Published in final edited form as:

J Psychiatr Res. 2011 July ; 45(7): 980–988. doi:10.1016/j.jpsychires.2011.01.006.

Mean diffusivity and fractional anisotropy as indicators of disease and genetic liability to schizophrenia

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Abstract

The goals of this study were to first determine whether the fractional anisotropy (FA) and mean diffusivity (MD) of major white matter pathways associate with schizophrenia, and secondly to characterize the extent to which differences in these metrics might reflect a genetic predisposition to schizophrenia. Differences in FA and MD were identified using a comprehensive atlas-based tract mapping approach using diffusion tensor imaging and high resolution structural data from 35 patients, 28 unaffected first-degree relatives of patients, 29 community controls, and 14 first-degree relatives of controls. Schizophrenia patients had significantly higher MD in the following tracts compared to controls: the right anterior thalamic radiations, the forceps minor, the bilateral inferior fronto-occipital fasciculus (IFO), the temporal component of the left superior longitudinal fasciculus (tSLF), and the bilateral uncinate. FA showed schizophrenia effects and a linear relationship to genetic liability (represented by schizophrenia patients, first-degree relatives, and controls) for the bilateral IFO, the left inferior longitudinal fasciculus (ILF), and the left tSLF. Diffusion tensor imaging studies have previously identified white matter abnormalities in all three of these tracts in schizophrenia; however, this study is the first to identify a significant genetic liability. Thus, FA of these three tracts may serve as biomarkers for studies seeking to identify how genes influence brain structure predisposing to schizophrenia. However, differences in FA and MD in frontal and temporal white matter pathways may be additionally driven by state variables that involve processes associated with the disease.

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Financial Disclosure: Dr. Nuechterlein has a research grant from Ortho-McNeil Janssen Scientific Affairs and has consulted for Wyeth and Merck.

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Keywords

diffusion tensor imaging; endophenotypes; genetic predisposition

Introduction

The symptomatic profile and disturbances of cognition characteristic of schizophrenia suggest that disease processes affect multiple brain systems and compromise the integrity of brain connectivity within several functional networks (Hoffman & McGlashan, 1997; Hubl et al., 2004; Reichenberg & Harvey, 2007; Schlosser et al., 2007). Advances in diffusion tensor imaging (DTI) and structural magnetic resonance imaging (MRI) methods now allow researchers to study such networks *in vivo* by integrating brain morphological findings with information regarding underlying tissue integrity and anatomical connectivity. Thus, new opportunities have emerged to identify biological markers for schizophrenia at the systems level. It is widely accepted from epidemiological evidence that schizophrenia has a large genetic component, although the genetic contributions and their interactions with environmental factors appear complex (Kirov et al., 2005; Sullivan et al., 2003). Identifying intermediate biological markers or 'endophenotypes' in unaffected biological relatives of patients may point to the involvement of specific genetic factors and/or help clarify genetically mediated mechanisms associated with the disorder (Braff et al., 2007; Gottesman & Gould, 2003; Harrison & Weinberger, 2005; Meyer-Lindenberg & Weinberger, 2006; Prasad & Keshavan, 2008; Tan et al., 2008). Several structural MRI abnormalities frequently reported in the brains of schizophrenia patients, such as cerebrospinal fluid (CSF) enlargement and regional gray matter volume deficits, have also been observed in healthy relatives of patients (Brans et al., 2008; Cannon et al., 1998; DeLisi et al., 2006; Honea et al., 2007; Lawrie et al., 2008; van Haren et al., 2008). For example, using a cohort of monozygotic (MZ) and dizygotic (DZ) twins discordant for schizophrenia, we previously found that an upward bowing of the corpus callosum and reduced hippocampal volume are neuroanatomical markers for genetic vulnerability for developing schizophrenia (Narr et al., 2002a; Narr et al., 2002b). Though one recent study found that although the nonpsychotic cotwins from discordant MZ pairs had less overall gray matter volume than healthy control twins, there were no significant regional differences in gray matter volume (Borgwardt et al., 2010), others have found that unaffected cotwins have decreased frontal, particularly the superior frontal (Ettinger et al., 2010), and temporal lobe volumes (Brans et al., 2008). Inconsistencies in regional findings and weak schizophrenia-related genetic liability effects have led researchers to search for more sensitive imaging markers indicating genetic susceptibility in unaffected relatives of patients.

Among the plethora of neurobiological deficits observed in schizophrenia, possible disruptions in white matter connectivity have become the focus of much current research (for reviews see (Kubicki et al., 2007; Kubicki et al., 2005). DTI allows the analysis of fractional anisotropy (FA), a measure indicating the overall directionality of water diffusion that is greater in organized white matter tracts and lower in CSF and disorganized fibers. Prior DTI studies of schizophrenia have suggested that deficits in white matter integrity, particularly within the frontal and temporal lobes, contribute towards disease pathophysiology (DeLisi et al., 2006; Hao et al., 2006; Mori et al., 2007; Phillips et al., 2009; Rose et al., 2006; Shergill et al., 2007; Szeszko et al., 2008). To date, very few studies have addressed whether differences in FA may represent intermediate phenotypes of schizophrenia-related genetic predisposition (Marenco & Radulescu, 2009). In spite of small sample sizes, a few recent studies investigating individuals at ultra high risk for developing schizophrenia and/or biological relatives of patients suggest that variations in FA represent biological indicators for disease vulnerability that could be explained, at least in part, by the

influence of schizophrenia-related genetic factors (Hoptman et al., 2008; Karlsgodt et al., 2009; Munoz Maniega et al., 2008). One study that compared relatives of schizophrenia patients to healthy controls reported FA reductions in medial prefrontal white matter in patient relatives that suggest genetic liability (Camchong et al., 2009a). Using a voxel-based analysis method, another group comparing schizophrenia patients, their healthy siblings and control subjects (N= 34 sibling pairs and 32 controls; age range: 17-45 years) found reduced white matter FA in discrete areas with left prefrontal cortex and in the vicinity of the hippocampus in patients and their first-degree relatives when compared to controls (Hao et al., 2009). A recent large study on schizophrenia and their unaffected relatives identified several regions, including some in the frontal lobes, where FA was shown to be heritable, suggesting that FA could serve as a useful endophenotype for schizophrenia (Bertisch et al., 2010). However, no study to date has employed an atlas-based mapping approach to simultaneously examine both the effects of schizophrenia and disease-related genetic predisposition within the major white matter tracts of the brain.

Mean diffusivity (MD), which describes the rotationally invariant magnitude of water diffusion within brain tissue, is another measure obtained from DTI data that has been used to examine differences of brain structural integrity in schizophrenia. Differences in MD could reflect variations within the intra- and extracellular space and a reduction in neuropil (Selemon & Goldman-Rakic, 1999), and/or index global increases in CSF. MD itself is a rather non-specific, albeit sensitive, measure that can be affected by any disease process that affects the barriers that restrict the motion of water, such as cell membranes (Bosch et al., 2010). While some of the earliest diffusion-weighted imaging studies reported an “apparent diffusion coefficient” or ADC, this means the same thing as current DTI studies that report MD. Most studies on schizophrenia report increased MD in frontal and temporal regions, particularly on the left side (Ardekani et al., 2005; DeLisi et al., 2006; Rose et al., 2006; Shin et al., 2006; White et al., 2007). Previous results showing increased mean diffusivity in first-degree relatives of patients also suggest that MD may provide a marker of genetic liability in schizophrenia (DeLisi et al., 2006). In a prior study restricted to the analyses of MD measurements, which included subjects that overlap with those under investigation here, we reported increases in superior temporal regions in both patients and their first-degree relatives that were present after correction for variance in CSF volumes (Narr et al., 2009). Though these results suggest differences in brain tissue architecture in both patients and their relatives, the ROIs used in that study were not defined based on specific white matter tracts. The two DTI studies cited above addressing disruptions of white matter integrity in biological relatives of schizophrenia patients did not examine group differences in MD (Camchong et al., 2009b; Hao et al., 2009).

