Mapping Corticocortical Structural Integrity in Schizophrenia and Effects of Genetic Liability

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Abstract

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.

Keywords
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-related 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 non-psychotic 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 diagnostian 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 mm³, 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 mm³; 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 GM and WM boundaries with Freesurfer (http://surfer.nmr.mgh.harvard.edu), where any topographic errors were corrected manually. Cortical pattern matching methods similar to those used in prior sMRI studies (e.g., Thompson et al. [60] and Narr et al. [74]) were used to spatially relate homologous cortical WM surface locations between individuals to allow comparisons of SWM FA to be assessed at anatomically comparable locations across subjects. First, the Freesurfer-generated WM/GM cortical surface models of each hemisphere were translated into a surface mesh consisting of 65,536 vertices. Next, validated anatomic protocols for which inter- and intra-rater reliability protocols have been established (74) were used to manually identify 26 sulcal landmarks on the hemispheric surfaces. The sulcal landmarks were then used as anchors to drive the surrounding WM/GM surface anatomy of each individual into spatial correspondence with surface-warping algorithms that compute the amount of x, y, and z coordinate shift to associate the same anatomical grid locations or vertices between individuals without scaling. That is, the vertices of the WM/GM cortical surface—which are mapped precisely to point locations on a sphere and planar map—were matched according to the sulcal pattern and surrounding anatomy of the entire sample. However, the warping algorithms are used only to regrid surface locations such that only coordinate points are changed without altering the underlying anatomy (60,74,75).

For DTI processing, the diffusion gradient table was corrected for slice prescription, and images were corrected for any residual eddy current distortions and motion artifacts with a combined nonlinear two-dimensional registration (76) and a three-dimensional rigid body registration (72,73) to minimize interpolation. FSL DTIFIT (http://www.fmrib.ox.ac.uk/fsl/fdt/fdt_dtifit.html) was used to obtain FA images that were then registered to each individual subject’s T1 data with affine transformations, employing the averaged b0 image for intermediate registration (72,73). The FA images were masked with the T1 WM tissue segmented images (77) and additionally thresholded at .15 to minimize partial volume effects and ensure that FA was computed for SWM only.

To allow cross-subject sampling of anatomically comparable SWM FA measures, FA was averaged voxel-wise within a 10-mm sphere, determined to best estimate SWM, centered at each of the 65,536 spatially matched WM/GM cortical surface vertices while referencing the corresponding masked and thresholded FA image. Measures of SWM FA were therefore obtained at thousands of spatially matched points. Finally, SWM FA values were also averaged across the entire hemisphere and within lobar regions of interest (ROIs) generated from the LPBA40 atlas (http://www.loni.ucla.edu/Atlases/LPBA40) (78). Thus, to examine the effects of schizophrenia and disease-related genetic liability on the integrity of fibers within the SWM, FA was compared at both the vertex level to capture highly localized changes in structural connectivity and within ROIs including frontal, temporal, parietal, and occipital lobar regions to determine more pervasive SWM pathology. Figure S1 in Supplement 1 provides an overview of the image preprocessing methods.

**Statistical Analysis**

At each cortical WM surface location, the General Linear Model implemented in R (http://www.r-project.org) was used to test for effects of schizophrenia, genetic liability for...
schizophrenia, and effects associated with disease processes specifically. To determine schizophrenia effects, patients were compared with unrelated control probands. To test for schizophrenia-related genetic liability, siblings and parents of patients were compared with siblings and parents of control subjects separately to better control for age disparities among sibling and parent groups, also allowing for the assessment of genetic liability in independent samples. However, because first-degree relatives of patients share on average only 50% of their genes with patient probands, effects of genetic liability are expected to be less pronounced or intermediate to those reflecting differences between patients and control subjects. Thus, additional follow-up analyses were performed by modeling the degree of relatedness to a schizophrenia proband as an independent variable to determine whether SWM FA changes linearly in accordance with genetic risk for schizophrenia. Finally, to determine effects associated with disease processes specifically, patients were compared with their siblings. Sex and age were included in the statistical models used for all five comparisons. Furthermore, for comparisons including related individuals, a mixed model was employed where family relatedness (defined as first-degree relatives belonging to the same family) was included as a random factor. The same statistical models were used to investigate changes in SWM FA values averaged across each hemisphere and within the lobar ROIs.

