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Fiber Tractography Reveals Disruption of Temporal Lobe White Matter Tracts in Schizophrenia

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Abstract

Diffusion tensor imaging (DTI) studies have demonstrated abnormal anisotropic diffusion in schizophrenia. However, examining data with low spatial resolution and/or a low number of gradient directions and limitations associated with analysis approaches sensitive to registration confounds may have contributed to mixed findings concerning the regional specificity and direction of results. This study examined three major white matter tracts connecting lateral and medial temporal lobe regions with neocortical association regions widely implicated in systems-level functional and structural disturbances in schizophrenia. Using DTIstudio, a previously validated regions of interest tractography method was applied to 30 direction diffusion weighted imaging data collected from demographically similar schizophrenia (n=23) and healthy control subjects (n=22). The diffusion tensor was computed at each voxel after intra-subject registration of diffusion-weighted images. Three-dimensional tract reconstruction was performed using the Fiber Assignment by Continuous Tracking (FACT) algorithm. Tractography results showed reduced fractional anisotropy (FA) of the arcuate fasciculi (AF) and inferior longitudinal fasciculi (ILF) in patients compared to controls. FA changes within the right ILF were negatively correlated with measures of thought disturbance. Reduced volume of the left AF was also observed in patients. These results, which avoid registration issues associated with voxel-based analyses of DTI data, support that fiber pathways connecting lateral and medial temporal lobe regions with neocortical regions are compromised in schizophrenia. Disruptions of connectivity within these pathways may potentially contribute to the disturbances of memory, language, and social cognitive processing that characterize the disorder.

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Contributors: Owen R. Phillips was responsible for data acquisition and analysis and manuscript preparation. Keith H. Nuechterlein and Robert F. Asarnow provided the clinical expertise for this study. Liberty S. Hamilton assisted in preparation of the manuscript and data acquisition. Kristi A. Clark was responsible for software development and expertise regarding registration algorithms. Nathan S. Hageman provided expertise regarding diffusion measurements. Arthur W. Toga and Katherine L. Narr contributed to the conception and overall design of the study. Substantial scientific contributions were made by all authors of this study.

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Keywords

diffusion tensor imaging; white matter; uncinate fasciculus; inferior longitudinal fasciculus; arcuate fasciculus; fractional anisotropy

1. Introduction

Some brain systems appear selectively vulnerable to disease processes in schizophrenia. Structural imaging studies have repeatedly demonstrated reductions of gray matter (Shenton et al., 2001; Narr et al., 2005b; Whitford et al., 2006) that appear most reproducible in lateral and medial temporal cortices, particularly the hippocampus (Narr et al., 2004; Goldman et al., 2008) and the superior temporal gyrus (Shenton et al., 2001; Honea et al., 2008). Disturbances of lateral and medial temporal lobe function including deficits in auditory sensory (Rabinowicz et al., 2000), language (DeLisi, 2001) memory (Saykin et al., 1994; Bilder et al., 2000; Harrison and Fowler, 2004; Harrison, 2004) and social cognitive processing (Green et al., 2005; Yamada et al., 2007) are also widely documented in schizophrenia. These behavioral disturbances may be associated with neuropathology in discrete brain regions and/or from disruptions of connectivity within functional networks (Frith et al., 1995; Walterfang et al., 2005). However, the effects of illness on the physiological connections linking fronto-limbic and other temporo-neocortical association areas are not fully understood.

With Diffusion tensor imaging (DTI) it is possible to address whether disturbances of white matter connectivity occur within particular cortical networks. That is, because the diffusion tensor approximating local diffusion is determined by the local tissue architecture, it can be used to generate an *in vivo* visualization of white matter tracts (Conturo et al., 1999; Ashburner and Friston, 2000; Catani et al., 2002a; Wakana et al., 2004). Tractography methods assemble the local diffusion tensor data into tracts where scalar metrics, such as fractional anisotropy (FA), along these tracts then allows for the precise localization of white matter abnormalities. Although some doubt exists that tractography may generate sufficiently reproducible neuroanatomical detail for use in quantitative analyses, growing evidence supports that tracking results agree well with postmortem definitions (Catani et al., 2002b; Jellison et al., 2004; Wakana et al., 2007). To investigate possible white matter abnormalities in schizophrenia, we examined three major white matter tracts: the arcuate fasciculus (AF), the inferior longitudinal fasciculus (ILF), and the uncinate fasciculus (UF). These tracts have been classically defined using postmortem studies and are easily identifiable using a multiple region of interest (ROI) approach in DTI data.

