Corpus Callosum Abnormalities and Their Association with Psychotic Symptoms in Patients with Schizophrenia

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Background: While the neuroanatomical underpinnings of the functional brain disconnectivity observed in patients with schizophrenia (SZ) remain elusive, white matter fiber bundles of the brain are a likely candidate, given that they represent the infrastructure for long-distance neural communication.

Methods: This study investigated for diffusion abnormalities in 19 patients with chronic SZ, relative to 19 matched control subjects, across tractography-defined segments of the corpus callosum. Diffusion-weighted images were acquired with 51 noncollinear gradients on a 3T scanner (1.7 mm isotropic voxels). The corpus callosum was extracted by means of whole-brain tractography and automated fiber clustering and was parcelled into six segments on the basis of fiber trajectories. The diffusion indexes of fractional anisotropy (FA) and mode were calculated for each segment.

Results: Relative to the healthy control subjects, the SZ patients exhibited mode increases in the parietal fibers, suggesting a relative absence of crossing fibers. Schizophrenia patients also exhibited FA reductions in the frontal fibers, which were underpinned by increases in radial diffusivity, consistent with myelin abnormalities. Significant correlations were observed between patients’ degree of reality distortion and their FA and radial diffusivity, such that the most severely psychotic patients were the least abnormal in terms of their frontal fiber diffusivity.

Conclusions: The SZ patients exhibited a variety of diffusion abnormalities in the corpus callosum, which were related to the severity of their psychotic symptoms. To the extent that diffusion abnormalities influence axonal transmission velocities, these results provide support for those theories that emphasize neural timing abnormalities in the etiology of schizophrenia.

Key Words: Corpus callosum, diffusion tensor imaging, fractional anisotropy, mode, schizophrenia, tractography

The unifying tenet of the increasingly popular disconnectivity theories of schizophrenia (SZ) (1–3) is that the disorder is ultimately caused by abnormal interactions between pathological brain regions, as opposed to regional neuropathology per se. In addition to providing a prima facie account of the cognitive disorganization characteristic of the disease, support for the disconnectivity theories has been provided by a number of electrophysiological and functional imaging studies that have reported abnormalities in the degree of correlated activity between spatially disparate brain regions in patients with schizophrenia (4–6). The neuroanatomical underpinnings of this aberrant functional connectivity are as yet unknown and represent a point of divergent focus (but not, it should be emphasized, contradiction) between the various disconnectivity theories. While some models have emphasized the role of aberrant synaptic plasticity in the etiology of the disorder (2), others have focused on the role of abnormalities in the physical infrastructure for long-distance neural communication, i.e., white matter (WM) (3). With respect to the latter, white matter is primarily constituted of the phospholipid processes (known as myelin) of a specialized class of neuroglia called oligodendrocytes (7). Myelin ensheathes axons in the nervous system, electrically insulating the axon membrane and increasing the conduction velocity of action potentials. Myelinated axons with similar destinations fasciculate into fiber bundles, which constitute the primary infrastructure for communication between spatially disparate brain regions. It has previously been suggested that abnormalities in WM fiber bundles could represent the neuroanatomical bases for many of the observed abnormalities in functional connectivity in patients with schizophrenia (3).