Although a growing body of data suggests that alterations in white matter microstructure contribute to disease processes in schizophrenia and some initial findings implicate the involvement of disease-related genetic factors, the regional specificity of findings is less clear. Voxel-based analysis methods employed by the majority of prior schizophrenia DTI studies are particularly sensitive to registration and partial volume confounds. Atlas-based tract mapping approaches, while not capable of isolating effects at the voxel level, may benefit from increased signal to noise since DTI metrics are averaged across the entire tract, similar to the averaging approach used in tractography studies utilizing data with higher angular resolution (Phillips et al., 2009). To confirm the regional specificity of FA and MD differences in schizophrenia and to investigate the presence of FA and/or MD differences in healthy biological relatives of patients that may indicate genetic predisposition towards the disorder, we thus used an atlas-based approach to measure alterations in FA and MD that are specific to white matter tracts in a large sample of schizophrenia patients and their family members as compared to healthy controls and their relatives. Based on the majority of previous findings, we predicted that patients would exhibit decreased FA and increased MD

in white matter pathways predominantly linking frontal and temporal regions when compared to controls. Unaffected relatives of patients were predicted to show similar, though less pronounced, differences in DTI metrics than those exhibited by patients.

Methods and Materials

Subjects

Data were acquired for 35 adult-onset schizophrenia patients, 54 unaffected first-degree relatives of patients, 30 healthy control subjects, and 48 first-degree relatives of controls, ranging in age from 18-77 years, as part of the recently completed second phase of the UCLA Family Study (Asarnow et al., 2001; Fogelson et al.; Nuechterlein et al., 2002). From this pool, subjects were selected to create age and gender matched groups for the analyses described below. The final number of subjects who were used in this study included: 35 adult-onset schizophrenia patients, 28 unaffected first-degree relatives of patients, 29 healthy controls subjects, and 14 first-degree relatives of controls, ranging in age 18-63 years. Some of these subjects (24 patients, 16 patient family members, 18 controls, and 7 control family members) were also included in a previous investigation of MD using a regions-of-interest (ROI) approach (Narr et al., 2009). The UCLA Institutional Review Board (IRB) approved all research procedures, and informed written consent was obtained from all participants.

Schizophrenia patients were recruited through current and past admissions to the UCLA Aftercare Research Program from local public and private psychiatric hospitals and clinics in the Los Angeles area. Schizophrenia diagnosis was confirmed using the Structured Clinical Interview (SCID) for DSM-IV (First et al., 1997b). All patients had recently received or were currently taking standard antipsychotic medications, including aripiprazole (n=8), clozapine (n=4), fluphenazine (n=1), haldol (n=2), olanzapine (n=5), quetiapine (n=4), risperidone (n=16), and ziprasidone (n=3), with 8 subjects taking a combination of these drugs; medication information was missing for 1 patient. The 24-item Brief Psychiatric Rating Scale (BPRS) was administered to 34 of the 35 patients (Lukoff et al., 1986). The following five scores were calculated from the BPRS for use as dependent measures: Anxiety-Depression (ANDP), Anergia (ANER), Thought Disturbance (THOT), Activation (ACTV), Hostile-Suspiciousness (HOST) (Guy, 1976) (Table 1).

Control subjects were recruited from demographically similar backgrounds using survey research lists and through telephone contact. First-degree relatives of schizophrenia patients and control subjects were included if they were biological relatives and met inclusion criteria requirements. The non-patient version of the Structural Clinical Interview for DSM-IV (SCID-NP) was administered to controls and the first-degree relatives of both controls and patients. No individual with a schizophrenia spectrum disorder (i.e. schizophrenia, schizoaffective disorder, or schizotypal, paranoid, avoidant, schizoid personality disorders) or a psychotic disorder was included in any of the control groups, including the first-degree relatives of the patients. Selected sections of the Structural Clinical Interview for DSM-IV Axis II disorders (First et al., 1997a) were also administered to subjects by clinical interview. Six control and eight patient relatives met additional diagnostic criteria for additional Axis I or II diagnoses (mood disorders: n = 3, n = 6, respectively, anxiety disorder: n = 2, n = 4, respectively, attention-deficit/hyperactivity disorder: n = 3, n = 1, respectively, conduct disorders n = 2, n = 1, respectively; and antisocial personality disorder: n = 0, n = 1, respectively). Control and patient relatives were receiving the following medications: vitamins: n = 6, n = 2, respectively; antihypertensives: n = 1, n = 3, respectively; hormones: n = 1, n = 0, respectively; pain control: n = 2, n = 3, respectively; insulin: n = 0, n = 1, respectively; antihistamines: n = 1, n = 0, respectively; antibiotics: n =

0, $n = 1$, respectively; arthritis/lupus: $n = 0$, $n = 1$, respectively; muscle relaxant: $n = 0$, $n = 1$, respectively.

Exclusion criteria for all subjects included neurological disorders (e.g. temporal lobe epilepsy) and mental retardation and any evidence of drug abuse or alcoholism within six months prior to assessment. Any abnormalities, e.g. calcifications or cysts, identified in the T1-weighted scans by a neuroradiologist were excluded from the study. Patients were additionally excluded if there was any evidence that a past history of substance abuse triggered the psychotic episode, interfered with diagnosis or was a prominent factor in the course of illness. Control subjects were excluded if they had any evidence of drug abuse or alcoholism in the six months prior to assessment or any past history of alcohol abuse.

Image Acquisition and Preprocessing

Whole brain, 6 non-collinear direction DTI data ($b=0$, 1000 sec/mm²; FOV: 192; voxel size: 3×3×3 mm³; 4 averages) and high-resolution T1-weighted 3D MPRAGE structural MR data (NEX=4; FOV: 256; voxel size: 1×1×1 mm³; TR=1900 ms; TE=4.38 ms; flip angle: 15°) were acquired on a Siemens 1.5T scanner (Erlangen, Germany). The T1 data was first skull stripped using BET (Smith, 2002); then brain masks were manually corrected on a slice-by-slice basis. The diffusion-weighted images were acquired using a sequence that was optimized to minimize eddy current induced distortions (Reese et al., 2003). Any remaining eddy current induced distortions were corrected using a 2D nonlinear registration algorithm to align these images to a non-diffusion-weighted image (Woods et al., 1998b). The DTI data were corrected for motion artifacts using a 3D rigid body registration, and the diffusion gradient table was corrected accordingly (Woods et al., 1998a). The diffusion tensor was computed at each voxel using a linear least squares method to fit the log-transformed data of the signal intensities (Basser et al., 1994). The resultant eigenvalues were used to compute the fractional anisotropy (FA) and mean diffusivity (MD). All processing of the DTI data was done using in-house software written in C, using the CLAPACK library (Anderson et al., 1999).

