in the schizophrenia spectrum may be relevant for the pathophysiology and the cognitive disturbances of these disorders, particularly with regard to the attention/executive and motor functioning deficits of schizophrenia which are less severe in SPD. It should be noted that there were more women in the HC group compared with both the SPD and schizophrenia groups (although this difference was not statistically significant).
Recent work demonstrates that women have greater FA in the CC, particularly in the genu. Further DTI work is needed to fully examine gender differences in FA across the spectrum. Our findings extend prior work showing FA reductions in the CC genu in schizophrenia, by indicating that symptom severity in both SPD and schizophrenia is associated with reduced FA in this WM tract.

Consistent with the notion that anatomical pathology may preferentially affect left hemisphere brain structures in schizophrenia, our tract-specific FA findings indicate left lateralized WM abnormalities in the ILF and CB in schizophrenia. Laterality disturbances in white and gray matter have been commonly reported in schizophrenia over the past several decades. This WM pathology in schizophrenia may represent disruptions in myelination during normal brain maturation. The ILF interconnects the temporal and occipital lobes, passes through the hippocampus and parahippocampus, and is a major associative connection between the fusiform gyrus, a region shown to be reduced in first-episode schizophrenia, and the lingual gyrus. FA reductions in the ILF have been reported previously in individuals at high risk for schizophrenia and patients with chronic schizophrenia. The SPD group was intermediate between HCs and schizophrenia patients for left ILF FA, not significantly differing from HCs but significantly higher than the schizophrenia patients. The TBSS analysis also showed reduced FA in the schizophrenia patients compared with HCs in a small but significant region of the medial temporal lobe in the region of the right ILF. This finding is consistent with prior schizophrenia work showing an association between lower right medial temporal lobe FA and reduced N-acetylaspartate which may result from compromised viability of underlying neurons. Furthermore, trend level FA decreases in the left and right ILF have been shown in first-episode schizophrenia compared with HCs, whereas chronic schizophrenia patients show significantly lower left ILF FA. Prior work has shown lower FA in the left ILF in younger, early-onset schizophrenia patients compared with demographically similar HCs that did not appear to differ when compared with an older patient group. This suggests that the ILF may be a particularly vulnerable area conferring risk for developing psychosis. Moreover, this FA reduction may contribute to, or be the result of reductions in gray matter volume in the left temporal lobe which is a well-replicated finding in schizophrenia and SPD patients.

Our finding of decreased cingulum FA in schizophrenia replicates prior DTI work, eg, . The CB is a key WM tract which connects the cingulate cortex to other frontal areas, as well as to the amygdala, mediodorsal thalamus, and nucleus accumbens. In contrast to schizophrenia, the SPD group showed sparing in the CB, consistent with the concept that they exhibit greater prefrontal capacity compared with schizophrenia patients and intact CB connectivity.
in SPD may protect these individuals from full-blown psychosis. Nakamura et al. also reported normal CB FA in SPD patients. However, our prior work which used a tracing method for distinguishing cingulum subdivisions reported lower posterior cingulum FA and higher anterior cingulum FA in SPD. Based on cytoarchitectonics, the CB is divided into anterior and posterior subdivisions which have different functions and WM connections. Thus, it will be important for future schizophrenia spectrum studies to compare FA in these CB subdivisions in SPD and schizophrenia patients. Finally, in our TBSS analysis, the FA reduction observed in the posterior limb of the internal capsule in schizophrenia adds to a small set of studies reporting similar findings.

Among the schizophrenia patients, lower FA in the CC genu and at a trend level, in the left ILF was associated with greater overall clinical symptom severity, consistent with prior work demonstrating strong correlations between WM disruptions in these regions and the symptoms of schizophrenia. Additionally, our findings indicate that lower FA in the genu is associated with greater positive symptom severity in schizophrenia, extending prior work in medicated schizophrenia patients. These tracts have been identified within a larger network of WM abnormalities in numerous DTI studies of schizophrenia. Our correlational findings are consistent with the concept that lower FA in the CC may confer psychosis but are in contrast with prior schizophrenia work indicating that lower FA in the CC genu is associated with greater negative symptom severity, as well as, higher FA in frontal-temporal WM being associated with greater positive symptom severity. Inconsistency between studies is likely due to differences in patient characteristics (eg, the schizophrenia patients in the present study were unmedicated and not chronic) and/or differences in DTI analysis.

Consistent with prior work, our study showed an association between lower FA in the CC genu and greater interpersonal-related symptom severity in SPD patients. This pattern of findings suggests that in SPD, dysconnectivity in the CC genu is a possible anatomical substrate of negative or deficit-like symptoms, whereas in schizophrenia, dysconnectivity in the genu may underlie overall symptom severity which is predominantly characterized by psychotic symptoms. Some prior schizophrenia work has shown lower CC FA was associated with all 3 Positive and Negative Syndrome Scale scores (total, positive, and negative symptoms) suggesting that abnormalities in the CC may not discriminate between symptom type. Future DTI work will need to employ a common measure of clinical symptom severity across the spectrum to determine more precisely whether these dimensions of psychopathology have distinct underlying pathophysiology related to frontal-striatal-temporal WM dysconnectivity.