The corpus callosum (CC) is the largest WM fiber bundle in the brain and connects homologous regions of the two cerebral hemispheres. The CC has been implicated in SZ by those who emphasize the role of abnormal hemispheric specialization and abnormal interhemispheric communication in the etiology of the disease (8). While conventional magnetic resonance imaging has provided only equivocal evidence for CC abnormalities in patients with schizophrenia (see [9] for a review), a more consistent picture of structural abnormality has been provided by those studies that have employed the more sensitive (at least with...
respect to WM pathology) modality of diffusion tensor imaging (DTI) (see [10] for a review). However, while these previous studies have provided novel and valuable information regarding the location and extent of SZ-specific structural abnormalities in the CC, they have also exhibited some methodological limitations. First, the majority of previous studies have employed a somewhat arbitrary protocol for segmenting the CC, often based on geometric rather than anatomical boundaries, which may be insufficiently sensitive to detect subtle, regionally specific diffusion abnormalities. Second, most previous DTI studies have investigated for group-wise differences on only a single diffusivity metric—namely fractional anisotropy (FA), which is a measure of the asphericity of water diffusion. However, as noted by Hasan (11), FA is only able to provide a limited picture as to the three-dimensional shape of the observed diffusion. Fractional anisotropy cannot, for example, distinguish between prolate (i.e., cigar shaped) and oblate (i.e., pancake shaped) diffusion, despite these presumably having markedly different microstructural underpinnings. The present study aimed to address these methodological limitations in two ways. First, this study employed a previously validated analysis method (12) to distinguish between fiber bundles on the basis of the cortical regions to which they projected, thus avoiding the need for an inflexible geometric schema. Second, in addition the stalwart metric of FA, this study also investigated a second, orthogonal diffusion index: mode (13). Mode is a measure of the prolateness/oblateness of a diffusion ellipsoid, thus providing additional insight into the three-dimensional shape (and hence microstructural underpinnings) of observed diffusion, relative to that provided by FA alone. The second aim of this study was to investigate the basis for a consistently reported, if somewhat paradoxical, finding of a positive correlation between SZ patients’ FA and the severity of their hallucinations and delusions (14-17). Although the explanation behind this curious relationship has not yet been established, we have recently suggested that while psychotic symptoms may arise when the brain attempts to integrate mildly temporally dysmetric activity in spatially disparate cerebral regions, more severe temporal discoordinations might not be able to be integrated and thus might be incapable of giving rise to psychotic symptoms (18). Given the role that WM (and especially myelin) is known to play in modulating the speed of neural transmission, we predicted that severely psychotic SZ patients would show less extensive myelin abnormalities relative to SZ patients with less severe psychotic symptoms. In summary, the two aims of the present study were 1) to provide a comprehensive description of the shape and extent of water diffusion across tractography-defined subregions of the CC, with the aim of inferring the microstructural underpinnings of any observed diffusion abnormalities in SZ patients, and 2) to investigate the relationship between psychotic symptom severity and WM integrity (as assessed with FA and radial diffusivity), the latter of which has been proposed as a putative measure of myelin integrity [19] in SZ patients.

### Methods and Materials

#### Participants

Nineteen male patients with chronic schizophrenia were recruited from outpatient, inpatient, day treatment, and foster care programs at the Veterans Administration Boston Healthcare System, Brockton, Massachusetts. Diagnosis of schizophrenia was made in accordance with DSM-IV criteria on the basis of the Structured Clinical Interview for DSM-IV (conducted by a clinically and research-trained psychologist [P.G.N.L.] and a review of the medical record. Nineteen male healthy control subjects were recruited from the general community. The control subjects were group matched to the patients on age, handedness, parental socioeconomic status (20), and estimated premorbid IQ, as assessed by performance on the reading scale of the Wide Range Achievement Test (21). More than 90% of the participants in this study were new (10% were previously tested on the 1.5T magnet), and none overlapped with the samples described in previous studies by our group (e.g., [22–24]). Exclusion criteria for all subjects were left-handedness, a history of electroconvulsive shock therapy, a history of neurological illness including epilepsy, a lifetime history of substance dependence or a history of substance abuse within the past 5 years, a history of steroid use, and estimated premorbid IQ below 75. Furthermore, control subjects were screened for the presence of an Axis I disorder using the Structured Clinical Interview for DSM-IV, Nonpatient Edition (25) and were also excluded if they reported having a first-degree relative with an Axis I disorder.

The study was approved by the Veterans Affairs Boston Healthcare System, the Harvard Medical School Internal Review Board, and the Massachusetts Department of Mental Health.
Board Committee, and the Brigham and Women’s Hospital Human Subjects Committee. After a detailed description of the study, each subject gave written informed consent to participate. The demographic details for the patients and control subjects are summarized in Table 1.