Tract-based atlasing

The Johns-Hopkins University white matter tractography atlas (Hua et al., 2008) was mapped to the diffusion data of each subject to identify the following regions of interest (ROIs): anterior thalamic radiation (ATR), cingulate cortex cingulum (CgC), hippocampal region cingulum (CgH), corticospinal tract (CST), inferior fronto-occipital fasciculus (IFO), inferior longitudinal fasciculus (ILF), superior longitudinal fasciculus (SLF), SLF temporal component (tSLF), and uncinate fasciculus (Unc) within each hemisphere, and the forceps major (Fmajor) and minor (Fminor) across hemispheres. Mapping was done by spatially aligning the T1 reference brain from the JHU atlas to each subject's MPRAGE using a nonlinear registration algorithm (Woods et al., 1998b). Accurate registration was evaluated by visual inspection of each subject. Mean MD and mean FA were calculated per tract.

Statistical analyses

Subjects were selected from the overall pool of 197 subjects to form groups that were similar in age and gender ratios. Using averaged FA and MD measures for each tract as dependent variables, statistical analyses were designed to test for: effects of schizophrenia (comparing 35 patients to 30 community controls), effects of genetic liability (comparing 32 controls, 31 patients, and 20 unaffected first-degree relatives of patients), and disease-related effects (comparing 11 pairs of patients with their unaffected siblings). In order to create age and gender balanced groups, 14 subjects who were recruited as first-degree relatives of the original community control group were treated as controls in the genetic liability analysis. These 14 subjects did not enter into any other analyses. Only the disease-related effects

analysis included any subjects who were genetically related to each other. While the genetic liability effects analyses included first-degree relatives, subjects were specifically selected from the pool to not include any subjects from the same families as the patients or other controls used in that analysis (Table 1).

Since a growing amount of literature supports disturbances of white matter integrity in schizophrenia where reductions in FA and increases in MD are typically observed (Di et al., 2009; Ellison-Wright & Bullmore, 2009; Kubicki et al., 2007; White et al., 2008), and the goal of this study was to identify differences in major white matter pathways in patients that were expected to be of lesser magnitude in biological relatives in patients, a two tailed p-value of .05 was considered the threshold for statistical significance. Only tracts that demonstrated a significant schizophrenia effect, e.g. a significant difference between schizophrenia patients and controls, were tested for genetic liability and disease-related effects. For tracts showing schizophrenia effects, follow-up analyses were performed to investigate relationships between DTI and BPRS cluster scores.

Results

Schizophrenia effects

Thirty-five patients (11 females, ages = 31.2 ± 9.2 years) and thirty control subjects (8 females, ages = 27.9 ± 8.3 years) were compared using a two-sample t-test. There were no significant differences between the two groups in mean age ($t(63)=1.84$, $p<0.07$) or gender distribution ($\chi^2(1, 65) = 0.18$, $p<0.67$). Patients had significantly *lower* FA in the following tracts: bilateral IFO, left ILF, and left tSLF (Table 2). Patients had significantly *higher* MD in the following tracts: right ATR, Fminor, bilateral IFO, left tSLF, and bilateral uncinate (Table 3). Although age was not significantly different between the two groups, *post-hoc* analyses were conducted including age as a covariate. In these analyses, the FA of the left ILF and left IFO were still significant as well the MD effects in the right ATR, Fminor, and bilateral UNC; all other effects became trend-level when age was included as a covariate. Because previous studies (Mori et al., 2007) have indicated that FA can sometimes correlate with illness and treatment duration, we examined this possibility within the tracts that demonstrated a significant schizophrenia effect: bilateral IFO, left ILF, and left tSLF. In all four tracts the correlation between FA and illness duration was not found to be statistically significant. Because some of these subjects were used in a previous study, we confirmed that effect sizes were not substantially different when these subjects were excluded.

Genetic liability effects

Thirty-one patients (9 females, ages = 32.7 ± 9.3 years), thirty-two control subjects (15 females, ages = 34.8 ± 14.0 years), and twenty first-degree unaffected relatives of patients (7 females, ages = 41.1 ± 13.0 years), none of whom were genetically related to the patients used in this analysis, were compared using a univariate analysis of variance (ANOVA). There were no significant main effects of group for age ($F(2,80)=2.95$, $p<0.06$) or gender distribution ($\chi^2(2, 83) = 2.2$, $p<0.33$). Genetic liability was determined based on a significant linear effect where unaffected relatives of patients showed values intermediate to those observed in patients and controls. Only those tracts that showed a significant difference between schizophrenia patients and controls were examined for genetic liability. There were significant genetic liability effects in the FA of the following tracts: bilateral IFO, bilateral ILF, and left tSLF (Table 2). There were no significant genetic liability effects for MD. Although age was not significantly different among these groups, *post-hoc* analyses were conducted including age as a covariate. In these analyses, the FA of the left ILF remained significant, while the other three became trend-level.

Disease-related effects

Eleven pairs of patients (5 females, ages = 32.2 ± 9.5 years) and their unaffected siblings (4 females, ages = 33.1 ± 12.8 years) were compared using an independent samples t-test. There were no significant differences between the two groups in age range ($t(10)=0.43$, $p<0.68$) or gender distribution ($\chi^2(1, 22) = 0.19$, $p<0.67$). Only those tracts that showed a significant difference between schizophrenia patients and controls were examined for disease-related effects. Patients had significantly *lower* FA compared to their unaffected siblings in the left tSLF with a trend for lower FA in the left ILF (Table 2). Patients also showed significantly *higher* MD compared to their unaffected siblings in the right UNC (Table 3). Finally, to ensure that results were not attributable to partial volume effects, follow-up analyses were performed including the volume of each tissue type obtained from the atlas tracts as covariates. Overall, the tissue proportions of gray matter ($F(2,80)=2.56$, $p<0.084$), white matter ($F(2,80)=1.92$, $p<0.154$), and CSF ($F(2,80)=0.31$, $p<0.738$) in the atlas did not differ significantly across groups, and effect sizes for the results reported above remained comparable when individual tissue volumes were included as covariates in analyses.

Correlations with BPRS scores

Spearman's correlations were used to compute the associations between BPRS cluster scores and all of the DTI measures that showed significant schizophrenia effects (bold values from the first columns of Tables 2 & 3). A non-parametric test was chosen because there were significant non-normalities in the BPRS cluster scores as measured by a Kolmogorov-Smirnov test. Significant negative correlations were identified between the ANDP cluster score and the fractional anisotropy of the left IFO (Spearman's $\rho = -0.394$; $p<0.02$) and left ILF (Spearman's $\rho = -0.361$; $p<0.04$). Trend-level correlations were identified between the ACTV scores and the fractional anisotropy of the left IFO and left ILF.

Discussion

The goals of this study were first to determine the relationship between having schizophrenia and the MD and FA of major white matter tracts within the human brain, and secondly to characterize to what extent differences in these metrics might reflect a genetic predisposition for schizophrenia. The main findings were that: a) schizophrenia patients had significantly increased MD values in the right ATR, the Fminor, the bilateral IFO, the left tSLF, and the bilateral uncinate, that did not show significant influence of genetic liability; b) FA values in the bilateral IFO, the left ILF, and the left tSLF decrease as a function of relationship to an individual with schizophrenia; and c) the FA values in the left ILF and left IFO were significantly negatively correlated with the ANDP cluster scores from the BPRS. By employing a comprehensive atlas-based tract mapping approach, this study provides further evidence to support that disturbances in white matter pathways linking frontal and temporal regions as well as other cortical and subcortical centers, contribute to the pathophysiology of schizophrenia. In addition, regional abnormalities in white matter microstructure may represent potential biomarkers of schizophrenia genetic vulnerability.