For the vertex-based analyses of SWM FA, permutation methods (79,80) were used to confirm the significance of effects made at thousands of spatially correlated locations. For permutation testing, the number of vertices showing significant group effects at a statistical threshold of $p < .05$ with the reduced model (i.e., permuting the residuals) and masked within each lobar ROI were compared with the number of vertices showing significant effects occurring by chance when randomly assigning subjects to groups in 10,000 new permutations. Finally, associations between averaged SWM FA values and BPRS cluster scores of Thinking Disturbance and Withdrawal were examined in patients.

**Results**

Patients and CC subjects did not differ significantly in age [$R(1,45) > .31, p = .57$]. Age was also similar between control and patient siblings [$R(1,42) = .25, p > .61$], control and patient parents [$R(1,57) = .08, p > .78$], and between patients and their siblings [$R(1,39) = .2484, p > .12$] (Table 1). The SWM FA measures were not shown to deviate from normality when averaged across each hemisphere or within lobar ROIs (Kolmogorov–Smirnov tests, all $p > .05$). Significant schizophrenia effects (patient vs. unrelated control probands) were observed for SWM FA averaged across hemisphere [left: $R(1,45) = 7.16, p > .01$; right: $R(1,45) = 6.92, p > .01$], left temporal [$R(1,45) = 13.46, p < .001$], and bilateral occipital lobar ROIs [left: $R(1,45) = 9.84, p < .003$, right: $R(1,45) = 6.14, p < .02$]. Although genetic liability effects—examined separately within sibling and parent groups—did not show significant effects for SWM FA values averaged across any of the lobar ROIs (all $p > .05$), follow-up analyses showed significant linear decreases of SWM FA in relatives of schizophrenia patients that were intermediate to those observed in patients and all CC subjects for the left and right temporal lobe [$R(2,108.73) = 5.70, p < .004$, and $R(2,110.18) = 3.33, p < .03$, respectively] and the left and right occipital lobe [$R(2,109.66) = 5.44, p < .006$, and $R(2,106.50) = 3.25, p < .04$]. Disease-related effects (patients vs. patient siblings) were observed for the left occipital ROI only [$R(1,28.45) = 4.53, p < .04$]. Statistical details for all comparisons are provided in Table S1 in Supplement 1, and mean FA values are also plotted in Figure 1 within each biological risk group. The BPRS cluster scores shown in Table 1 did not show significant associations with SWM FA within any of the ROIs examined (all $p > .05$).
Statistical results showing SWM FA effects at high spatial density for each of the two-group comparisons are shown in Figure 2, where uncorrected probability values are indexed by the colorbar. The corresponding maps are provided in Figure 3. Statistical maps showing linear changes in SWM FA modeled according to biological risk for schizophrenia are shown in Figure 4. Comparisons between schizophrenia and control probands showed significant focal reductions of SWM FA over distributed regions (p < .01 indicated in pink) in patients with only a few isolated surface points showing increased SWM FA (p < .01 indicated in dark blue) (Figure 2A). Permutation-corrected p values shown in Table 2 confirmed effects of diagnosis within the left hemisphere, left temporal and bilateral occipital lobes. Significant changes in SWM FA suggesting disease-related genetic liability—predominately reflecting reduced FA in unaffected relatives of patients—were observed in similar patterns but were less spatially distributed, when comparing patient siblings and parents with CC siblings and CC parents (Figures 2B and 2C), although results did not withstand permutation correction. However, comparisons of SWM FA modeled according to degree of relatedness to a schizophrenia proband shown in Figure 4 revealed more pronounced effects, indicating significant linear decreases in SWM FA with increased genetic liability for schizophrenia—which survived permutation testing in left temporal and bilateral occipital regions (mean SWM FA values for these regions are also shown in Figure 4). Finally, for disease-related effects examined by comparing patients and their siblings, findings seemed more bidirectional (Figure 2D) and were not confirmed by permutation testing (Table 2), although occipital effects seemed consistent with the analyses of SWM FA averaged across lobar regions described in the preceding text.