Image Acquisition
Diffusion data were collected on 3 Tesla GE Echospeed system (General Electric Medical Systems, Milwaukee, Wisconsin). Diffusion-weighted images were acquired using an echo planar imaging sequence and a double echo option to reduce eddy current-related distortions. To reduce impact of echo planar imaging spatial distortion, an eight-channel coil and Array Spatial Sensitivity Encoding techniques (General Electric Medical Systems, Milwaukee, Wisconsin) with a SENSE-factor (speed-up) of two was used. Eighty-five axial slices parallel to the anterior commissure-posterior commissure line covering whole brain were acquired in 51 diffusion directions with $b = 900$. In addition, eight baseline scans with $b = 0$ were also acquired. The scan parameters were as follows: repetition time 17,000 msec, echo time 78 msec, field of view 24 cm, $144 \times 144$ matrix, 1.7 mm slice thickness, producing isotropic $1.7 \times 1.7 \times 1.7$ mm voxels. The total scanning time was 17 minutes.

Whole-Brain Tractography
The methods used in this study have been described in detail elsewhere (12). For each subject and each image element (voxel), diffusion tensors were estimated from the 59 diffusion-weighted images. The resultant DTIs were first edited to remove extracerebral voxels via a semiautomated generation of a brain “mask.” Deterministic (streamline) tractography was then performed via a Runge-Kutta second-order protocol with a fixed step size of .5 mm. Seed points were placed at every point for which Westin’s linear anisotropy measure (CL) was greater than .3 (the seeding criterion). Tractography proceeded from each seed point in .5-mm steps and followed the principal direction of the diffusion ellipsoid. Tracking was stopped when CL fell below .15. The seeding and stopping thresholds were based on the CL rather than on FA to avoid the circularity inherent in using a dependent variable to define the trajectories of the fiber tracts being measured. A length threshold was also employed whereby fibers were excluded if they were shorter than 20 mm.

Fiber Clustering
The fiber-clustering procedure has been described in detail previously (26). The whole-brain tractography procedure (Figure 1A) generated somewhere in the vicinity of 20,000 fibers per subject. The purpose of fiber clustering was to group fibers with similar shapes and spatial positions into clusters. First, FA maps calculated for each subject were mapped into a common coordinate system using a congealing registration (27), and the parameters for this registration were applied to each subject’s three-dimensional set of fiber trajectories. Second, each fiber was compared with every other fiber in the trajectory set, and the average distance between pairs of nearest points on the fibers was calculated. This mean fiber-distance ($D_{ij}$) was then converted into a similarity value ($W_{ij}$) via the formula

$$W_{ij} = e^{-\frac{D_{ij}^2}{\theta}}$$

where $\theta = 60$ mm. The role of $\theta$ was to set the distance over which fibers could be considered similar (26). The similarity value of each fiber to every other fiber was entered into an affinity matrix (W), and the top 15 eigenvectors of W were used to calculate the most important shape similarity information for each fiber. The clustering algorithm used k-way normalized cuts, which produces clusters with high within-cluster similarity and low between-cluster similarity (28). Fiber clustering was performed on the amalgamated fiber tracts of all subjects in the study (as opposed to clustering each subject separately), as this enabled the identification of homologous fiber clusters (FCs) between subjects. Tractography and fiber clustering were performed using MATLAB 7.0 (http://www.mathworks.com, The MathWorks, Natick, Massachusetts) and 3D-Slicer (http://www.slicer.org, Surgical Planning Laboratory, Brigham and Women’s Hospital, Boston, Massachusetts), which is freely available to the research community.

