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Micro- and Macrostructural White Matter Integrity in Never-Treated and Currently Unmedicated Patients With Schizophrenia and Effects of Short-Term Antipsychotic Treatment

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ABSTRACT

BACKGROUND: Schizophrenia is associated with progressive white matter changes, but it is unclear whether antipsychotic medications contribute to these. Our objective was to characterize effects of short-term treatment with risperidone on white matter diffusion indices.

METHODS: We recruited 42 patients with schizophrenia (30 never treated and 12 currently untreated) and 42 matched healthy control subjects in this prospective case-control neuroimaging study. Patients received a 6-week trial of risperidone. Using diffusion tensor imaging, we assessed microstructural (fractional anisotropy, mean diffusivity, and radial diffusivity) and macrostructural (radial fiber trophy) white matter integrity deficits in unmedicated patients compared with control subjects and change in white matter integrity in patients before and after antipsychotic treatment (mean risperidone dose at end point was 3.73 $\pm$ 1.72 mg).

RESULTS: At baseline, fractional anisotropy was decreased in the left medial temporal white matter (cluster extent: 123 voxels; Montreal Neurological Institute peak coordinates: x = -51, y = -44, z = -7; $\alpha < .05$), and mean diffusivity was increased in the fusiform/lingual gyrus white matter extending to the hippocampal part of the cingulum (cluster extent: 185 voxels; peak coordinates: x = -27, y = -49, z = 2; $\alpha < .04$) in patients compared with control subjects. Radial diffusivity and macrostructure were not abnormal. None of the diffusion indices showed a significant change after 6 weeks of treatment with both voxelwise and whole-brain white matter analyses.

CONCLUSIONS: We demonstrate microstructural white matter integrity abnormalities in the absence of macrostructural impairment in unmedicated patients with primarily early-stage schizophrenia. In our data, we found no significant white matter changes after short-term treatment with risperidone.

Keywords: Diffusion tensor imaging, Fractional anisotropy, Longitudinal, Mean diffusivity, Radial diffusivity, Treatment response

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Schizophrenia is a complex neuropsychiatric syndrome associated with subtle changes in brain structure that progress over the course of the illness (1,2). While causes underlying this phenomenon remain poorly understood, a number of mechanisms, including accelerated aging (1), glutamate-related excitotoxicity (3,4), and a variety of environmental influences, are being contemplated (5). Antipsychotic medication exposure is probably the most widely debated putative environmental factor (6,7). However, only a limited number of studies have directly investigated antipsychotic medication effects on gray matter volume, and even fewer have examined effects on white matter integrity, perhaps because imaging sequences optimized to examine white matter have only more recently become widely available.

With diffusion tensor imaging (DTI), scalar diffusion indices can be derived to describe white matter microstructural properties and to characterize pathological processes in the microstructural composition of white matter (8,9). Fractional anisotropy (FA) measures the degree of orientational coherence of water diffusion within a voxel and is a nonspecific biomarker of microstructural architecture and neuropathology. Mean diffusivity (MD) measures the extent to which water is able to diffuse into any direction within the voxel and is typically elevated in inflammatory states and with edema (10), whereas cell proliferation and neoplasia can decrease MD (8). Radial diffusivity (RD) quantifies diffusion perpendicular to the principal diffusion direction (i.e., the axon) and is thought to be increased in dysmyelination and demyelination (11).

However, because changes in fiber diameter and tract spacing may also affect these measures, it is important to interpret microstructural alterations in the context of macrostructure (i.e., radial fiber trophy, a surrogate marker of white matter atrophy/hypertrophy) (12).