The AF (or temporal component of the superior longitudinal fasciculus [SLF]) connects the superior temporal gyrus with dorsal prefrontal cortex (Brodmann areas 8 and 46) (Petrides and Pandya, 1984; Makris et al., 2005). By linking frontal and temporal cortices, the AF may provide a means by which the prefrontal cortex receives and modulates auditory and audiospatial information (Leinonen et al., 1980; Petrides M., 2002). Several prior investigations have implicated fronto-temporal processing disruptions in schizophrenia (Frith et al., 1995; Liddle, 1996; Andreasen, 2000). Further, some prior voxel-based DTI studies suggest that white matter abnormalities occur in the vicinity of the AF (Burns et al., 2003; Kubicki et al., 2005; Douaud et al., 2007) and may be associated with the experience of hallucinations in the auditory modality (Hubl et al., 2004). To our knowledge, however, no prior studies have examined the AF using DTI tractography methods, which may provide a more powerful means to examine changes in the physiology of this tract in schizophrenia.

The ILF has been demonstrated by postmortem and DTI studies to be a major associative connection between the anterior temporal and occipital lobe and plays an important role in

visual memory (Bauer and Trobe, 1984; Shinoura et al., 2007). It also connects the parahippocampal gyrus and amygdala (Catani et al., 2002a), regions implicated in the structural and functional neuropathology of schizophrenia (Benes and Berretta, 2000; Narr et al., 2001; Harrison, 2004; Surguladze et al., 2006). At least one prior schizophrenia DTI tractography study has reported reduced FA for the left ILF (Ashtari et al., 2007a) where negative associations between FA and visual hallucinations were further observed.

The UF links the temporal lobe with ventral, medial, and orbital frontal cortices (Ebeling and von Cramon, 1992). This tract plays an important role in the formation and retrieval of memories (Levine et al., 1998; Squire et al., 2004). Though patients with schizophrenia exhibit generalized cognitive impairment, declarative memory deficits appear particularly pronounced (Bilder et al., 2000). However, while some DTI studies have observed lower FA in the UF in schizophrenia (Nestor et al., 2008), other reports have been mixed (Jones et al., 2006).

In spite of the evidence suggesting disturbances of fiber connectivity in schizophrenia, the regional specificity of results remains unclear. Discrepancies in prior findings may be at least partially attributable to the methodological limitations associated with examining data with a low number of gradient directions and low spatial resolution in small cohorts, using voxel-based methods sensitive to registration confounds (Alexander et al., 2001), and the paucity of studies using methods that allow the precise mapping of tract anatomy within subjects (Kubicki et al., 2007). We thus examined the connectivity of the AF, ILF, and UF in 23 schizophrenia and 22 healthy subjects using 30 direction DTI data and sensitive fiber tracking methods that do not rely on registration procedures to align imaging data across subjects. We predicted that each of these fiber pathways would be disturbed in schizophrenia. We further explored whether positive and negative symptom cluster scores are associated with fiber tract abnormalities within medial and lateral temporal lobe systems in schizophrenia patients.