Extraction and Segmentation of the Corpus Callosum
The output of the clustering procedure was 400 FCs, each consisting of a spatially and morphologically similar subset of the

Figure 1. A summary of the image processing procedures. First, whole-brain tractography was performed on each subject’s diffusion-weighted image (A), and the resultant fibers combined for all subjects. Fibers with similar shapes and spatial positions were then grouped together into one of 400 fiber clusters (B). The fiber clusters constituting the corpus callosum were then identified for a randomly selected subject (C) and subsequently subdivided into six segments on the basis of which cortical regions the fiber clusters projected (D). The fiber clusters constituting each of the six corpus segments were then automatically extracted for all subjects and the average fractional anisotropy and mode of these fiber clusters calculated. As illustrated in (D), the six corpus segments were CC1 (red)—frontal fibers (defined as fibers projecting anterior to the supplementary motor area), CC2 (blue)—premotor fibers (defined as fibers projecting to the supplementary motor area or premotor areas), CC3 (green)—sensorimotor fibers (defined as fibers projecting to the primary motor or primary sensory cortices), CC4 (pink)—parietal fibers (defined as fibers projecting to the superior or inferior parietal lobules), CC5 (orange)—occipital fibers (defined as fibers projecting posterior to the parieto-occipital sulcus), and CC6 (yellow)—temporal fibers (defined as fibers projecting ventrally to the temporal cortices). The corpus segmentations of four randomly selected subjects are displayed in (E).
fibers generated from the whole-brain tractography (Figure 1B).
Of these 400 FCs, 75 were judged to constitute the corpus
callosum, based on the consensus of two independent raters
(T.H.W. and J.S.S.) on three randomly selected participants (intrarater reliability = .901). These 75 corpus callosum FCs were
automatically extracted from all participants (on the basis of their
unique cluster labels [29]), and the validity of these extracted FCs
was confirmed by a third rater (M.K.). These CC FCs were then
subdivided into six segments on the basis of the cortical regions
to which they projected (Figure 1C). Using these cluster labels,
the FCs constituting the CC were automatically extracted for each
subject and subsequently subdivided into six segments on the
basis of the cortical regions to which they projected. The six
segments, which are described and illustrated in Figure 1D, were
frontal fibers (CC1), premotor fibers, sensorimotor fibers, parietal
fibers, occipital fibers, and temporal fibers.

**Diffusion Indexes**

Fractional anisotropy and mode were calculated at every
voxel for each subject.

Mode is an index of the three-dimensional shape of diffusion—specifically whether it is better described by an oblate
(shaped like a pancake; mode ≈ -1) or prolate (shaped like a
cigar; mode ≈ 1) ellipsoid.

\[
\text{Mode} = \frac{\left(2\lambda_1 - \lambda_2 - \lambda_3\right)\left(\lambda_1 - 2\lambda_2 + \lambda_3\right)\left(\lambda_1 + \lambda_2 - 2\lambda_3\right)}{2\left(\sqrt{\lambda_1\lambda_2 + \lambda_2\lambda_3 + \lambda_3\lambda_1 - \lambda_1\lambda_2 - \lambda_2\lambda_3 - \lambda_3\lambda_1}\right)^3}
\]

Fractional anisotropy is an index of the asphericity of diffusion,
and is calculated as:

\[
\text{FA} = \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_1 - \lambda_3)^2}}{2\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}
\]

Mean values of the diffusivity indexes were calculated for
each CC segment for each subject. This was done by averaging
the diffusivity values (i.e., FA and mode) of all voxels through
which passed any of the FCs that constituted a given CC segment.

To help further infer the microstructural underpinnings of any
abnormalities in FA, two additional diffusion indexes were

calculated for only those segments for which group-wise differ-
ences in FA were observed. These two indexes—namely radial
diffusivity and axial diffusivity—have been proposed as being
sensitive to abnormalities in myelination [19,30] and axon integ-

\[
\text{Radial diffusivity} = \frac{\lambda_1 + \lambda_3}{2}
\]

\[
\text{Axial diffusivity} = \frac{\lambda_2}{2}
\]


city (31), respectively. Radial diffusivity is a measure of the extent
diffusion perpendicular to the principal axis of the diffusion
ellipsoid and is calculated as \(\frac{\lambda_1 + \lambda_3}{2}\). Axial diffusivity is a
measure of the absolute extent of diffusion along the principal
axis of the diffusion ellipsoid and is calculated as \(\frac{\lambda_2}{2}\).