Discussion

This study applied cortical pattern matching methods to identify disturbances in the structural integrity of short-range association fibers and axonal processes sampled in the SWM at the juncture of the neuropil in schizophrenia. The influences of schizophrenia-related genetic predisposition on local and global SWM changes were further assessed. Two important and novel findings emerged from study results: 1) patients with schizophrenia show relatively pervasive reductions in SWM FA, compared with demographically similar control subjects, particularly in left temporal and bilateral occipital lobar regions; and 2) SWM FA varies linearly in accordance with biological relatedness to a schizophrenia proband, where effects are again pronounced in the temporal and occipital lobes, suggesting the influence of genetic factors. However, two-way comparisons between patient and CC relatives indicate that effects of genetic liability are relatively subtle (Figures 2B and 2C). Several prior DTI studies have implicated disturbances in the integrity of the deep WM in schizophrenia (17,24,25). Our results extend this previous work by demonstrating that microstructural abnormalities in the WM directly beneath the cortex associate with schizophrenia. Moreover, findings of temporal and occipital SWM FA values that are intermediate between those of patients and CC subjects suggest that disturbances in fiber coherence and organization are attributable, at least in part, to schizophrenia genetic factors. However, the influence of environmental factors shared by patients and their relatives cannot be completely excluded; and processes specific to having schizophrenia, particularly in the left occipital lobe (Table S1 in Supplement 1), are also shown to influence results.

The SWM comprises short association fibers (or U-fibers) and neighborhood association fibers that connect proximal and more distal cortical gyri, respectively, and include some merging fibers from long association tracts (41,43). Although no study to our knowledge has focused on investigating the integrity of the SWM in schizophrenia, disturbances in deep WM pathways are relatively frequently reported. That is, although regional findings are mixed, quantitative and qualitative reviews suggest that deep frontal and temporal fiber pathways might be preferentially affected (21,24,25). For example, several studies
examining tracts within the temporal lobe—such as the UF, ILF, SLF, and AF—report FA reductions within one or more of these pathways (e.g., [22,26,28,81–87]). In the current study, distributed regions across all four lobes showed reductions of SWM FA in patients, compared with control subjects (Figure 2A), although effects survived permutation testing in left temporal and bilateral occipital regions only. Disrupted corticocortical connections might thus impact clinical and cognitive features of schizophrenia such as auditory hallucinations, thought disorder and disturbances in declarative memory, and emotional processing associated with temporal lobe function (88–92). Although relationships between symptom cluster scores (67) and averaged SWM FA values were not significant in this study, it is important to note that patients were largely asymptomatic at the time of assessment, thus precluding a more meaningful examination of associations with state variables (Table 1).

Although less implicated than fronto-temporal pathways, WM disturbances in occipital regions have been observed in many prior DTI studies (e.g., [83,93–97]). Furthermore, FA reductions in long-range fiber pathways—such as the ILF, superior fronto-occipital fasciculus, and inferior fronto-occipital fasciculus—that connect with occipital cortices are widely documented (22,85,98). In accordance with these earlier findings, results from this study showed significant schizophrenia-related SWM FA reductions in the left and right occipital lobe that survived permutation correction when mapped at high spatial density (Figure 2A). Altered occipital corticocortical connectivity might contribute toward early visual processing and magnocellular pathway abnormalities and/or sensory and motion detection deficits reported in schizophrenia (99–103). Although FA reductions in the frontal lobe did not survive permutation testing, long-range tracts such as the SLF previously implicated in schizophrenia (22,104) connect frontal with temporal and parietal cortices, whereas neighborhood association fibers in the SWM link proximal parietal and temporal gyral regions. Thus, disturbed SWM microstructure in proximal lobar regions might impact connectivity in frontal or parietal regions or vice versa (105).