While there is a general theme of decreased FA in schizophrenia (13,14) and evidence of increased MD and RD (15,16), findings in the literature are variable. Similarly, prospective studies investigating antipsychotic effects on white matter integrity have been inconsistent. Szeszko *et al.* reported FA reduction and increased RD following 12 weeks of treatment with risperidone or aripiprazole in minimally treated patients with first-episode psychosis (17). Another group reported increased FA, decreased MD and RD, but unchanged white matter volume after 12 weeks of first- or second-generation antipsychotic treatment in patients with first-episode psychosis who were medicated at the time of enrollment (18). Wang *et al.* reported a significant decrease in absolute FA of white matter around the anterior cingulate gyrus and corona radiata in drug-naïve patients with first-episode schizophrenia compared with healthy control subjects after 6 weeks of treatment with various clinician-selected antipsychotic medications (19). Similarly, Meng *et al.* found a widespread decrease in FA after 6 weeks of treatment with different second-generation antipsychotic medications; in that study, the medication dose expressed in chlorpromazine equivalents was correlated with the extent of FA reduction during the treatment trial (20). Yet others found no medication-related changes in FA or MD after 8 weeks of treatment with different second-generation antipsychotics (21) or in FA after various timeframes of treatment with a number of medications (22). The within-subject design in longitudinal studies controls for a number of subject-level confounding factors, but it is possible that discrepancies in findings may be secondary to differential effects of a variety of antipsychotic drugs and to differences in data analysis and quality control techniques mitigating DTI measurement error.

The goal of this study was to characterize the effects of short-term treatment with a single antipsychotic medication on white matter diffusion indices. We scanned a group of patients with schizophrenia and schizoaffective disorder (SZ) before and after 6 weeks of treatment with risperidone and scanned a group of matched healthy control subjects (HCs) twice approximately 6 weeks apart. We examined 1) whether FA would be decreased, but MD and RD would be increased, in never-treated and currently unmedicated SZs compared with HCs, 2) whether macrostructural white matter integrity would differ between HCs and never-treated and currently unmedicated SZs, and 3) whether 6 weeks of treatment with risperidone would affect micro- and macrostructural white matter integrity. In addition, we tested the hypothesis that greater duration of untreated psychosis (DUP) would be associated with poorer microstructural white matter integrity.

METHODS AND MATERIALS

Participants and Study Design

SZs were recruited from outpatient clinics, inpatient units, and the emergency room at the University of Alabama at Birmingham (UAB). HCs matched on age, sex, and parental occupation were recruited by advertisements. Written informed consent was obtained prior to enrollment in this UAB Institutional Review Board–approved study.

Diagnoses were established by review of medical records, the Diagnostic Interview for Genetic Studies, and consensus of two board-certified psychiatrists (ACL and NVK). The Brief Psychiatric Rating Scale (23) and Repeatable Battery for the Assessment of Neuropsychological Status (24) were used to assess symptom severity and cognition, respectively. Participants were excluded if they had major neurological or medical conditions, had history of head trauma with loss of consciousness, had substance use disorders (excluding nicotine) within 6 months of imaging, were prescribed medications known to affect brain function, were pregnant or breastfeeding, or had magnetic resonance imaging contraindications. Control subjects with a personal or family history in a first-degree relative of an Axis I disorder were excluded.

We enrolled 42 SZs who were medication naïve or off antipsychotic medications for at least 2 weeks (determined by self-report; patients were not taken off medications to meet this criterion) in a 6-week trial of oral risperidone using a flexible dosing regimen. We chose this medication because it is commonly prescribed, now available as generic medication, and thus one of the more affordable second-generation antipsychotic medications in the United States and is considered a first-line treatment in schizophrenia, specifically patients with first-episode schizophrenia (25). Scans were obtained prior to treatment and after 6 weeks of treatment. Nine SZs dropped out before study completion. Medication was managed by ACL and NVK. Risperidone was started at 1 to 3 mg and titrated in 1- to 2-mg increments; dosing was based on therapeutic and side effects. Use of concomitant medications was permitted as clinically indicated. Fourteen patients were prescribed benztropine, two were prescribed trazodone, two were prescribed fluoxetine, one was prescribed sertraline, one was prescribed desvenlafaxine, one was prescribed mirtazapine, one was prescribed amitriptyline, and one was prescribed clonazepam. Compliance was monitored with pill counts at each visit. We also enrolled 42 HCs, and 38 of those were scanned twice, on average 51.5 $\pm$ 19.8 days apart.

