Mapping Corticocortical Structural Integrity in Schizophrenia and Effects of Genetic Liability

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Background: Structural and diffusion tensor imaging studies implicate gray and white matter (WM) abnormalities and disruptions of neural circuitry in schizophrenia. However, the structural integrity of the superficial WM, comprising short-range association (U-fibers) and intracortical axons, has not been investigated in schizophrenia.

Methods: High-resolution structural and diffusion tensor images and sophisticated cortical pattern matching methods were used to measure and compare global and local variations in superficial WM fractional anisotropy between schizophrenia patients and their relatives and community comparison subjects and their relatives ($n = 150$).

Results: Compared with control subjects, patients showed reduced superficial WM fractional anisotropy distributed across each hemisphere, particularly in left temporal and bilateral occipital regions (all $p < .05$, corrected). Furthermore, by modeling biological risk for schizophrenia in patients, patient relatives, and control subjects, fractional anisotropy was shown to vary in accordance with relatedness to a patient in both hemispheres and in the temporal and occipital lobes ($p < .05$, corrected). However, effects did not survive correction procedures for two-group comparisons between patient relatives and control subjects.

Conclusions: Results extend previous findings restricted to deep WM pathways to demonstrate that disturbances in corticocortical connectivity are associated with schizophrenia and might indicate a genetic predisposition for the disorder. Because the structural integrity of WM plays a crucial role in the functionality of networks linking gray matter regions, disturbances in the coherence and organization of fibers at the juncture of the neuropil might relate to features of schizophrenia at least partially attributable to disease-related genetic factors.

Key Words: Diffusion tensor imaging (DTI), fractional anisotropy (FA), magnetic resonance imaging (MRI), short-range association fibers, U-fibers, white matter (WM)

A large body of structural magnetic resonance imaging (sMRI) research supports that cortical gray matter (GM) abnormalities are associated with the pathophysiology of schizophrenia (1–3). Diffusion tensor imaging (DTI), which tracks the diffusion properties of water through brain tissue, provides a sensitive means to determine whether altered white matter (WM) microstructure might also contribute to disease processes. Specifically, scalar values derived from the diffusion tensor, such as fractional anisotropy (FA), allow local estimates of tissue organization and coherence by determining the extent to which water diffusion is directionally restricted in each brain voxel (4–8). Human and animal studies support that in regions where the tensor model is valid (i.e., regions with minimal partial volume effects), increases in FA associate with increased myelination, fiber coherence and/or overall number of axons, and/or a decrease in mean axonal diameter (9–13).

Converging lines of evidence implicate WM pathology in schizophrenia, providing a basis for further examination with DTI (14–19). Despite the use of different DTI analysis methods and mixed regional findings, WM abnormalities—typically reduced FA—have been reported within most primary association and projection pathways and the corpus callosum in schizophrenia. Although FA reductions within fiber bundles connecting frontal and/or temporal regions such as the superior longitudinal fasciculus (SLF) or arcuate fasciculus (AF), uncinate fasciculus (UF), inferior longitudinal fasciculus (ILF), cingulum bundle, and anterior callosum seem most reproducible (17,20–24). White matter abnormalities are also reported in recent onset schizophrenia (25), including in patients with little or no antipsychotic medication exposure (26), suggesting these disturbances represent an early marker of schizophrenia (25,27–29). Schizophrenia is highly heritable (30), and disease risk increases as the degree of genetic affinity with the affected family member increases (31). Because recent evidence suggests whole brain FA has a high level of heritability (32,33), disease-associated changes in FA might relate to schizophrenia genetic risk factors. A few prior studies have examined FA in individuals at increased risk for developing schizophrenia (34–36). Although regional findings vary, results suggest that FA abnormalities represent biological indicators for disease vulnerability attributable in part to schizophrenia genetic factors (37–40).

Although schizophrenia has been relatively widely studied with DTI, prior studies have focused almost exclusively on examining changes in the microstructure of long-range fiber pathways within the deep WM. The WM directly beneath the cortex contains a mixture of short association fibers that include intracortical axons, which extend directly from the GM; subcortical fibers (U-fibers) that arch through the cortical sulci to connect adjacent gyri; and some termination fibers from deep fiber pathways (collectively termed "superficially located or superficial white matter" [SWM]) (41–43). Because microstructural abnormalities of the cortical neuropil are reported in schizophrenia postmortem studies (44–46) and cortical GM deficits are widely observed in patients (3,47), are present at first episode (48–50), and have been documented in biological relatives (47,51,52), it is possible that disturbances in the organization and coherence of fibers within the SWM might contribute to disease processes and represent a biological marker for schizophrenia-re-

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lated genetic predisposition. Most DTI analysis procedures, however, are limited with regard to the spatial alignment of the cortical boundary, which is highly variable across subjects (53,54). Therefore, voxel- or tract-based atlasing methods might lack the sensitivity for quantifying corticocortical connectivity at the juncture of the neuropil. Similarly, because the SWM has less-defined trajectories, tract-based atlasing methods are limited for extracting these pathways with certainty (43). The current study thus sought to employ a more sensitive computational analysis approach to address the hypothesis that disturbances in corticocortical connectivity present a biological marker for schizophrenia and disease-related genetic predisposition.