2. Methods

2.1 Subjects

23 patients with schizophrenia and 22 healthy control subjects participated in this study. Diagnostic groups did not differ significantly in age or sex (Table 1). All participants provided informed consent as approved by the University of California, Los Angeles (UCLA) Institutional Review Board. Schizophrenia patients were recruited from the UCLA Aftercare Research Program through the UCLA Family Study protocol. Control subjects were recruited through direct calls using a survey sampling methodology as well as community outreach via advertisement in newspapers and fliers. Exclusion criteria for all subjects included mental retardation, neurological disorder (e.g., temporal lobe epilepsy), and recent or past history of significant and habitual drug abuse or alcoholism. Control subjects were screened by clinical interview using the SCID-NP (First et al., 1994) to exclude schizophrenia and schizoaffective disorder and potential schizophrenia spectrum disorders. A radiologist reviewed any suspected abnormalities in the high-resolution T1-weighted data. However, using this sequence only, it was not possible to rule out the presence of all possible brain abnormalities. No incidental brain lesions were observed in the current sample, and no subjects were excluded from analysis. Schizophrenia diagnosis was confirmed by consensus of specially trained diagnosticians (Ventura et al., 1998) as determined by DSM-IV criteria using the Structured Clinical Interview for DSM-IV (SCID-I/P) (First et al., 1994; First et al., 1996; First et al., 2001) and by informant information. Clinical symptoms were assessed using the expanded 24-item Brief Psychiatric Rating Scale (BPRS; (Ventura et al., 1993; Ventura et al., 2000) and clustered into withdrawal and thinking disorder scores (Burger et al., 1997). Withdrawal (negative symptoms factor) scores were calculated as the mean of BPRS scores for emotional withdrawal, motor retardation, blunted affect, disorientation, and self-neglect. Thinking disorder (positive symptoms factor) scores were calculated as the mean of BPRS scores for conceptual

disorganization, grandiosity, hallucinatory behavior, unusual thought content, and bizarre behavior. Handedness was determined based on a modified version of the Edinburgh Inventory. (Oldfield, 1971)

2.2. Image Acquisition

DTI data was acquired on a 1.5T Siemens Sonata scanner (Erlangen, Germany) at the UCLA Ahmanson-Lovelace Brain Mapping Center using an 8-channel head coil. The DTI acquisition protocol included 3 averages of a whole brain sequence with 30 non-collinear diffusion directions and 55 brain slices oriented obliquely to the anterior/posterior commissure (AC-PC) line (TR=6400 ms, TE=83 ms, b=0, 1000 sec/mm², FOV: 240×240 mm, matrix: 96×96, voxel size: 2.5 mm³, acquisition time: 3.52 min per average). Parallel imaging used GRAPPA reconstruction with an acceleration factor of 2. High-resolution T1-weighted MPRAGE sequences were also collected (TR=1900 ms; TE=4.38 ms; flip angle: 15°, FOV: 256×256; voxel size: 1 mm³; NEX=4; TI=1100, acquisition time: 8.08 min per average). The DTI sequence was designed to have minimal eddy current induced distortions (Reese et al., 2003), whereas parallel imaging was employed to substantially reduce EPI distortions (Heidemann et al., 2003).

2.3. Image Processing

DTI data processing was performed using the LONI Pipeline environment (Rex et al., 2003). After image reconstruction, the diffusion gradient table was corrected for slice prescription. To correct for eddy current induced distortions, diffusion-weighted images were aligned to a non-diffusion-weighted image (b=0 sec/mm²) using a nonlinear 2D registration (Jezzard et al., 1998). Motion artifacts were corrected by applying a 3D rigid body registration (Woods et al., 1998a; Woods et al., 1998b), using the non-diffusion-weighted image as the target image. The transformation files from the two registrations were combined and only applied to the data once in order to minimize interpolation. The non-diffusion-weighted images were skull stripped using FSL's Brain Extraction Tool (BET) (<http://www.fmrib.ox.ac.uk/fsl/bet2/index.html>), and used to mask all diffusion-weighted images (Smith, 2002). The diffusion tensor was estimated at each voxel using a linear least squares algorithm applied to the log-transformed signal intensities. Each diffusion tensor was diagonalized to obtain the eigenvalues that were then used to compute fractional anisotropy (FA) (Pierpaoli and Basser, 1996).