**Statistical Analysis**

The statistical analysis was performed using SPSS v11 (http://
associated with using a repeated-measures design in the
context of severe violations of sphericity (32), a multivariate
analysis of variance was used to identify between-group differ-
ences in FA and mode. To control for multiple comparisons,
Fisher’s Protected Test was employed (33). If (and only if) the
multivariate analysis of variance identified an overall between-
group difference in a diffusion index were post hoc contrasts
(Fisher’s Least Significant Difference) used to identify the CC
segments responsible for the omnibus effect.

Pearson’s partial correlations (controlling for chlorpromazine
[CPRZ]-equivalent medication dosage) were used to investigate
the relationship between patients’ FA and radial diffusivity and
their reality distortion symptom score. As per Liddle (34), reality
distortion was calculated for each patient as the sum of their
scores on the hallucination and delusion subscales of the Positive
and Negative Symptom Scale (PANSS). Correlations between
FA/radial diffusivity and patients’ scores on the PANSS negative
and general subscales were also investigated. To limit the
number of statistical comparisons, these correlations were only
investigated for those CC segments that were identified as being
abnormal in the patient group.

**Results**

Figure 2 shows the scatterplots for FA (Figure 2A) and mode
(Figure 2B) across the six CC segments, for the SZ (red) and
control (blue) groups.

![Figure 2](image-url)
Multivariate analysis of variance revealed significant between-group differences in FA \( F(6,31) = 3.537, p = .009 \). Post hoc analysis revealed that the FA of CC1 (i.e., the frontal fibers) was significantly decreased in the SZ patients relative to control subjects \( t(1,36) = 2.282, p = .029 \). Additional analyses were performed to determine whether the FA reductions in CC1 were underpinned by changes in axial or radial diffusivity. The SZ patients exhibited significant increases in radial diffusivity in CC1 \( t(1,36) = 2.218, p = .033 \) but no differences in axial diffusivity \( t(1,36) = .113, p = .911 \) relative to control subjects (Figure 3).

Significant between-group differences in mode were also observed \( F(6,31) = 2.417, p = .049 \) (Figure 2B). Post hoc analysis revealed that mode was significantly increased (indicating a more cigar-shaped diffusion ellipsoid) in the parietal fibers in the SZ patients relative to control subjects \( t(1,36) = 2.291, p = .028 \).

Significant positive correlations (controlling for patients’ CPZ-equivalent medication dosage) were observed between FA in CC1 and SZ patients’ reality distortion scores \( r(16) = .601, p = .008 \) (Figure 4A). Conversely, significant negative correlations were observed between radial diffusivity in CC1 and SZ patients’ reality distortion scores \( r(16) = -.538, p = .021 \) (Figure 4B). The results of these correlations were similar (and remained statistically significant) when CPZ-equivalent medication dosage was removed as a covariate.

There was a (nonsignificant) trend for a negative correlation between patients’ FA in CC1 and their total score on the PANSS negative subscale, controlling for medication dosage \( r(16) = -.341, p = .166 \). Each of the individual PANSS negative items was found to be negatively correlated with FA in CC1, although this only reached statistical significance for difficulty in abstract thinking \( r(16) = -.477, p = .046 \). No statistically significant correlations were observed between patients’ FA in CC1 and their scores on the PANSS general scale or subscales.

Figure 3. Scatterplots illustrating the variations in fractional anisotropy (top), radial diffusivity (middle), and axial diffusivity (bottom) between groups (schizophrenia in red, control subjects in blue) for frontal fibers. The black bars represent corpus callosum segment means, and the asterisks represent significant between-group differences in diffusivity. CC1, frontal fibers; CON, control subjects; FA, fractional anisotropy; SZ, schizophrenia.