We have identified specific WM abnormalities in SPD that are less severe than those observed in schizophrenia. Reduced FA may be attributed to impairments in myelination of axons or axonal membranes, and/or decreased density of axons. Postmortem neuropathological studies of patients with schizophrenia have shown evidence of atrophy and swelling of periaxonal oligodendrocyte processes, abnormalities in oligodendrocytes, including abnormalities in density and oligodendrocyte-specific gene expression in the internal capsule, dysfunction in myelin and fatty acid biosynthesis, as well as abnormal cortical subplate development and maldistribution of neurons within subcortical white WM that may be genetically derived. Our DTI findings are consistent with the model proposed by Siever and Davis suggesting that greater frontal lobe reserves, or “sparking” in SPD compared with schizophrenia protect the SPD individual from the severe cognitive deterioration and social deficits associated with chronic schizophrenia. Further, this model hypothesizes that genetic factors independent of the vulnerability to the schizophrenia spectrum per se and/or more favorable environmental influences leave the SPD individual better buffered with regard to frontal lobe structure and function. Consistent with this concept, the present data indicate that individuals with SPD show less frontal (CC genu) and frontal-striatal (ALIC) WM dysconnectivity compared with schizophrenia patients. Previous DTI work in healthy adolescent WM development suggests the importance of connectivity in frontal lobe WM tracts as a specific target for neurodevelopmental disorders including those in the schizophrenia spectrum. In a recent large, cross-sectional, multicenter tractography study of bipolar disorder patients, lower FA values in the CC were similar to those reported in schizophrenia. Interestingly, patients with psychotic features had lower CC FA compared with patients without such features, suggesting that interhemispheric dysconnectivity may be a core feature of psychosis which is consistent with our CC finding of relative sparing in SPD—a schizophrenia spectrum disorder without full-blown psychosis.

This study has some limitations that merit discussion. Our methods did not allow us to examine the uncinate fasciculus—an important WM tract connecting frontal and temporal lobes, or the anterior vs posterior subdivisions of the cingulum. Future schizophrenia spectrum research should include these additional regions. It could be argued that our sample is unrepresentative of schizophrenia given that the patients were either off psychoactive medication, or medication-naïve at the time of scanning. Similarly, our SPD sample was medication naïve which is not unusual for a community sample. However, the clear advantage to this approach is that we minimized the potential confound of antipsychotic medications on WM integrity in schizophrenia and avoided it altogether in SPD.
Unfortunately, we were unable to employ a measure of symptom severity common to both groups. We obtained the BPRS for the schizophrenia group and factor scores from the SIDP-IV for the SPD group. Future DTI work needs to examine symptom severity as a dimensional variable across the schizophrenia spectrum. The diagnostic groups in this study were scanned under different fMRI protocols (ie, schizophrenia patients performed a fMRI task that was different than the SPD group), yet they received the same DTI protocol allowing for a novel schizophrenia-spectrum comparison. Multimodal neuroimaging studies are needed in order to elucidate the complex interplay between WM integrity and functional changes across the schizophrenia spectrum.

Our findings are consistent with recent DTI work from the Bipolar Schizophrenia Network on Intermediate Phenotypes study\textsuperscript{31} that reported a significant stepwise progression pattern for FA values within the CC genu: HCs > relatives without cluster A > cluster A relatives (primarily SPD) > schizophrenia probands. Thus, it is possible that genetic risk factors present in SPD differ from those observed in schizophrenia, insofar as protective genetic variants exert effects visible at the level of frontal lobe WM tracts. It is also possible that neurodevelopmental abnormalities in WM may occur in individuals with SPD but to a lesser degree than in schizophrenia patients. Future work targeting brain circuitry, including postmortem morphometric, molecular, biological, and genetic studies of WM will help to further characterize WM pathology across the spectrum. Finally, our findings also indicate that in the spectrum, FA in the CC genu and ILF are associated with symptom severity, suggesting that frontal-temporal WM tracts may constitute a target area for novel pharmacological development and interventions.

Funding
National Institutes of Health and the Veterans Administration (NIMH-R01-MH073911 and VA MERIT-I01CX00026 to E.A.H.). Partial support for the schizophrenia sample was also provided (NIMH-R01-MH069947 to H.W.K.).

Acknowledgment
The authors have declared that there are no conflicts of interest in relation to the subject of this study.

References


60. Nakamura K, Kawasaki Y, Takahashi T, et al. Reduced white matter fractional anisotropy and clinical symptoms in...