In the current study, regional FA differences were shown to occur in accordance with the degree of genetic relation to a patient with schizophrenia. That is, in tracts showing significant schizophrenia effects, relatives of patients exhibited reductions intermediate to those observed in patients and controls. Since unaffected first-degree relatives share on average 50% of their genes with patients, these results support that schizophrenia genetic factors contribute to these structural differences, although the influence of shared environmental effects cannot be excluded. Findings in the IFO, ILF and tSLF are consistent with those of a voxel-based study reporting reductions in FA in the vicinity of the left

prefrontal cortex and hippocampus in patients and their unaffected siblings (Hao et al., 2009) though the employment of different methodological approaches precludes a direct comparison of results across studies. Several lines of evidence have implicated genes expressed in oligodendrocytes and involved in myelination in schizophrenia (Karoutzou et al., 2008; Marenco et al., 2009). Further, variations in genes such as neuregulin 1 (NRG1) and ErbB4 that have been identified as genetic risk factors in the disorder may disrupt the development of neural pathways providing possible explanations for genetically mediated disturbances of white matter integrity. Since for MD measurements only comparisons between patients and controls and patients and siblings of patient achieved significance, findings of increased MD may represent alterations in white matter microstructure related more directly to disease processes. Increases in MD have been attributed to atrophy or differences in tissue density and may represent different pathophysiological processes, as evidenced by our previous observations of genetic liability effects in superior temporal lobe regions in an overlapping sample where measurements were not restricted to white matter (Narr et al., 2009).

Results from this study showing schizophrenia effects in the bilateral IFO, left ILF, and left tSLF are consistent with a recent meta-analysis of FA findings obtained from schizophrenia studies using voxel based analysis methods that implicate white matter dysconnectivity in two major circuits. Investigators describe one network as centered in the deep frontal white matter that interconnects the frontal lobe, thalamus and cingulate gyrus. The second network, encompassing deep temporal white matter, is described to interconnect the frontal lobe, insula, hippocampus–amygdala, and occipital lobe (Ellison-Wright et al., 2009). The IFO forms the main connection between the fusiform and lingual gyri and the frontal cortex. Several lines of evidence support links between schizophrenia and disruptions in this white matter pathway. For example, damage to the left IFO has been associated with the development of psychosis (Walterfang et al., 2008). Damage to the right IFO has also been associated with deficits in the recognition of the facial expressions, particularly with emotional content (Philippi et al., 2009; Thomas et al., 2008). Such impairments have been recognized to be a prominent feature of schizophrenia (Lee et al., 2010; Morris et al., 2009) and also appear present in unaffected relatives of patients (Bediou et al., 2007) suggesting they may represent an endophenotype in schizophrenia. Furthermore, in a recent DTI study of 104 patients with schizophrenia, the FA of the bilateral IFO was significantly lower in patients with poor (“Kraepelinian”) as compared to good outcomes, and the FA of the IFO correlated inversely with the negative syndrome subscale scores of the Positive and Negative Syndrome Scale (PANSS) (Mitelman et al., 2007). Thus, disruptions in IFO integrity may represent deficits influencing the severity of schizophrenia

The ILF and IFO have considerable overlap in the atlas, as can be seen in Figure 1, particularly in the fusiform and lingual gyri. As for the IFO, significant schizophrenia effects, and effects of genetic liability were also observed for FA of the ILF; only significant schizophrenia effects were observed for MD. The ILF, which forms the main connection between the fusiform and lingual gyri and the temporal cortex, also passes through the hippocampus and parahippocampal region (Catani et al., 2003) and has been implicated by prior studies to be associated with schizophrenia. For example, decreases in the FA of the left ILF has been associated with visual hallucinations in adolescents with schizophrenia (Ashtari et al., 2007). The FA of the ILF correlated inversely with the positive syndrome subscale scores of the PANSS (Mitelman et al., 2007). Results from our study showing trends for differences between siblings of patients and patients themselves (disease-related effects) for both the ILF and IFO and significant schizophrenia effects of MD in the IFO in the absence of genetic liability effects, may thus argue that fiber integrity is compromised by both disease-related and genetic factors. Though we report associations between ANDP cluster scores and FA in both the ILF and IFO, it is important to note that patients in this

study were receiving standard antipsychotic medication treatment and were largely asymptomatic at the time of scanning, perhaps accounting for our failure to detect associations with other symptom cluster scores. Finally, decreases in FA in the ILF-IFO region have been associated with subclinical psychotic symptoms in children ages 11-13 (Jacobson et al., 2010) supporting a role for disturbed neurodevelopmental processes in the integrity of these pathways.

The superior longitudinal fasciculus is a complex entity; while most studies agree that at least one subcomponent connects Broca's and Wernicke's areas, some studies have also identified connections to the inferior parietal lobe (Catani et al., 2005; Makris et al., 2005). In the atlas used in this study, there were two ROIs for the SLF: one that included the connections to the inferior parietal region (SLF) and one that did not (tSLF). Significant genetic liability to schizophrenia effects were identified in the FA data from the left tSLF, but only trend-level effects were observed in the larger left SLF ROI. In two recent studies by Karlsgodt et al., decreases in the FA of the SLF (in voxels contained in both SLF ROIs from the atlas) were observed in recent-onset schizophrenia patients and those at ultra-high risk for developing schizophrenia (Karlsgodt et al., 2009; Karlsgodt et al., 2008). The FA of the left SLF, but not the right, correlated with performance on a verbal working memory task (Karlsgodt et al., 2008). In multiple studies, the FA of the SLF, particularly the left arcuate, of schizophrenia patients has been observed to be reduced compared to controls (Hubl et al., 2004; Seok et al., 2007; Shergill et al., 2007). Several of these previous studies have also shown correlations between SLF FA and auditory hallucinations. In the current cohort, only 8 patients were experiencing any hallucinations at the time of assessment; therefore, correlations of auditory hallucinations ratings specifically were not examined. Based on observations of increased MD and decreased FA in patients compared to controls as well as trends for differences between patients and their siblings, findings may again suggest that factors associated with disease processes in schizophrenia may further account for abnormalities in the tSLF.

Limitations of the study may include six direction DTI acquisition, though with multiple repeats obtained to increase signal to noise. Although this is no longer considered a sophisticated acquisition protocol, this data was collected over a long period of time to get such large numbers of a difficult population, and we feel that six directions is sufficient to estimate MD and FA, particularly when the values are averaged over a large number of voxels, such as in the tract ROIs used in this study. Another potential limitation is the number of hypotheses tested; however, given previous studies, we hypothesized decreases in FA and increases in MD for tracts in the frontal and temporal lobes. While these hypotheses were confirmed, e.g. IFO, we did not find significant effects in other non-hypothesized tracts, e.g. CgC. Furthermore, the findings were in the predicted direction, i.e. patients had lower FA and higher MD compared to controls. Another potential limitation is that this particular group of patients had low symptomatology, precluding the opportunity to fully address the contributions of disease state, and the role of antipsychotics cannot be ruled out. However, since relatives of patients showed differences in FA that were intermediate to those observed in patients and controls, these results suggest that effects are not be solely attributable to state or medication status. The groups for these analyses were formed by selecting subjects from a larger pool in an effort to match age and gender; however, in two of the analyses, trend-level age differences remained. Although all of the significant results remained either significant or trend-level once age was included as a covariate, it is possible that age remained a potential confound in this study. The relatively small number of control relatives is also a potential limitation. This study lays the groundwork for several future studies. For example, future investigations incorporating more sophisticated acquisition and analysis protocols may provide more precise spatial information concerning white matter abnormalities influenced by schizophrenia-related genetic predisposition, studies employing

longitudinal designs may determine the predictive value of these abnormalities regarding subsequent transition to psychosis in high-risk individuals (e.g. (Smieskova et al., 2010)), and studies including more acutely ill patients might better address whether symptom profiles (state variables) influence white matter disturbances in the disorder.