Schizophrenia has a large heritable component where multiple genes acting in concert with harmful environmental factors seem to account for disease processes (106). Imaging research has identified several neuroanatomical abnormalities in schizophrenia that also suggest genetic predisposition in unaffected at-risk individuals (e.g., [107–113]). Such markers or endophenotypes might help determine the influences and/or aid in the search for schizophrenia risk genes. Several oligodendrocyte/myelin-related genes, neuregulin 1 and ErbB4 in particular, have been implicated in schizophrenia (16,34,114), providing possible explanations for genetically mediated disturbances of structural connectivity. However, relatively few studies have addressed whether DTI metrics might represent intermediate phenotypes of schizophrenia genetic predisposition (34). Notwithstanding, despite methodological differences and the study of relatively small samples, some regional changes in WM microstructure have been observed in high-risk and/or first-degree family members of patients (37–39,115). Our results add to these findings to show that SWM FA reductions vary linearly in accordance with biological relatedness to a schizophrenia proband in focal regions across the SWM and when averaged across temporal and occipital lobar regions specifically. These findings complement observations from a ROI study that included overlapping subjects to show significant increases of superior temporal mean diffusivity within first-degree relatives of patients (116), indicating that altered tissue architecture is associated with genetic predisposition for schizophrenia. However, regional changes in SWM FA were also observed when comparing patients and their relatives (in occipital regions, Table S1 in Supplement 1) (Figure 2D), suggesting that processes associated with the disorder itself further influence WM microstructure at the juncture of the cortex.
Taken together, findings of schizophrenia-associated SWM disturbances in distributed regions—although particularly in the temporal and occipital lobes—and observations of less-pronounced genetic liability effects in overlapping regions argue against the notion that these abnormalities are associated with one specifically identifiable brain system. Rather, findings are consistent with mounting evidence suggesting that the pathophysiology of schizophrenia affects multiple brain systems and functional networks (45,117–120).

Interestingly, a recent study shows schizophrenia patients exhibit significant increases in nonspatially overlapping WM “potholes,” suggesting that WM pathology might vary across the brain in particular patients (121). Because short association and neighborhood fibers make extensive connections beneath the cortex to integrate functionally connected cortical regions, the nature of distributed SWM abnormalities fits with the heterogeneous clinical and functional profile of schizophrenia but does not necessarily exclude that some neural networks might be more affected than others. Although the biological determinants of diffusion parameters are not yet fully understood, reductions in SWM FA observed in this study could reflect decreased numbers of short-range fibers or indicate reduced axonal myelination (122). However, it is also possible that reductions in oligodendrocyte density in the neuropil and/or adjacent WM (18,123,124) might contribute to the observed findings by impacting cellular microstructure in addition to myelination.

Some potential study limitations are worth noting. Firstly, although DTI protocols with more diffusion directions might be optimal in some contexts, the 6-direction protocol employed in this study included four averages, which serves to increase signal to noise. Thus, this protocol is much superior to a 6-direction protocol including only one average, and no bias is expected with regard to the statistical findings because DTI parameter estimates are the same for all groups. Furthermore, we also compared mean WM FA obtained from 14 study participants who were scanned with both the current DTI protocol and a 30-direction DTI protocol (22) to show highly significant correlations for FA measures (Pearson’s $r = .828$, $p < .0001$), indicating both protocols are sensitive to the same underlying biology.

Nonetheless, future studies including higher angular resolution DTI data and more sophisticated tractography methods might help confirm the regional specificity of corticocortical disconnectivity in schizophrenia and clarify relationships with specific functional impairments. Another possible limitation to the study is the influence of patient medications toward structural connectivity. A positive association between FA and antipsychotic treatment has been observed in at least one prior study (125), although FA changes are also reported in never-medicated patients (26). The presence of genetic liability effects, however, would suggest that reductions in SWM FA are not solely due to medication effects. Although we are unable to resolve the important question of whether deficits in structural connectivity contribute to the onset of psychosis or whether it is a secondary effect brought on by changes in GM, it is likely—because reduced FA of SWM seems to have a genetic liability associated with it—that WM connectivity plays role in both the predisposition toward and progression of schizophrenia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Mean superficial white matter (SWM) fractional anisotropy (FA) averaged across the left and right hemisphere and within each lobar region in schizophrenia (SZ) and community control (CC) probands and in siblings and parents of patients and CC probands, respectively. The error bars represent the SEM.
Figure 2.
Statistical maps showing significant regional changes in fractional anisotropy measured at thousands of locations within the superficial white matter in (A) schizophrenia versus control probands; (B) schizophrenia siblings versus control subjects and control siblings; (C) schizophrenia parents versus control parents; (D) schizophrenia patients versus schizophrenia siblings. The direction and significance of effects are indicated by the color bar. Red/pink regions indicate lower fractional anisotropy in patients and patient family members. L, left; R, right.
Figure 3.
The maps that correspond to the statistical maps in Figure 2 showing changes in superficial white matter fractional anisotropy in (A) schizophrenia versus control probands; (B) schizophrenia siblings versus control subjects and control siblings; (C) schizophrenia parents versus control parents; (D) schizophrenia patients versus schizophrenia siblings. The direction of effects is indicated by the color bar, where blue and purple indicate lower fractional anisotropy in patients and patient family members.
Figure 4.
Statistical maps (left) and corresponding β maps (middle) showing regional changes FA measured at thousands of points within the SWM when genetic risk for SZ is modeled as a continuous variable in patients with SZ, relatives of patients, and control subjects and their relatives. The significance and direction of effects are indicated by the color bars. Mean SWM FA values for left temporal and occipital lobar regions are shown on the right in the three groups categorized by genetic risk for SZ. The error bars represent the SEM. Abbreviations as in Figure 1.
## Table 1