Data from 5 HC (one time point) and 14 SZ baseline scans, as well as 5 SZ end-point scans, were included in a prior publication (16). No longitudinal DTI data were included in prior publications.

Data Acquisition

Imaging was performed on a 3T head-only magnetic resonance imaging scanner (Magnetom Allegra; Siemens, Erlangen, Germany) using a circularly polarized transmit/receive head coil. A T1-weighted scan was acquired for anatomical reference (magnetization prepared rapid acquisition gradient-echo; repetition time = 2300 ms, echo time = 3.93 ms, inversion time = 1100 ms, flip angle = 12°, phase encoding direction = A>P, field of view = 256 $\times$ 256 mm, 1-mm isotropic voxel size). Two diffusion-weighted runs were acquired, each noncollinearly distributed along 30 directions (b = 1000 s/mm^2, repetition time = 9200 ms, echo time = 96 ms, field of view = 246 $\times$ 246 mm, matrix = 112 $\times$ 112, 60 slices, interleaved acquisition, 2.2-mm isotropic voxel size). Both runs were

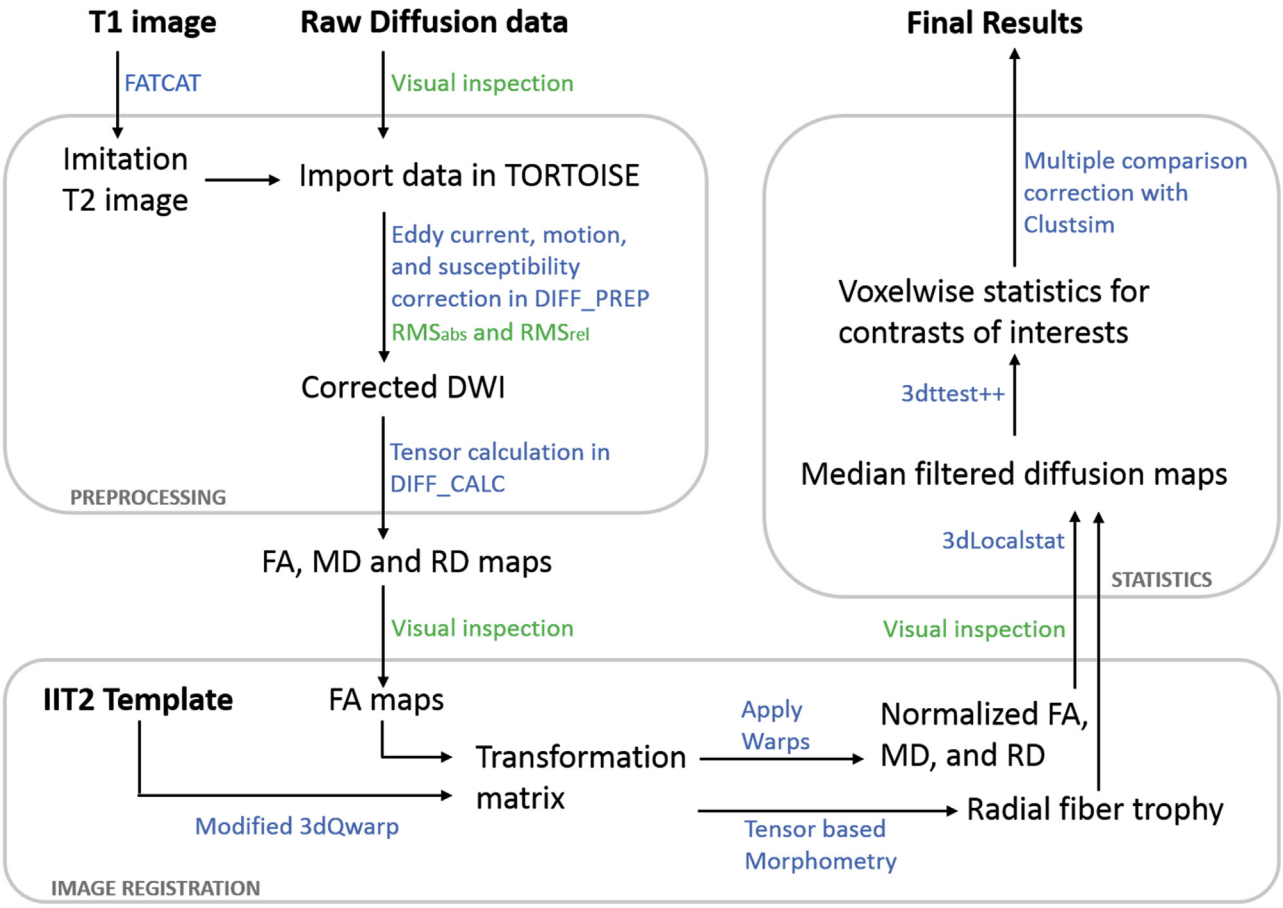

Figure 1. Schematic of the diffusion data processing pipeline. Major steps in preprocessing, image registration, and statistical analyses are depicted here. The blue color signifies software programs used or data processing steps applied, and the green color signifies quality control steps. DWI, diffusion-weighted image; FA, fractional anisotropy; IIT2, Illinois Institute of Technology atlas; MD, mean diffusivity; RD, radial diffusivity; RMS_{abs}, absolute head motion; RMS_{rel}, relative head motion.

concatenated to increase the signal-to-noise ratio (for three SZ datasets, only one run was acquired). Five images with no diffusion gradients (b_0; b = 0 s/mm^2) were also acquired.

Data Processing

In preparation for DTI registration in TORTOISE (version 2.5.2) (26), the T1-weighted images were skull stripped and processed through FATCAT in AFNI (27,28) to create a volume with an approximate T2-weighted contrast. This imitation T2 image was spatially aligned with the DTI images and used solely for providing an anatomical reference with requisite contrast similar to the DTI b_0 volume (29).