Conclusion

The main finding of this study was that schizophrenia patients have reduced FA in the bilateral IFO, the left ILF, and the left tSLF, and that first-degree relatives show a parallel but less severe reduction. Prior DTI studies have found white matter abnormalities in all three of these tracts in schizophrenia; however, this study is the first to identify significant indications that these white matter pathways reflect schizophrenia genetic predisposition. Thus, FA levels of these three tracts may serve as endophenotypes that may help elucidate the role of specific genetic risk factors in schizophrenia and serve as biomarkers for studies seeking to identify how genes influence altered brain tissue microstructure associated with the disorder. Results from this study also indicated increases in white matter MD in patients with schizophrenia compared to controls in the right ATR, Fminor, bilateral IFO, left tSLF, and bilateral uncinate that were not shown to indicate significant effects of genetic liability. These observations together with trends for differences in FA observed between patients and their first-degree relatives suggest that disease-related processes further contribute to white matter disturbances in schizophrenia. Overall, results from this study are broadly consistent with quantitative and qualitative reviews of FA findings in schizophrenia implicating prominent involvement of frontal and temporal white matter pathways (Ellison-Wright et al., 2009; Kyriakopoulos et al., 2008; White et al., 2008). These results are consistent with our recent study that used tractography to identify ILF, tSLF, and UNC ROIs in a cohort of partially overlapping schizophrenic patients and controls, in which we found that patients had lower FA values compared to controls in the ILF and the tSLF, but in not the uncinate (Phillips et al., 2009). Results are also in line with observations of white matter volume reductions, observed primarily in left frontal and temporoparietal regions that have previously been shown to associate with genetic risk for schizophrenia (McDonald et al., 2004).

Acknowledgments

This research was supported by NIMH research grants MH049716, MH037705, and MH066286 to K.H.N. and MH073990 to K.L.N. Additional support was provided through the NIH/National Center for Research Resources through grants P41 RR013642 and U54 RR021813 (Center for Computational Biology (CCB)).

References

- Anderson, E.; Bai, Z.; Bischof, C.; Blackford, S.; Demmel, J.; Dongarra, J.; Du Croz, J.; Greenbaum, A.; Hammarling, S.; McKenney, A.; Sorensen, D. LAPACK Users' Guide. Third. Philadelphia, PA: Society for Industrial and Applied Mathematics; 1999.
- Ardekani BA, Bappal A, D'Angelo D, Ashtari M, Lencz T, Szeszko PR, Butler PD, Javitt DC, Lim KO, Hrabec J, Nierenberg J, Branch CA, Hoptman MJ. Brain morphometry using diffusion-weighted magnetic resonance imaging: application to schizophrenia. *Neuroreport*. 2005; 16:1455–9. [PubMed: 16110271]
- Asarnow RF, Nuechterlein KH, Fogelson D, Subotnik KL, Payne DA, Russell AT, Asamen J, Kuppinger H, Kendler KS. Schizophrenia and schizophrenia-spectrum personality disorders in the first-degree relatives of children with schizophrenia: the UCLA family study. *Arch Gen Psychiatry*. 2001; 58:581–8. [PubMed: 11386988]
- Ashtari M, Cottone J, Ardekani BA, Cervellione K, Szeszko PR, Wu J, Chen S, Kumra S. Disruption of white matter integrity in the inferior longitudinal fasciculus in adolescents with schizophrenia as revealed by fiber tractography. *Arch Gen Psychiatry*. 2007; 64:1270–80. [PubMed: 17984396]

- Basser PJ, Mattiello J, LeBihan D. Estimation of the effective self-diffusion tensor from the NMR spin echo. *J Magn Reson B*. 1994; 103:247–54. [PubMed: 8019776]
- Bediou B, Asri F, Brunelin J, Krolak-Salmon P, D'Amato T, Saoud M, Tazi I. Emotion recognition and genetic vulnerability to schizophrenia. *Br J Psychiatry*. 2007; 191:126–30. [PubMed: 17666496]
- Bertisch H, Li D, Hoptman MJ, Delisi LE. Heritability estimates for cognitive factors and brain white matter integrity as markers of schizophrenia. *Am J Med Genet B Neuropsychiatr Genet*. 2010; 153B:885–94. [PubMed: 20052692]
- Borgwardt SJ, Picchioni MM, Ettinger U, Touloupoulou T, Murray R, McGuire PK. Regional gray matter volume in monozygotic twins concordant and discordant for schizophrenia. *Biol Psychiatry*. 2010; 67:956–64. [PubMed: 20006324]
- Bosch B, Arenaza-Urquijo EM, Rami L, Sala-Llonch R, Junque C, Sole-Padullés C, Pena-Gomez C, Bargallo N, Molinuevo JL, Bartres-Faz D. Multiple DTI index analysis in normal aging, amnesic MCI and AD. Relationship with neuropsychological performance. *Neurobiol Aging*. 2010
- Braff DL, Freedman R, Schork NJ, Gottesman II. Deconstructing schizophrenia: an overview of the use of endophenotypes in order to understand a complex disorder. *Schizophr Bull*. 2007; 33:21–32. [PubMed: 17088422]
- Brans RG, van Haren NE, van Baal GC, Schnack HG, Kahn RS, Hulshoff Pol HE. Heritability of changes in brain volume over time in twin pairs discordant for schizophrenia. *Arch Gen Psychiatry*. 2008; 65:1259–68. [PubMed: 18981337]
- Camchong J, Lim KO, Sponheim SR, Macdonald AW. Frontal white matter integrity as an endophenotype for schizophrenia: diffusion tensor imaging in monozygotic twins and patients' nonpsychotic relatives. *Front Hum Neurosci*. 2009a; 3:35. [PubMed: 19893757]
- Camchong J, Macdonald AW 3rd, Bell C, Mueller BA, Lim KO. Altered Functional and Anatomical Connectivity in Schizophrenia. *Schizophr Bull*. 2009b
- Cannon TD, van Erp TG, Huttunen M, Lonnqvist J, Salonen O, Valanne L, Poutanen VP, Standertskjold-Nordenstam CG, Gur RE, Yan M. Regional gray matter, white matter, and cerebrospinal fluid distributions in schizophrenic patients, their siblings, and controls. *Arch Gen Psychiatry*. 1998; 55:1084–91. [PubMed: 9862551]
- Catani M, Jones DK, Donato R, Ffytche DH. Occipito-temporal connections in the human brain. *Brain*. 2003; 126:2093–107. [PubMed: 12821517]
- Catani M, Jones DK, Ffytche DH. Perisylvian language networks of the human brain. *Ann Neurol*. 2005; 57:8–16. [PubMed: 15597383]
- DeLisi LE, Szulc KU, Bertisch H, Majcher M, Brown K, Bappal A, Branch CA, Ardekani BA. Early detection of schizophrenia by diffusion weighted imaging. *Psychiatry Res*. 2006; 148:61–6. [PubMed: 17070020]
- Di X, Chan RC, Gong QY. White matter reduction in patients with schizophrenia as revealed by voxel-based morphometry: an activation likelihood estimation meta-analysis. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009; 33:1390–4. [PubMed: 19744536]
- Ellison-Wright I, Bullmore E. Meta-analysis of diffusion tensor imaging studies in schizophrenia. *Schizophr Res*. 2009; 108:3–10. [PubMed: 19128945]
- Ettinger U, Schmechtig A, Touloupoulou T, Borg C, Orrells C, Owens S, Matsumoto K, van Haren NE, Hall MH, Kumari V, McGuire PK, Murray RM, Picchioni M. Prefrontal and Striatal Volumes in Monozygotic Twins Concordant and Discordant for Schizophrenia. *Schizophr Bull*. 2010
- First, MB.; Gibbon, M.; Spitzer, RL.; Williams, JBW.; Benjamin, LS. Structured Clinical Interview for DSM-IV Axis II Disorders. Washington, D.C.: American Psychiatric Press, Inc; 1997a.
- First, MB.; Spitzer, RL.; Gibbon, M.; Williams, JBW. Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition. New York, NY: State Psychiatric Institute; 1997b.
- Fogelson DL, Asarnow RA, Sugar CA, Subotnik KL, Jacobson KC, Neale MC, Kendler KS, Kuppinger H, Nuechterlein KH. Avoidant personality disorder symptoms in first-degree relatives of schizophrenia patients predict performance on neurocognitive measures: The UCLA family study. *Schizophr Res*.
- Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003; 160:636–45. [PubMed: 12668349]