Figure 4. Scatterplots illustrating the relationships between schizophrenia patients’ reality distortion score (i.e., the sum of the Positive and Negative Symptom Scale hallucinations and delusions subscales) and their fractional anisotropy (A) and radial diffusivity (B) in frontal fibers. The solid lines represent the line of best linear fit for the data. The dotted lines show the mean values of fractional anisotropy and radial diffusivity exhibited by the healthy control subjects. CC1, frontal fibers; FA, fractional anisotropy.
No significant correlations were observed between patients' CPZ-equivalent medication dosage and their FA or mode in any of the six CC segments (Supplement 1). In contrast, significant negative correlations were observed between age and FA across groups, consistent with several previous studies (35–37) (Supplement 1).

Discussion

The primary findings of this study were of FA and radial diffusivity abnormalities in the frontal CC fibers and mode abnormalities in the parietal CC fibers in 19 SZ patients relative to 19 matched healthy control subjects. Furthermore, the severity of patients' symptoms of reality distortion (i.e., hallucinations and delusions) were found to be positively correlated with FA and negatively correlated with radial diffusivity in the frontal CC fibers. In light of the FA reductions and radial diffusivity increases that were observed in the SZ patients in this CC segment, these results suggest that the most severely psychotic patients were the least abnormal in terms of their FA and radial diffusivity in these fibers.

While FA reductions in the genu of the CC in SZ patients have been reported previously (38,39), including in patients with first-episode SZ (40) (see [10,41] for reviews), their microstructural underpinnings have not been well established. Fractional anisotropy reductions have been found to occur in response to axon death, myelin damage, damage to the axon membrane, and reduced “fiber coherence” (i.e., more variable fiber trajectories within a WM bundle) (10,42). While there is little evidence to suggest the presence of any substantial degree of abnormal neuron death in SZ patients (e.g., see [43]), there is, in contrast, a growing body of evidence suggesting that SZ patients exhibit abnormalities in both their myelin and in the integrity of their axon membranes (44,45). Distinguishing between these two distinct neuropathologies was one motivation behind the development of the diffusion indexes axial and radial diffusivity. In a series of animal studies, Song et al. (19) demonstrated that while damage to the myelin of the optic nerve resulted in increased radial (but unchanged axial) diffusivity, damage to the axonal membrane of the optic nerve (but preservation of the myelin) resulted in reduced axial but unchanged radial diffusivity (31). The results of these studies support the claim that radial diffusivity is a putative measure of myelin integrity, while axial diffusivity is a putative measure of axonal integrity. Hence, the results of the present study in which the SZ patients were observed to exhibit abnormally increased radial diffusivity but unchanged axial diffusivity, relative to control subjects, in the frontal CC fibers suggest that the FA abnormalities in these fibers were more likely underpinned by myelin abnormalities as opposed to damage to the axon membrane.

If the observed diffusion abnormalities in the frontal CC fibers were indeed the result of myelin damage, then this might be expected to result in slowed impulse conduction (46). Furthermore, it might also seem likely that those SZ patients with the most profound diffusion abnormalities (and hence presumably the most severe conduction delays) would exhibit the most severe psychopathology. Such a relationship, however, was not observed in the present study. On the contrary, those SZ patients with the most subnormal levels of FA (and most supranormal levels of radial diffusivity) exhibited the least severe symptoms of reality distortion. Far from being an unprecedented finding, this seemingly paradoxical result of a positive correlation between FA and psychotic symptom severity has been reported many times previously, including in the CC (17,47), cingulum bundle (17), arcuate fasciculus (17), superior longitudinal fasciculus (14,15), and inferior fronto-occipital fasciculus (16). It was also notable that, in the present study, the most severely psychotic patients did not show abnormally high levels of FA but instead exhibited FA values lower than the healthy control subjects but higher than the less psychotic patients (Figure 4). What is the explanation for this seemingly paradoxical finding that the more floridly psychotic a SZ patient, the less severe their FA abnormalities?