After visual inspection of raw images, we calculated bulk motion indices. The root mean square (RMS) of the six motion parameters (translations and rotations) was calculated for both absolute movement (RMS_{abs}; average of absolute displacement of each image and the first b_0 image) and relative movement (RMS_{rel}; average of absolute displacement between adjacent images, which reduces the likelihood of a few large movements biasing the outcome of motion estimates) (30,31). Datasets with RMS_{abs} of greater than half the voxel edge length (1.1 mm) or RMS_{rel} of greater than 0.05 mm per run were excluded from further analyses. One SZ baseline dataset and one SZ week 6 dataset were rejected based on these criteria.

Artifacts due to between-volume bulk body motion, eddy currents, and echo-planar imaging susceptibility–induced geometric distortions were removed using DIFF_PREP with a single interpolation step (32). For each dataset, the first b_0 image was selected as the reference for registration; subsequent b_0 images were affine registered to the initial b_0 image. Prior to registration, diffusion-weighted and structural images were upsampled at a factor 2 using a bicubic algorithm and smoothed with a Perona–Malik anisotropic edge favoring gradient-based filter (33) to compute the transformations from moving to fixed images. After computation of transformations, original images were used to create the registered images. B-spline correction was done using the imitation T2 image. Diffusion images were resampled to 1.5-mm isotropic voxels. Gradient tables were rotated along with motion correction (34,35). Tensors were computed with DIFF_CALC using a linear fitting algorithm. We computed maps for FA, MD, and RD. Resulting maps were visually inspected for anomalies in scalar diffusion parameters. After quality control, a total of 10 datasets