Three-dimensional tract reconstruction was performed using DTIstudio (Jiang et al., 2006). DTIstudio estimates fiber tracts using the Fiber Assignment by Continuous Tracking (FACT) algorithm, which has been shown to be a reliable method for identifying several neuroanatomically valid tracts (Mori et al., 1999; Xue et al., 1999; Mori and van Zijl, 2002; Wakana et al., 2004; Okada et al., 2006). In our study, an FA threshold of 0.2 and a turning angle threshold of 41° were used for each tract to restrict the algorithm to yield biologically plausible results (Wakana et al., 2007). ROIs were applied using the FA-weighted color maps for each subject and by following the protocols detailed in Wakana et al. (2007). Briefly, for the AF, the first ROI was identified by selecting the coronal slice at the middle of the posterior limb of the internal capsule where the AF is visible running anterior to posterior with a triangular shape. The second ROI was defined on the axial slice at the anterior commissure. For the ILF, a sagittal plane off midline was first identified at the level of the cingulum. The first ROI was selected at the posterior edge of the cingulum in the coronal plane encompassing the whole hemisphere. The second ROI included the entire temporal lobe in a coronal section towards the anterior pole of the temporal lobe. Finally, for the UF, the most posterior coronal slice in which the temporal lobe is separated from the frontal lobe was selected. The first ROI included the entire temporal lobe and the second ROI included the projections passing towards the frontal lobe in this plane (Wakana et al., 2007). Figure 1 illustrates the trajectories of each

fiber pathway obtained using the ROIs described above. The locations of ROI placement for each tract are illustrated in supplementary Figures 1-3. If a tract showed a fiber that was clearly anatomically incorrect, the NOT function was used to remove the fiber from the bundle. Intra-rater reliability was estimated by identifying each of the tracts using ROI placement in 8 randomly chosen volumes duplicated in the dataset. To determine inter-rater reliability, fiber tracks were identified in 9 randomly chosen brain volumes by two independent raters. Excellent intra- and inter-rater reliability was achieved for ROI placement as determined by computing the inter-class correlation coefficients for tract volume, the volume for the number of voxels through which the tract passes, and mean FA, a value representing the average intra-voxel FA across the tract of interest in each subject (Table 2).

To obtain measures of intracranial brain volume and volumes of segmented brain tissue compartments, the T1-weighted MPRAGE images were processed as previously detailed (Narr et al., 2005b; Narr et al., 2005a). Briefly, image volumes were corrected for head tilt and alignment using six-parameter rigid-body transformations. To scalp edit the T1-weighted data, FSL's BET was used to generate a temporary mask that was then manually edited on a slice-by-slice basis to correct any small errors using MNI Display (<http://www.bic.mni.mcgill.ca/software/Display/Display.html>), (scalp editing inter-rater reliability, $r_1 = .99$). Edited brain volumes were then corrected for signal intensity inhomogeneities (Sled et al., 1998), and segmented into gray matter, white matter, and CSF using a partial volume classification method (Shattuck et al., 2001) after which whole brain and brain tissue volumes were computed.

2.4. Statistical Analysis

Mean FA and tract volume (the number of voxels the tract traverses multiplied by the 2.5 mm³ voxel size) were estimated for each fiber tract within subjects. A repeated measures analysis of variance (ANOVA) examined group differences in left and right mean FA, which were included as dependent variables in order to test fewer hypotheses and avoid potential Type 1 error while simultaneously assessing the presence of hemisphere effects for the AF, ILF, and UF. Diagnosis and sex were included as between-subject factors. To reduce potential bias due to less precise estimates in subjects contributing fewer voxels, mean FA measures were corrected for overall tract volume. That is, since hemisphere was a within-subject variable, left and right mean FA values were residualized for left and right tract volume respectively. Repeated measures ANOVAs were followed-up by univariate tests when appropriate.

As noted above, we controlled for tract volume when examining changes in mean FA between groups. However, to determine whether this measure itself was different across groups, the same statistical model was used to examine diagnostic group differences in fiber tract volume. For these comparisons, total brain white matter volume was included as a covariate to control bias in the overall number of white matter voxels expected in individuals with larger brain tissue volumes. Finally, correlations between mean FA and positive and negative symptom cluster scores were examined. Two patients were excluded from these analyses because BPRS data was unavailable. Demographic differences were assessed using chi-square or independent sample t-tests as appropriate.

3. Results

Patient and control groups did not significantly differ in age or gender distribution or in total brain or white matter volume (Table 1). The repeated measures ANOVA showed significantly lower FA values in patients compared to controls in the ILF [$F(1,41)=6.55$, $p=0.014$] and AF [$F(1, 41)=4.78$, $p=0.035$], but not in the UF, [$F(1,41)=0.09$, $p=0.758$]. There were no sex or asymmetry effects or interactions between diagnosis and sex or hemisphere. Follow-up univariate tests revealed significant effects of diagnosis for the Left ILF [$F(1,44)=4.84$, $p=0.03$]

and Right ILF [$F(1,44)=6.06$, $p=0.018$] and the Left AF [$F(1,45)=5.01$, $p=0.03$]. Table 3 lists means and standard deviations (SDs) for mean FA values, and Figure 2 shows the 95% confidence intervals of the means within diagnostic groups. Follow-up tests performed after excluding the one left-handed control subject from the analysis produced similarly significant results.