- Guy, W. ECDEU assessment manual for psychopharmacology, revised. In: M. U. D. o. H. a. H. S. Rockville. , editor. DHEW Publication No ADM 76-338. 1976.
- Hao Y, Liu Z, Jiang T, Gong G, Liu H, Tan L, Kuang F, Xu L, Yi Y, Zhang Z. White matter integrity of the whole brain is disrupted in first-episode schizophrenia. *Neuroreport*. 2006; 17:23–6. [PubMed: 16361944]
- Hao Y, Yan Q, Liu H, Xu L, Xue Z, Song X, Kaneko Y, Jiang T, Liu Z, Shan B. Schizophrenia patients and their healthy siblings share disruption of white matter integrity in the left prefrontal cortex and the hippocampus but not the anterior cingulate cortex. *Schizophr Res*. 2009; 114:128–35. [PubMed: 19643580]
- Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry*. 2005; 10:40–68. image 5. [PubMed: 15263907]
- Hoffman RE, McGlashan TH. Synaptic elimination, neurodevelopment, and the mechanism of hallucinated “voices” in schizophrenia. *Am J Psychiatry*. 1997; 154:1683–9. [PubMed: 9396946]
- Honea RA, Meyer-Lindenberg A, Hobbs KB, Pezawas L, Mattay VS, Egan MF, Verchinski B, Passingham RE, Weinberger DR, Callicott JH. Is Gray Matter Volume an Intermediate Phenotype for Schizophrenia? A Voxel-Based Morphometry Study of Patients with Schizophrenia and Their Healthy Siblings. *Biol Psychiatry*. 2007
- Hoptman MJ, Nierenberg J, Bertisch HC, Catalano D, Ardekani BA, Branch CA, Delisi LE. A DTI study of white matter microstructure in individuals at high genetic risk for schizophrenia. *Schizophr Res*. 2008; 106:115–24. [PubMed: 18804959]
- Hua K, Zhang J, Wakana S, Jiang H, Li X, Reich DS, Calabresi PA, Pekar JJ, van Zijl PC, Mori S. Tract probability maps in stereotaxic spaces: Analyses of white matter anatomy and tract-specific quantification. *Neuroimage*. 2008; 39:336–47. [PubMed: 17931890]
- Hubl D, Koenig T, Strik W, Federspiel A, Kreis R, Boesch C, Maier SE, Schroth G, Lovblad K, Dierks T. Pathways that make voices: white matter changes in auditory hallucinations. *Arch Gen Psychiatry*. 2004; 61:658–68. [PubMed: 15237078]
- Jacobson S, Kelleher I, Harley M, Murtagh A, Clarke M, Blanchard M, Connolly C, O'Hanlon E, Garavan H, Cannon M. Structural and functional brain correlates of subclinical psychotic symptoms in 11-13 year old schoolchildren. *Neuroimage*. 2010; 49:1875–85. [PubMed: 19770054]
- Karlsgodt KH, Niendam TA, Bearden CE, Cannon TD. White Matter Integrity and Prediction of Social and Role Functioning in Subjects at Ultra-High Risk for Psychosis. *Biol Psychiatry*. 2009
- Karlsgodt KH, van Erp TG, Poldrack RA, Bearden CE, Nuechterlein KH, Cannon TD. Diffusion tensor imaging of the superior longitudinal fasciculus and working memory in recent-onset schizophrenia. *Biol Psychiatry*. 2008; 63:512–8. [PubMed: 17720147]
- Karoutzou G, Emrich HM, Dietrich DE. The myelin-pathogenesis puzzle in schizophrenia: a literature review. *Mol Psychiatry*. 2008; 13:245–60. [PubMed: 17925796]
- Kirov G, O'Donovan MC, Owen MJ. Finding schizophrenia genes. *J Clin Invest*. 2005; 115:1440–8. [PubMed: 15931379]
- Kubicki M, McCarley R, Westin CF, Park HJ, Maier S, Kikinis R, Jolesz FA, Shenton ME. A review of diffusion tensor imaging studies in schizophrenia. *J Psychiatr Res*. 2007; 41:15–30. [PubMed: 16023676]
- Kubicki M, Westin CF, McCarley RW, Shenton ME. The application of DTI to investigate white matter abnormalities in schizophrenia. *Ann N Y Acad Sci*. 2005; 1064:134–48. [PubMed: 16394153]
- Kyriakopoulos M, Bargiotas T, Barker GJ, Frangou S. Diffusion tensor imaging in schizophrenia. *Eur Psychiatry*. 2008; 23:255–73. [PubMed: 18524546]
- Lawrie SM, McIntosh AM, Hall J, Owens DG, Johnstone EC. Brain structure and function changes during the development of schizophrenia: the evidence from studies of subjects at increased genetic risk. *Schizophr Bull*. 2008; 34:330–40. [PubMed: 18227083]
- Lee J, Gosselin F, Wynn JK, Green MF. How Do Schizophrenia Patients Use Visual Information to Decode Facial Emotion? *Schizophr Bull*. 2010
- Lukoff D, Liberman RP, Nuechterlein KH. Symptom monitoring in the rehabilitation of schizophrenic patients. *Schizophr Bull*. 1986; 12:578–602. [PubMed: 3810065]