Table 1. Demographics and Clinical Measures

	SZ (n = 42)	HC (n = 42)	$t/\chi^2/F$	p Value
Gender, % Male	61.9	61.9	–	–
Age, Years	26.62 (9.00)	27.88 (9.43)	0.63	.53
Parental Occupation[a]	7.16 (6.13)	5.45 (4.18)	16.28	.30
Smoking, Packs per Day	0.38 (0.53)	0.23 (0.43)	−1.47	.15
Diagnosis, *n*				
Schizophrenia	34			
Schizoaffective disorder	5			
Brief psychotic disorder	3			
Illness Duration, Years, Mean (SD, Median, Range)[b]	15.00 (8.67, 18.00, 1–25)			
Prior Antipsychotic Treatment				
Antipsychotic naïve, yes/no	30/12			
Antipsychotic-free interval, months, mean (SD, median, range)[b]	17.33 (36.91, 3.25, 0.5–120)			
Risperidone Dose at Week 6, mg, Mean (SD, Median, Range)	3.73 (1.72, 4.0, 1–8)			
BPRS[c]				
Total				
Baseline	50.26 (9.30)			
Week 6[d]	32.36 (9.60)[e]			
Positive				
Baseline	10.93 (3.46)			
Week 6[d]	5.24 (2.55)[f]			
Negative				
Baseline	7.19 (3.36)			
Week 6[d]	5.73 (2.41)[g]			
RBANS				
Total index	71.82 (14.37)	89.67 (12.73)	5.89	<.01
Immediate memory	77.42 (16.35)	97.07 (15.33)	5.55	<.01
Visuospatial	73.24 (16.52)	82.48 (15.41)	2.59	.01
Language	85.50 (12.82)	96.64 (14.04)	3.76	<.01
Attention span	80.39 (19.67)	94.07 (18.45)	3.21	<.01
Delayed memory	71.79 (20.57)	91.38 (10.13)	5.32	<.01

Values are mean (SD) unless otherwise indicated.

BPRS, Brief Psychiatric Rating Scale; HC, healthy control subjects; RBANS, Repeatable Battery for the Assessment of Neuropsychological Status; SZ, patients with schizophrenia.

[a]Ranks determined from Diagnostic Interview for Genetic Studies (scale of 1–18); higher rank (lower numerical value) corresponds to higher socioeconomic status.

[b]Includes only patients who are not antipsychotic naïve (n = 12), illness duration since first diagnosis.

[c]Scale of 1 to 7: positive (conceptual disorganization, hallucinatory behavior, and unusual thought content); negative (emotional withdrawal, motor retardation, and blunted affect).

[d]n = 33.

[e]t = 11.19, $p < .01$.

[f]t = 9.45, $p < .01$.

[g]t = 2.98, $p < .01$.

were excluded from further analysis (1 HC and 3 SZ baseline scans as well as 2 HC and 4 SZ week 6 scans); in addition, 5 datasets were processed without imitation T2 images.

To spatially normalize diffusion images to the Illinois Institute of Technology atlas space (36), we implemented an optimized nonlinear image registration procedure using a modified version of 3dQwarp in AFNI (37). The warping optimization implements an iterative refinement, where an input image is repeatedly processed through an optimizer in smaller and smaller patches, incorporating convergence criteria at each level to better resolve artifacts, with a final patch size of 5 × 5 × 5 mm. Resulting deformation maps were then used together with diffusion images to calculate radial fiber trophy, a surrogate marker of macrostructural white matter change (12). Briefly, stretch of the deformation field in the plane perpendicular to the predominant direction of diffusion is computed using slight modifications of traditional tensor-based morphometry, a method for identifying macroscopic differences in brain structure based on the Jacobian determinant of the deformation matrix (38,39). Before statistical analyses, a 5-mm median filter was applied with 3dLocalstat to improve the signal-to-noise ratio while maintaining edges (40).

Statistical Analyses

HCs were considered negative control subjects, facilitating descriptive characterization of abnormalities in SZs and