Analyses of fiber volume showed a significant reduction in left AF volume only [$F(1,45)=7.725$, $p=0.008$]. Means and SDs for AF, ILF, and UF volume are provided in Table 3. Spearman's correlation analyses between mean FA and positive (thinking disorder) and negative symptom (withdrawal) cluster scores revealed a significant negative association ($r=-0.439$) between thinking disorder (positive symptoms) and mean FA within the right ILF ($p=0.046$) (Figure 3).

4. Discussion

Using a validated ROI approach for identifying major fiber tracts (Wakana et al., 2007), we were able to examine highly localized changes of white matter integrity in brain systems widely implicated in the pathophysiology of schizophrenia. Specifically, we examined three major white matter tracts that form integral connections between lateral and medial temporal lobe regions with neocortical association areas. Results revealed significant reductions of mean FA within the ILF bilaterally and the left AF in schizophrenia patients compared to healthy controls. A significant negative association between thinking disorder and mean FA of the right ILF was further observed. Although the neurobiological mechanisms underlying altered FA are not known, prior human and animal studies of neural development and of related disturbances in brain function support that an increase in FA is related to an increase in the connectivity of white matter bundles (Dong et al., 2004). Our results are consistent with several previous diffusion imaging findings despite differences in patient populations (e.g. early onset, first episode, and chronic schizophrenia) and analysis approaches. However, our findings provide more detailed information concerning the localization of fiber tract abnormalities in the disorder that may be of particular functional relevance.

4.1. Inferior Longitudinal Fasciculus

Our observations of significantly reduced mean FA in patients in bilateral ILF support prior findings in adolescent and never-medicated first-episode schizophrenia patients (Ashtari et al., 2007b; Cheung et al., 2007) identified using tractography and voxel-based methods respectively. Our findings are also consistent with those of (Friedman et al., 2008) showing reduced FA in the left ILF in chronic patients and trend level FA reductions in first episode schizophrenia. Although the functions of the ILF are not fully characterized, this tract appears to mediate the fast transfer of visual signals to anterior temporal regions and neuromodulatory back-projections from the amygdala to early visual areas (Catani et al., 2003). The ILF, which is the major occipital-temporal white matter connection, is suggested to play a role in visual memory and in processing the emotional valence of a visual stimulus (Catani et al., 2003). Disturbances in the structural integrity of this tract may thus relate to observations that schizophrenia patients are impaired in their ability to recognize and respond appropriately to emotional facial expressions (Mueser et al., 1996; Penn et al., 1996; Brune, 2005) and contribute to developmental differences in social cognition as well as visual-spatial integration (Barnea-Goraly et al., 2005). Our finding of an association between mean FA in the right ILF and thinking disorder (positive symptoms) cluster scores, which includes a visual hallucination rating, is partially consistent with a report of a negative association between mean FA of the left ILF in early onset patients with a history of visual hallucinations (Ashtari et al., 2007a), although individual BPRS factor scores were not examined in our study.