- Makris N, Kennedy DN, McInerney S, Sorensen AG, Wang R, Caviness VS Jr, Pandya DN. Segmentation of subcomponents within the superior longitudinal fascicle in humans: a quantitative, in vivo, DT-MRI study. *Cereb Cortex*. 2005; 15:854–69. [PubMed: 15590909]
- Marenco S, Radulescu E. Imaging genetics of structural brain connectivity and neural integrity markers. *Neuroimage*. 2009
- McDonald C, Bullmore ET, Sham PC, Chitnis X, Wickham H, Bramon E, Murray RM. Association of genetic risks for schizophrenia and bipolar disorder with specific and generic brain structural endophenotypes. *Arch Gen Psychiatry*. 2004; 61:974–84. [PubMed: 15466670]
- Meyer-Lindenberg A, Weinberger DR. Intermediate phenotypes and genetic mechanisms of psychiatric disorders. *Nat Rev Neurosci*. 2006; 7:818–27. [PubMed: 16988657]
- Mitelman SA, Torosjan Y, Newmark RE, Schneiderman JS, Chu KW, Brickman AM, Haznedar MM, Hazlett EA, Tang CY, Shihabuddin L, Buchsbaum MS. Internal capsule, corpus callosum and long associative fibers in good and poor outcome schizophrenia: a diffusion tensor imaging survey. *Schizophr Res*. 2007; 92:211–24. [PubMed: 17329081]
- Mori T, Ohnishi T, Hashimoto R, Nemoto K, Moriguchi Y, Noguchi H, Nakabayashi T, Hori H, Harada S, Saitoh O, Matsuda H, Kunugi H. Progressive changes of white matter integrity in schizophrenia revealed by diffusion tensor imaging. *Psychiatry Res*. 2007; 154:133–45. [PubMed: 17276660]
- Morris RW, Weickert CS, Loughland CM. Emotional face processing in schizophrenia. *Curr Opin Psychiatry*. 2009; 22:140–6. [PubMed: 19553867]
- Munoz Maniega S, Lymer GK, Bastin ME, Marjoram D, Job DE, Moorhead TW, Owens DG, Johnstone EC, McIntosh AM, Lawrie SM. A diffusion tensor MRI study of white matter integrity in subjects at high genetic risk of schizophrenia. *Schizophr Res*. 2008; 106:132–9. [PubMed: 18849149]
- Narr KL, Cannon TD, Woods RP, Thompson PM, Kim S, Asuncion D, van Erp TG, Poutanen VP, Huttunen M, Lonnqvist J, Standersjold-Nordenstam CG, Kaprio J, Mazziotta JC, Toga AW. Genetic contributions to altered callosal morphology in schizophrenia. *J Neurosci*. 2002a; 22:3720–9. [PubMed: 11978848]
- Narr KL, Hageman N, Woods RP, Hamilton LS, Clark K, Phillips O, Shattuck DW, Asarnow RF, Toga AW, Nuechterlein KH. Mean diffusivity: a biomarker for CSF-related disease and genetic liability effects in schizophrenia. *Psychiatry Res*. 2009; 171:20–32. [PubMed: 19081707]
- Narr KL, van Erp TG, Cannon TD, Woods RP, Thompson PM, Jang S, Blanton R, Poutanen VP, Huttunen M, Lonnqvist J, Standersjold-Nordenstam CG, Kaprio J, Mazziotta JC, Toga AW. A twin study of genetic contributions to hippocampal morphology in schizophrenia. *Neurobiol Dis*. 2002b; 11:83–95. [PubMed: 12460548]
- Nuechterlein KH, Asarnow RF, Subotnik KL, Fogelson DL, Payne DL, Kendler KS, Neale MC, Jacobson KC, Mintz J. The structure of schizotypy: relationships between neurocognitive and personality disorder features in relatives of schizophrenic patients in the UCLA Family Study. *Schizophr Res*. 2002; 54:121–30. [PubMed: 11853986]
- Philippi CL, Mehta S, Grabowski T, Adolphs R, Rudrauf D. Damage to association fiber tracts impairs recognition of the facial expression of emotion. *J Neurosci*. 2009; 29:15089–99. [PubMed: 19955360]
- Phillips OR, Nuechterlein KH, Clark KA, Hamilton LS, Asarnow RF, Hageman NS, Toga AW, Narr KL. Fiber tractography reveals disruption of temporal lobe white matter tracts in schizophrenia. *Schizophr Res*. 2009; 107:30–8. [PubMed: 19028423]
- Prasad KM, Keshavan MS. Structural cerebral variations as useful endophenotypes in schizophrenia: do they help construct “extended endophenotypes”? *Schizophr Bull*. 2008; 34:774–90. [PubMed: 18408230]
- Reese TG, Heid O, Weisskoff RM, Wedeen VJ. Reduction of eddy-current-induced distortion in diffusion MRI using a twice-refocused spin echo. *Magn Reson Med*. 2003; 49:177–82. [PubMed: 12509835]
- Reichenberg A, Harvey PD. Neuropsychological impairments in schizophrenia: Integration of performance-based and brain imaging findings. *Psychol Bull*. 2007; 133:833–58. [PubMed: 17723032]

- Rose SE, Chalk JB, Janke AL, Strudwick MW, Windus LC, Hannah DE, McGrath JJ, Pantelis C, Wood SJ, Mowry BJ. Evidence of altered prefrontal-thalamic circuitry in schizophrenia: an optimized diffusion MRI study. *Neuroimage*. 2006; 32:16–22. [PubMed: 16626974]
- Schlosser RG, Nenadic I, Wagner G, Gullmar D, von Consbruch K, Kohler S, Schultz CC, Koch K, Fitzek C, Matthews PM, Reichenbach JR, Sauer H. White matter abnormalities and brain activation in schizophrenia: a combined DTI and fMRI study. *Schizophr Res*. 2007; 89:1–11. [PubMed: 17085018]
- Selemon LD, Goldman-Rakic PS. The reduced neuropil hypothesis: a circuit based model of schizophrenia. *Biol Psychiatry*. 1999; 45:17–25. [PubMed: 9894571]
- Seok JH, Park HJ, Chun JW, Lee SK, Cho HS, Kwon JS, Kim JJ. White matter abnormalities associated with auditory hallucinations in schizophrenia: a combined study of voxel-based analyses of diffusion tensor imaging and structural magnetic resonance imaging. *Psychiatry Res*. 2007; 156:93–104. [PubMed: 17884391]
- Shergill SS, Kanaan RA, Chitnis XA, O'Daly O, Jones DK, Frangou S, Williams SC, Howard RJ, Barker GJ, Murray RM, McGuire P. A diffusion tensor imaging study of fasciculi in schizophrenia. *Am J Psychiatry*. 2007; 164:467–73. [PubMed: 17329472]
- Shin YW, Kwon JS, Ha TH, Park HJ, Kim DJ, Hong SB, Moon WJ, Lee JM, Kim IY, Kim SI, Chung EC. Increased water diffusivity in the frontal and temporal cortices of schizophrenic patients. *Neuroimage*. 2006; 30:1285–91. [PubMed: 16406258]
- Smieskova R, Fusar-Poli P, Allen P, Bendfeldt K, Stieglitz RD, Drewe J, Radue EW, McGuire PK, Riecher-Rossler A, Borgwardt SJ. Neuroimaging predictors of transition to psychosis--a systematic review and meta-analysis. *Neurosci Biobehav Rev*. 2010; 34:1207–22. [PubMed: 20144653]
- Smith SM. Fast robust automated brain extraction. *Hum Brain Mapp*. 2002; 17:143–55. [PubMed: 12391568]
- Sullivan PF, Kendler KS, Neale MC. Schizophrenia as a complex trait: evidence from a meta-analysis of twin studies. *Arch Gen Psychiatry*. 2003; 60:1187–92. [PubMed: 14662550]
- Szeszko PR, Robinson DG, Ashtari M, Vogel J, Betensky J, Sevy S, Ardekani BA, Lencz T, Malhotra AK, McCormack J, Miller R, Lim KO, Gunduz-Bruce H, Kane JM, Bilder RM. Clinical and neuropsychological correlates of white matter abnormalities in recent onset schizophrenia. *Neuropsychopharmacology*. 2008; 33:976–84. [PubMed: 17581532]
- Tan HY, Callicott JH, Weinberger DR. Intermediate phenotypes in schizophrenia genetics redux: is it a no brainer? *Mol Psychiatry*. 2008; 13:233–8. [PubMed: 18285755]
- Thomas C, Moya L, Avidan G, Humphreys K, Jung KJ, Peterson MA, Behrmann M. Reduction in white matter connectivity, revealed by diffusion tensor imaging, may account for age-related changes in face perception. *J Cogn Neurosci*. 2008; 20:268–84. [PubMed: 18275334]
- van Haren NE, Bakker SC, Kahn RS. Genes and structural brain imaging in schizophrenia. *Curr Opin Psychiatry*. 2008; 21:161–7. [PubMed: 18332664]
- Walterfang M, McGuire PK, Yung AR, Phillips LJ, Velakoulis D, Wood SJ, Suckling J, Bullmore ET, Brewer W, Soulsby B, Desmond P, McGorry PD, Pantelis C. White matter volume changes in people who develop psychosis. *Br J Psychiatry*. 2008; 193:210–5. [PubMed: 18757979]
- White T, Kendi AT, Lehericy S, Kendi M, Karatekin C, Guimaraes A, Davenport N, Schulz SC, Lim KO. Disruption of hippocampal connectivity in children and adolescents with schizophrenia--a voxel-based diffusion tensor imaging study. *Schizophr Res*. 2007; 90:302–7. [PubMed: 17141478]
- White T, Nelson M, Lim KO. Diffusion tensor imaging in psychiatric disorders. *Top Magn Reson Imaging*. 2008; 19:97–109. [PubMed: 19363432]
- Woods RP, Grafton ST, Holmes CJ, Cherry SR, Mazziotta JC. Automated image registration: I. General methods and intrasubject, intramodality validation. *J Comput Assist Tomogr*. 1998a; 22:139–52. [PubMed: 9448779]
- Woods RP, Grafton ST, Watson JD, Sicotte NL, Mazziotta JC. Automated image registration: II. Intersubject validation of linear and nonlinear models. *J Comput Assist Tomogr*. 1998b; 22:153–65. [PubMed: 9448780]