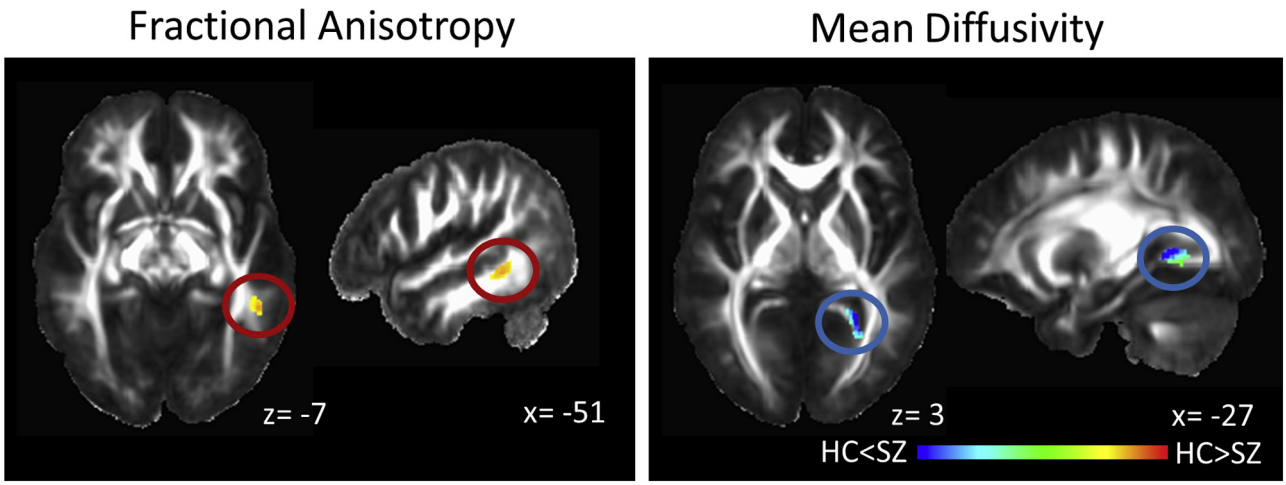

Figure 2. White matter microstructural integrity abnormalities in never-treated and currently unmedicated patients with schizophrenia (SZ) compared with healthy control subjects (HCs). Fractional anisotropy is decreased in the left medial temporal white matter (cluster extent: 123 voxels; Montreal Neurological Institute peak coordinates: x = −51, y = −44, z = −7; $\alpha < .05$), and mean diffusivity is increased in the fusiform/lingual gyrus white matter extending to the hippocampal part of the cingulum (cluster extent: 185 voxels; peak coordinates: x = −27, y = −49, z = 2; $\alpha < .04$) in SZs compared with HCs. Clusters are projected on the Illinois Institute of Technology atlas white matter template. Numbers adjacent to slices indicate x, y, and z coordinates in Talairach convention. Color bar indicates *z* scores.

assessing temporal stability of diffusion indices. To examine whole-brain voxelwise group differences in scalar diffusion indices and atrophy measures within an Illinois Institute of Technology atlas–based white matter mask, we used AFNI's 3dttest++; a priori defined covariates included age and gender (15,41). Because baseline head motion differed between groups (RMS_{abs} baseline: HC = 0.56 ± 0.10 mm, SZ = 0.62 ± 0.14 mm, $t = -2.18$, $p = .03$; RMS_{abs} week 6: HC = 0.56 ± 0.10 mm, SZ = 0.62 ± 0.16 mm, $t = -1.83$, $p = .09$; RMS_{rel} baseline: HC = 0.14 ± 0.002 mm, SZ = 0.17 ± 0.005 mm, $t = -3.24$, $p = .002$; RMS_{rel} week 6: HC = 0.15 ± 0.03 mm, SZ = 0.16 ± 0.05 mm, $t = -1.33$, $p = .19$), we included RMS_{rel} as an additional covariate in analyses. To examine change over time in voxelwise analyses, we used AFNI's 3dttest++ to compare diffusion indices at baseline and after 6 weeks in each group separately. Clustsim, an algorithm that uses randomization/permutation simulation to produce 10,000 iterations of noise only–generated *t* tests and determine global cluster-level threshold values, was implemented to control for the false positive rate (voxelwise threshold Bonferroni-corrected $p = .0008$ [accounting for 12 comparisons at $p_{uncorrected} = .01$]; cluster threshold $\alpha = .05$) (42). As a post hoc analysis, we extracted whole-brain white matter scalar diffusion indices for each participant and compared baseline group differences and changes over time in each group using linear models with age, gender, and RMS_{rel} included as covariates. We also examined the relationship between DUP (in patients who were antipsychotic medication naïve) and voxelwise white matter integrity in the subgroup of medication-naïve patients with 3dttest++ including the log-transformed DUP as regressor. In an exploratory fashion, we also examined partial correlations between clinical measures in SZs and whole-brain