4.2. Arcuate Fasciculus

Some diffusion studies have reported reduced FA in the vicinity of the left AF in adolescent onset (Douaud et al., 2007) and in adult schizophrenia patients (Burns et al., 2003; Kubicki et al., 2005; Douaud et al., 2007), consistent with our results. At least two prior studies using voxel-based methods further report positive associations between FA values and the symptom of auditory hallucinations, particularly in the left AF (Hubl et al., 2004; Shergill et al., 2007). Specifically, one study reported significantly greater FA values compared to controls in patients with current and past history of hallucinations (Hubl et al., 2004). However, a second study observing positive associations between FA and hallucination ratings still showed lower FA values in patients with a propensity for current or past hallucinations compared to healthy subjects (Shergill et al., 2007). A third study failed to observe AF associations, although positive relationships between the severity of auditory and tactile hallucinations and the inferior fronto-occipital fasciculus FA were detected (Szeszko et al., 2008). Finally, Seok et al., (2007) reported positive associations between auditory hallucinations and FA values in the frontal as opposed to the temporal component of the SLF. Unfortunately, we were not able to clarify these relationships in the current investigation, since patients were not acutely ill at the time of scan, and symptom scores for auditory hallucinations were low and narrow in range. Regardless, our results suggest that reduced FA within the AF persist during periods of relative symptom stability. Our investigation also revealed a reduction in the overall size of the left AF in patients compared to controls. This finding may suggest that the length of AF fibers are less extensive in patients or indicate tract shape differences. Although tractography is sensitive to anatomical variations in fiber pathways (Wakana et al., 2007), it is possible that the extent of this fiber tract was not fully resolved with our choice of ROIs, which were devised based on the fiber anatomy of healthy individuals (Wakana et al., 2007).

4.3. Uncinate Fasciculus

The UF connects parahippocampal and prefrontal regions and is involved in declarative memory processing, for which patients exhibit pronounced deficits (Bilder et al., 2000). At least one investigation supports relationships between UF FA and memory functioning in schizophrenia specifically (Nestor et al., 2008). In this study, however, we failed to detect significant differences of mean UF FA in schizophrenia patients compared to controls. These results contrast with one prior tractography study (Price et al., 2008) and with some voxel-based investigations. Specifically, reduced FA of the UF has been documented in chronic schizophrenia (Seal et al., 2008) and in first episode patients bilaterally (Szeszko et al., 2008) and in the left UF exclusively (Szeszko et al., 2005), and at trend-level in a cluster at the border of the UF and the ILF (Burns et al., 2003). Still, several studies, like the present investigation, have failed to detect significant diagnostic group differences of FA within the UF (Jones et al., 2006). Some studies, however, have revealed altered FA asymmetries in schizophrenia (Kubicki et al., 2002; Park et al., 2004), although hemisphere by diagnosis effects in UF cross-sectional area and fiber numbers were not detected in post mortem data (Highley et al., 2002). In the absence of diagnostic group effects, another group reported a trend level age by group interaction for FA within the UF (Rosenberger et al., 2008). Inconsistencies in findings may be partially attributable to clinical heterogeneity amongst patient samples and to methodological differences, where it is worth noting that reported cluster coordinates locations are highly variable between voxel-based studies. Measurements for the UF may also be complicated by the tightly curved shape and smaller trajectory of this fiber bundle in relation to other larger tracts and/or could indicate that disturbances of UF connectivity in schizophrenia are subtler than those of other tracts.

4.4. Potential Limitations

A possible limitation to the study is the influence of patient medications on white matter connectivity and/or myelination. A positive association between FA and antipsychotic treatment has been observed in at least one prior study (Kuroki et al., 2006), although FA changes are also reported in never-medicated patients (Cheung et al., 2007). Whether other factors including intelligence, social economic status and past history of drug and alcohol use, which is shown to affect FA in non-schizophrenia samples e.g., (Pfefferbaum et al., 2006), influence fiber integrity warrants further study. However, some these factors may be more difficult to dissociate from other disease-related characteristics. In spite of excellent reliability for ROI placements, it is possible that the anatomic definitions imposed for ROI placement may have influenced results. Still, our method, which focused on well documented tracts from previous studies using anatomical constraints (multiple ROIs), made it possible to isolate and examine tracts based on the individual's morphology that do not appear influenced by ROI placement. Furthermore, this method does not require perfect anatomical registration across subjects and is thus not sensitive to registration-related confounds that continue to be an issue for the analysis of DTI data. Finally, it is possible that other diffusion measures such as radial, axial and mean diffusivity may reveal subtler cytoarchitectonic disturbances in schizophrenia. Future studies including larger sample sizes may address broader hypotheses relating to these diffusion measures.