Demographic and Clinical Details of Study Participants

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<tr>
<th></th>
<th>Patients (n = 26)</th>
<th>CC Probands (n = 21)</th>
<th>SZ Parents (n = 33)</th>
<th>CC Parents (n = 26)</th>
<th>SZ Siblings (n = 16)</th>
<th>CC Siblings (n = 28)</th>
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<tr>
<td>Age (mean ± SD)</td>
<td>29.50 ± 7.36</td>
<td>25.86 ± 6.65</td>
<td>54.42 ± 8.28</td>
<td>55.65 ± 8.48</td>
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<td>Age (range)</td>
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<td>43–70</td>
<td>17–58</td>
<td>13–50</td>
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<tr>
<td>Gender (M/F)</td>
<td>16/10</td>
<td>15/6</td>
<td>13/20</td>
<td>12/14</td>
<td>10/6</td>
<td>12/16</td>
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<tr>
<td>TSEI</td>
<td>28.20 ± 10.60</td>
<td>38.77 ± 18.39</td>
<td>41.04 ± 20.44</td>
<td>37.03 ± 19.83</td>
<td>36.28 ± 19.67</td>
<td>42.99 ± 15.93</td>
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<td>Yrs of Education</td>
<td>13.76 ± 1.87</td>
<td>15.19 ± 2.77</td>
<td>14.78 ± 4.53</td>
<td>14.03 ± 3.21</td>
<td>14.18 ± 2.45</td>
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<td>Age of Onset</td>
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<td>Duration of Illness</td>
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<td>Withdrawal</td>
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<td>Thinking Disorder</td>
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<td>BPRS Total</td>
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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.
Table 2
Permutation-Corrected Probability Values Within Hemisphere and Lobar ROIs Shown for Each Group Comparison

<table>
<thead>
<tr>
<th>ROIs</th>
<th>SZ Effects Patients/CC Probands (n = 47)</th>
<th>Genetic Liability Effects SZ Siblings/CC Siblings (n = 44)</th>
<th>Genetic Liability Effects SZ Parents/CC Parents (n = 59)</th>
<th>Genetic Liability: Linear Patients/SZ Relatives/All CC Subjects (n = 150)</th>
<th>Disease-Related Effects Patients/SZ Siblings (n = 42)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L Hemis</td>
<td>.04</td>
<td>.65</td>
<td>.66</td>
<td>.03</td>
<td>.57</td>
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<tr>
<td>R Hemis</td>
<td>.12</td>
<td>.82</td>
<td>.69</td>
<td>.05</td>
<td>.60</td>
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<tr>
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<td>.65</td>
<td>.58</td>
<td>.36</td>
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<td>.58</td>
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<tr>
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<tr>
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<tr>
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<td>.90</td>
<td>.60</td>
<td>.006</td>
<td>.12</td>
</tr>
</tbody>
</table>

CC, community comparison; Hemis, hemisphere; L, left; R, right; ROI, region of interest; SZ, schizophrenia.