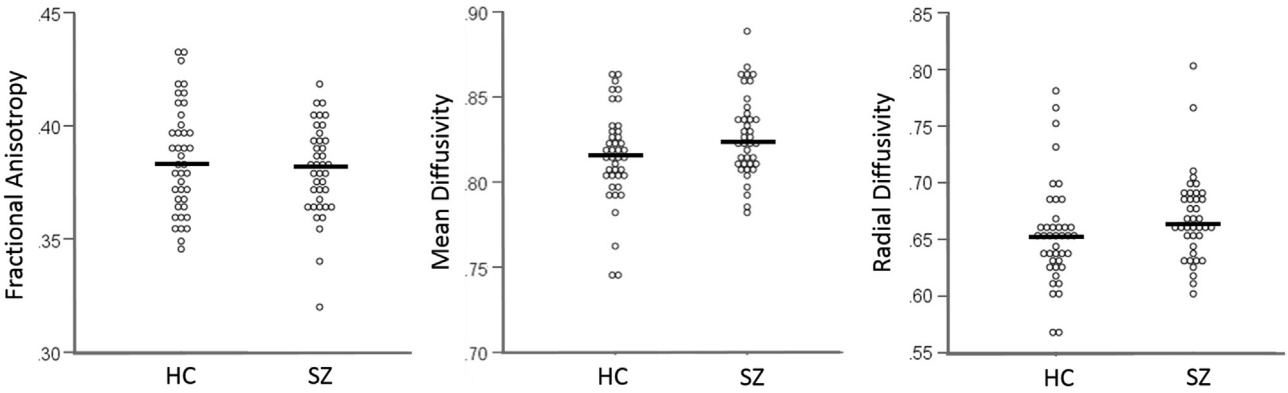

Figure 3. White matter scalar diffusion indices in healthy control subjects (HC; $n = 41$) and never-treated and currently unmedicated patients with schizophrenia (SZ; $n = 38$). We observed no significant group differences in fractional anisotropy, mean diffusivity, or radial diffusivity. Dots represent individual measurements, and horizontal lines represent the group mean.

white matter scalar diffusion indices as well as diffusion indices in areas of abnormal white matter integrity, controlling for age, gender, and RMS_{rel}.

A schematic of our data analysis pipeline can be found in Figure 1.

Final analyses included good-quality datasets from 41 HCs and 38 SZs at baseline and from 36 HCs and 28 SZs at week 6. In total, 36 HCs and 27 SZs had good-quality datasets for both baseline and week 6 scans.

RESULTS

HCs and SZs did not differ in gender, age, or parental socioeconomic status (Table 1). Brief Psychiatric Rating Scale scores significantly decreased after 6 weeks of treatment.

White Matter Integrity in Medication-Naïve and Unmedicated SZs Compared With HCs

At baseline, FA was reduced in the left medial temporal white matter and MD was increased in the left fusiform/lingual gyrus white matter extending to the hippocampal part of the cingulum in SZs compared with HCs (Figure 2). RD and radial fiber trophy did not differ between groups, both when the entire SZ group was considered and when only antipsychotic medication–naïve subjects were considered. Post hoc analysis did not show group differences in whole-brain white matter scalar diffusion indices (Figure 3). We found no associations between DUP and FA, MD, or RD.

In a secondary analysis, we repeated the same computations but included only patients who were antipsychotic naïve and their matched control subjects. Findings in this subgroup were largely consistent with those in the larger group, where FA was decreased in the left medial temporal white matter (cluster extent: 80 voxels; Montreal Neurological Institute peak coordinates: x = −51, y = −36, z = −14; $\alpha < .10$) and MD was increased in the fusiform/ lingual gyrus white matter extending to the hippocampal part of the cingulum (cluster extent: 199 voxels; peak coordinates: x = −28, y = −49, z = 2; $\alpha < .04$) in antipsychotic-naïve SZs compared with HCs. No group differences were seen in RD.