4.5. Conclusion

Our observations of reduced mean FA in the AF and ILF support the hypothesis that abnormal white matter connectivity influences systems-level processing deficits involving fronto-limbic and temporo-neocortical networks in schizophrenia. Abnormal connectivity of the AF may contribute to language and auditory deficits in patients. Disturbances of ILF integrity may contribute to visual memory impairments and to deficits in social cognition. Furthermore, IFL connectivity may be influenced by clinical state as suggested by our observations of negative associations with positive symptom ratings. It remains unclear whether white matter abnormalities serve as primary or complicating mechanisms for impairments in specific brain systems in schizophrenia or whether these abnormalities are secondary to changes in brain morphology, particularly of gray matter. Future studies may clarify these questions and address whether FA changes are the result of disturbed white matter developmental trajectories.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Fiber tracts including the (a) arcuate fasciculus (AF), (b) inferior longitudinal fasciculus (ILF), and (c) uncinate fasciculus (UF) are shown for a representative control subject. Fiber pathways were obtained using multiple region of interest approach and tract statistics were collected across the whole tract. Colors represent individual fibers within the greater body of the tract.

Figure 2. Means and the 95% confidence intervals for mean FA measures obtained from each of the three fiber tracts in patients with schizophrenia (blue) and control subjects (red).

Figure 3.
Correlation between right ILF mean FA and thinking disorder scores in schizophrenia patients.

Table 1

Subject demographic Information.

	Schizophrenia	Controls	Statistic	P Value
Age (mean $\pm$ SD)	34.65 $\pm$ 9.17	30.87 $\pm$ 9.52	t=-1.36	0.18
Gender (male/female)	17/6	17/5	$\chi^2=0.07$	0.79
Handedness (dextral/non-dextral)	23/0	21/1	$\chi^2=1.07$	0.30
Years of Education	14.17 $\pm$ 1.85	15.31 $\pm$ 2.05	t=1.96	0.06
Duration of Illness	10.14 $\pm$ 7.94	-	-	-
Age of Onset	21.93 $\pm$ 4.22	-	-	-
Total Brain Volume (cc)	1442.6	1431.4	t=-0.29	0.77
White Matter Volume (cc)	566.5	556.3	t=0.61	0.54
Anergia (mean $\pm$ SD)*	1.69 $\pm$ 0.65	-	-	-
Thought Disturbance (mean $\pm$ SD)*	1.63 $\pm$ 0.60	-	-	-

* Missing data for 2 patients.

Table 2
Intra-class correlation coefficients (*r*) for ROI tracing. AF=arcuate fasciculus, ILF=inferior longitudinal fasciculus, UF=uncinate fasciculus.

Tract	Intra-rater reliability			Inter-rater reliability		
	Mean FA	Volume		Mean FA	Volume	
	Left	Right	Left	Left	Right	Left
AF	0.995	0.991	0.992	0.928	0.988	0.963
ILF	0.997	0.996	0.957	0.994	0.988	0.921
UF	0.998	0.994	0.942	0.978	0.986	0.993

Values in the table represent intraclass correlation coefficients (RI)

Table 3

Tract measurements for the arcuate fasciculus (AF), inferior longitudinal fasciculus (ILF), and uncinate fasciculus (UF).

Fiber Tract Measures	FA (Mean $\pm$ SD)		Volume (Mean $\pm$ SD), (cc)	
	Controls	Patients	Controls	Patients
AF Left	0.48 $\pm$ 0.02 *	0.45 $\pm$ 0.03 *	5.58 $\pm$ 2.99 *	4.53 $\pm$ 2.45 *
AF Right	0.48 $\pm$ 0.04	0.46 $\pm$ 0.03	4.32 $\pm$ 2.90	3.24 $\pm$ 2.15
ILF Left	0.47 $\pm$ 0.02 *	0.45 $\pm$ 0.02 *	10.67 $\pm$ 4.07	9.76 $\pm$ 3.02
ILF Right	0.47 $\pm$ 0.02 *	0.45 $\pm$ 0.02 *	11.34 $\pm$ 3.13	10.39 $\pm$ 3.55
UF Left	0.40 $\pm$ 0.03	0.39 $\pm$ 0.02	3.34 $\pm$ 1.88	2.52 $\pm$ 1.71
UF Right	0.42 $\pm$ 0.03	0.40 $\pm$ 0.04	2.66 $\pm$ 1.2	3.11 $\pm$ 2.13

* Significant effects