To quantify regional disturbances in the structural connectivity of short-range and neighborhood association fibers in the SWM, DTI and sMRI scans were collected from a large sample of schizophrenia patients and their relatives and community comparison (CC) subjects and their family members ($n = 150$). After the extraction of the WM/GM cortical surfaces and coregistration of DTI and sMRI data, cortical pattern matching algorithms—which have been extensively validated and used for integrating data across imaging modalities (55–60)—were employed to estimate and compare FA values at thousands of spatially matched locations within the SWM across groups defined by diagnosis or biological risk for schizophrenia. The SWM FA values were also examined within lobar regions to detect more subtle and/or broadly distributed abnormalities. Although this is the first study to our knowledge to address SWM changes in schizophrenia patients and their relatives and because fronto-temporal GM deficits are widely reported in the disorder (48,49,61,62), we predicted that disturbances of SWM fiber integrity would be pronounced within these regions in patients and that unaffected relatives of patients would exhibit similar but less-pronounced abnormalities.

Methods and Materials

Subjects

Study participants were recruited from among 76 separate families and included 26 adult-onset schizophrenia patients, 49 nonpsychotic first-degree biological relatives of patients (16 siblings and 33 parents), 21 healthy CC subjects, and 54 nonpsychotic first-degree relatives of CC subjects (28 siblings and 26 parents) as part of the recently completed second phase of the University of California, Los Angeles (UCLA) Family Study. Table 1 provides demographic and clinical details for each group. Schizophrenia patients were recruited through admissions and referrals from the UCLA Aftercare Research Program and local public and private psychiatric hospitals and clinics in the Los Angeles area. Schizophrenia diagnosis was confirmed by diagnostician consensus (63) as determined by DSM-IV criteria with the Structured Clinical Interview for DSM-IV (SCID-I/P) (64) and by informant information. Clinical symptoms were assessed with the expanded 24-item Brief Psychiatric Rating Scale (BPRS) (65,66) and clustered into withdrawal and thinking disorder scores (67). Handedness was determined with a modified version of the Edinburgh Inventory (68).

Healthy CC subjects with demographic profiles similar to those of the schizophrenia probands were recruited with lists provided by a survey research company and telephone contact, and their family members were also invited to participate. The CC subjects were screened by clinical interview with the SCID-NP to exclude the presence of schizophrenia spectrum or other psychiatric disorder. Exclusion criteria for all subjects included mental retardation, neurological disorder, and recent or past history of significant and habitual drug abuse or alcoholism. A radiologist reviewed any suspected abnormalities in the sMRI data. Information including years of education and current social economic status obtained from the Total Socioeconomic Index (69) was collected from subjects. All participants provided informed consent approved by the UCLA Institutional Review Board.

Image Acquisition and Preprocessing

Image data were obtained on a Siemens 1.5T Sonata system (Erlangen, Germany). Diffusion was measured in six noncolinear directions with a diffusion encoded spin echo/echo planar imaging sequence optimized to minimize eddy current distortions (70) with four separate averages: (field-of-view: 192 × 192; matrix: 64 × 64; voxel size: 3 mm^3, repetition time = 6000 msec, echo time = 78 msec, *b*-values 0, 1000; 50 axially oriented brain slices). High-resolution T1-weighted sMRI data, collected on the same scanner, included a three-dimensional magnetization prepared rapid gradient echo sequence also with four averages (number of excitations): (field-of-view: 256 × 256; matrix 256 × 256; voxel size: 1 mm^3; repetition time = 1900 msec; echo time = 4.38; inversion time: 1100 msec; flip angle: 15°).

Structural magnetic resonance imaging preprocessing included: 1) correction of field inhomogeneities (71); 2) removal of extracortical tissue with FSL's Brain Extraction Tool (BET) (http://www.fmrib.ox.ac.uk/fsl/bet2/index.html) with manual correction of errors; 3) correction for head tilt and alignment with a 6-parameter rigid-body transformation (72,73); and 4) extraction of the cortical

Table 1. Demographic and Clinical Details of Study Participants

	Patients ($n = 26$)	CC Probands ($n = 21$)	SZ Parents ($n = 33$)	CC Parents ($n = 26$)	SZ Siblings (n=16)	CC Siblings (n=28)
Age (mean ± SD)	29.50 ± 7.36	25.86 ± 6.65	54.42 ± 8.28	55.65 ± 8.48	30.06 ± 11.45	26.93 ± 9.82
Age (range)	19–46	18–40	37–72	43–70	17–58	13–50
Gender (M/F)	16/10	15/6	13/20	12/14	10/6	12/16
TSEI	28.20 ± 10.60	38.77 ± 18.39	41.04 ± 20.44	37.03 ± 19.83	36.28 ± 19.67	42.99 ± 15.93
Yrs of Education	13.76 ± 1.87	15.19 ± 2.77	14.78 ± 4.53	14.03 ± 3.21	14.18 ± 2.45	15.17 ± 2.22
Age of Onset	22.23 ± 4.03					
Duration of Illness	7.26 ± 6.49					
Withdrawal	1.59 ± .66					
Thinking Disorder	1.52 ± .83					
BPRS Total	36.77 ± 8.17					

All values apart from gender are reported as means and SD. Withdrawal and thinking disorder are cluster scores, computed as described in Burger *et al.* (67). Total current socioeconomic level (TSEI) and years of education data were not available for one parent and five siblings. CC, community comparison; SZ, schizophrenia; BPRS, Brief Psychiatric Rating Scale.

BPRS, Brief Psychiatric Rating Scale; CC, community comparison; F, female; M, male; SZ, schizophrenia.