Figure 1. Regions of reduced fractional anisotropy (FA) suggest a genetic predisposition to schizophrenia

In all four of the tracts shown in the left-hand panel (left and right inferior fronto-occipital fasciculus; left inferior longitudinal fasciculus; and left temporal component of the superior longitudinal fasciculus (tSLF)), there were significant effects of both schizophrenia and genetic liability. Disease-related effects were only significant in the left tSLF. The graphs on the right-hand panel show the mean FA; error bars indicate standard error. See text and table 2 for full details.

Table 1

Demographics

	‡Schizophrenia Effects		** controls	‡Genetic Liability Effects		‡Disease-related Effects	
	controls	patients		1 st degree relatives of patients	patients	patients' siblings	patients
Age in years: mean±SD (range)	27.9±8.3 (18-50)	31.2±9.3 (18-50)	34.8±14.0 (20-63)	41.1±13.0 (18-62)	32.7±9.3 (19-50)	33.1±12.8 (21-58)	32.2±9.5 (22-46)
Number of subjects	30	35	32	20	31	11	11
Gender	22m/8f	24m/11f	17m/15f	13m/7f	22m/9f	7m/4f	6m/5f
Type of statistic used	two-sample t-test			linear effects univariate ANOVA		two-sample t-test	
⌊Age of Onset, mean±SD, (range)	*22.1±3.9 years, (14-33 years)						
⌊Duration of Illness, mean±SD (range)	*9.5±8.0 years, (1-25 years)						
⌊BPRS cluster scores, mean±SD	*ANDP: 2.2±0.9						
	*ANER: 1.5±0.6						
	*THOT: 1.7±1.0						
	*ACTV: 1.3±0.4						
	*HOST: 1.4±0.6						

‡ None of the subjects in these tests were related to each other.

‡ In five pairs, the sibling was younger; in five pairs, the sibling was older; the remaining pair was a set of dizygotic twins.

⌊ For the schizophrenia patients only.

* Data missing for 1 patient.

** Included fourteen first-degree relatives of controls.

Table 2
Significant Fractional Anisotropy (FA) effects (dimensionless)

	Means	Effect size
<i>Schizophrenia effects</i>		
Left IFO	C: 0.225	$\eta^2_{\text{partial}} = 0.107^{**}$
	P: 0.215	
Right IFO	C: 0.222	$\eta^2_{\text{partial}} = 0.072^*$
	P: 0.215	
Left ILF	C: 0.204	$\eta^2_{\text{partial}} = 0.160^{***}$
	P: 0.193	
Left tSLF	C: 0.236	$\eta^2_{\text{partial}} = 0.060^*$
	P: 0.227	
<i>Genetic liability effects</i>		
Left IFO	C: 0.224	$\eta^2_{\text{partial}} = 0.053^*$
	R: 0.220	
	P: 0.215	
Right IFO	C: 0.223	$\eta^2_{\text{partial}} = 0.048^*$
	R: 0.218	
	P: 0.215	
Left ILF	C: 0.204	$\eta^2_{\text{partial}} = 0.084^{**}$
	R: 0.198	
	P: 0.193	
Left tSLF	C: 0.240	$\eta^2_{\text{partial}} = 0.066^*$
	R: 0.235	
	P: 0.228	
<i>Disease-related effects</i>		
Left tSLF	R: 0.234	$\eta^2_{\text{partial}} = 0.184^*$
	P: 0.221	

Abbreviations: C = controls, P = patients, R = relatives, IFO = inferior fronto-occipital fasciculus, ILF = inferior longitudinal fasciculus, tSLF = superior longitudinal fasciculus temporal component

$p < 0.05$, $**0.01$, $***0.001$ significant effect of group

Table 3
Significant Mean Diffusivity (MD) effects (in $10^{-9} \text{ m}^2/\text{s}$)

	Means	Effect size
<i>Schizophrenia effects</i>		
Right ATR	C: 0.955	$\eta^2_{\text{partial}} = 0.098^*$
	P: 0.989	
Fminor	C: 0.951	$\eta^2_{\text{partial}} = 0.129^{**}$
	P: 0.998	
Left IFO	C: 0.887	$\eta^2_{\text{partial}} = 0.060^*$
	P: 0.907	
Right IFO	C: 0.886	$\eta^2_{\text{partial}} = 0.075^*$
	P: 0.906	
Left tSLF	C: 0.844	$\eta^2_{\text{partial}} = 0.086^*$
	P: 0.861	
Left UNC	C: 0.899	$\eta^2_{\text{partial}} = 0.158^{***}$
	P: 0.927	
Right UNC	C: 0.924	$\eta^2_{\text{partial}} = 0.117^{**}$
	P: 0.950	
<i>Disease-related effects</i>		
Right UNC	R: 0.940	$\eta^2_{\text{partial}} = 0.185^*$
	P: 0.965	

Abbreviations: C = controls, P = patients, R = relatives, ATR = anterior thalamic radiation, CgC = cingulate cortex cingulum, CgH = hippocampal region cingulum, CST = corticospinal tract, Fmajor = forceps major, Fminor = forceps minor, IFO = inferior fronto-occipital fasciculus, ILF = inferior longitudinal fasciculus, SLF = superior longitudinal fasciculus, tSLF = SLF temporal component, UNC = uncinate

$p < 0.05$, $**0.01$, $***0.001$ significant effect of group