To the extent that axonal conduction delays can be inferred from diffusion abnormalities in DTI, these results suggest that while some amount of neural desynchronization may be necessary for the development of psychotic symptoms, too much desynchronization may, in fact, preclude the development of highly systematized hallucinations and delusions such as would score highly on a clinical rating scale such as the PANSS. This idea has some support in the WM literature. For example, while psychotic symptoms have been commonly reported in patients with the degenerative demyelinating disease metachromatic leukodystrophy (48), they are more likely to occur in the early stages of the disease when myelin pathologies are relatively minor compared with the late stages of the disease when severe demyelination is apparent (49). If it is true that psychotic symptoms represent the brain's attempt to incorporate disjointed neural activity into a coherent (albeit pathological) framework (50), then perhaps this pathological integration is only possible up to a certain level of temporal desynchronization. In other words, while mild asynchronies between the activities of spatially discrete brain regions might give rise to psychotic symptoms (such as, for example, between the different brain regions stimulated by a primary discharge and its corollaries [51], severe asynchronies (such as might be caused by severe WM damage) might not be incorporable into a coherent phenomenological framework and thus not give rise to psychotic symptoms. Such severe WM damage could instead result in something of a cognitive shutdown that could underlie the negative symptoms of SZ. This would explain the negative correlation between FA and negative symptom severity that has been observed previously in SZ patients (16,47,52) and for which there was a nonsignificant trend in the present study. Testing these hypotheses could potentially provide a fruitful avenue for future research.

Our finding of abnormally increased mode (i.e., abnormally prolate diffusion ellipsoids) in the parietal CC fibers in the SZ patients has not (to our knowledge) been reported previously. Mode is a relatively recently developed measure that provides independent and complementary information to the stalwart index of FA (13). In terms of its physiological determinants, mode has been found to decrease in the presence of fiber crossings (13). Thus, one explanation as to why the SZ patients exhibited abnormally increased mode but normal levels of FA in the parietal CC fibers might be that the patients evince abnormalities in a fiber bundle adjacent to these CC fibers (e.g., the cingulum bundle, as recently suggested by Maddah et al. [53]), resulting in a reduction in the density of fiber crossings and hence elevated mode in this region of the CC. Our finding of diffusion abnormalities in the parietal CC fibers is also consistent with the results of several early-onset studies that have reported parietal lobe white matter to be among the first cerebral areas to evince structural abnormalities in patients with schizophrenia—abnormalities that have been argued to contribute to the emer-
gence of psychotic symptoms through their effects on frontal-parietal connectivity (54,55).

A limitation of the present study relates to the fact that all the SZ patients were suffering from chronic schizophrenia and had been at least intermittently (and in many cases chronically) exposed to neuroleptic medications. This is relevant in light of evidence from primate studies suggesting that exposure to both typical and atypical neuroleptics can influence brain structure in and of itself (56). Notwithstanding the fact that 1) patients' chlorpromazine-equivalent medication dosages were statistically controlled for in the present study and 2) there were no significant correlations between patients' CPZ-equivalent medication dosages and their FA, mode, or radial diffusivity in any of the six CC segments (Supplement 1), replicating these results in a population of first-episode, neuroleptic-naive SZ patients would strengthen confidence into their validity and would be a worthwhile aim for future research. A second limitation relates to the fact that all the patients were male. While this was advantageous in the sense that it increased the homogeneity of the sample and thus the power, it obviously limited the extent to which the results can be generalized to female patients.

In summary, the main findings of this study were of FA reductions and radial diffusivity increases in frontal CC fibers (consistent with dysmyelination) and mode increases in parietal CC fibers (consistent with a relative absence of crossing fibers) in 19 patients with schizophrenia relative to 19 matched healthy control subjects. Significant correlations were also observed between patients' FA and radial diffusivity in the frontal fibers and the severity of their psychotic symptoms, such that patients with the most abnormal levels of FA and radial diffusivity exhibited the least severe symptoms of reality distortion. This result, we suggest, provides support for those theories that emphasize neural timing abnormalities in the etiology of psychotic symptoms.

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(TJW, MK, RK, JLA, UK, DM, MN, PGN), the interpretation of neuropsychological measures (PGN), or the writing (TJW, MK, MES, JSS, LJO, MN, RWJ).

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Supplementary material cited in this article is available online.