Changes in White Matter Integrity After 6 Weeks

In HCs, none of the white matter measures changed over time. We also observed no changes in micro- or macrostructural white matter integrity after 6 weeks of treatment in SZs. This was true even when lowering the statistical threshold to $p_{uncorrected} < .001$. Post hoc analyses did not show significant change in whole-brain white matter scalar diffusion indices after 6 weeks in either group (Table 2 and Figure 4). When we examined change in diffusion indices over time in each group separately with paired-sample t tests, we again did not find significant changes over time in HCs (FA: $t = -1.00$, $p = .32$; MD: $t = -0.96$, $p = .34$; RD: $t = -0.01$, $p = .99$) and after 6 weeks of treatment in SZs (FA: $t = 0.21$, $p = .76$; MD: $t = 1.45$, $p = .16$; RD: $t = 0.14$, $p = .89$).

Secondary analyses in the antipsychotic-naïve sample again were consistent with those in the larger group, showing no significant change in voxelwise FA, MD, and RD after 6 weeks of treatment with risperidone. This again was true even when lowering the statistical threshold to $p_{uncorrected} < .001$.

Table 2. Whole-Brain White Matter Microstructural Integrity Measurements

	SZ (n = 39)	HC (n = 41)	F	p Value
Baseline[a]				
FA	0.38 ± 0.02	0.39 ± 0.02	0.23	.63
MD	0.83 ± 0.02	0.82 ± 0.03	1.72	.19
RD	0.67 ± 0.04	0.65 ± 0.05	0.99	.32
Change From Baseline to Week 6[b]				
FA	0.001 ± 0.018	−0.002 ± 0.010	0.32	.57
MD	0.004 ± 0.015	−0.002 ± 0.013	2.99	.09
RD	0.001 ± 0.030	−0.000 ± 0.027	0.03	.86

Values are mean ± SD.

FA, fractional anisotropy; HC, healthy control subjects; MD, mean diffusivity; RD, radial diffusivity; SZ, patients with schizophrenia.

[a]All linear models controlled for age, gender, and relative movement of the participant at baseline.

[b]All linear models controlled for age, gender, and relative movement of the participant at both baseline and week 6.

Relationship Between White Matter Integrity and Clinical Variables

Exploratory analyses revealed a modest positive correlation between MD in the left fusiform/lingual gyrus white matter and Brief Psychiatric Rating Scale positive symptoms in SZs at baseline ($r = .34$, $p = .04$ when age and RMS_{rel} were included as covariates; $r = .36$, $p = .07$ when age, RMS_{rel}, and gender were included as covariates) (Figure 5) but found no relationship between whole-brain scalar diffusion indices at baseline and clinical symptom severity. Risperidone dose was not associated with baseline diffusion indices or change in diffusion indices (FA, MD, and RD). We also did not find correlations between whole-brain diffusion indices (baseline and week 6) and Repeatable Battery for the Assessment of Neuropsychological Status total scores in either HCs or SZs.

DISCUSSION

The purpose of this longitudinal prospective study was to examine whole-brain micro- and macrostructural white matter integrity in schizophrenia and to study effects of short-term antipsychotic treatment on these measures. We report focal decreased FA and increased MD in never-treated and currently unmedicated SZs; baseline MD abnormalities showed a modest association with positive symptom severity. No macrostructural white matter or RD alterations were observed at baseline; the latter was inconsistent with our a priori hypotheses. In addition, we did not observe a relationship between DUP and white matter microstructure in medication-naïve patients. While 6 weeks of treatment with risperidone did improve psychosis severity, we did not observe significant changes associated with short-term risperidone treatment in any of the white matter indices.

Our report of decreased FA localized in the left medial temporal white matter in a group of mostly patients with early-stage schizophrenia replicates findings of a recent activation likelihood estimation meta-analysis showing that abnormalities in the left temporal and right frontal lobe in patients with first-episode psychosis (43) and is in agreement with a recent

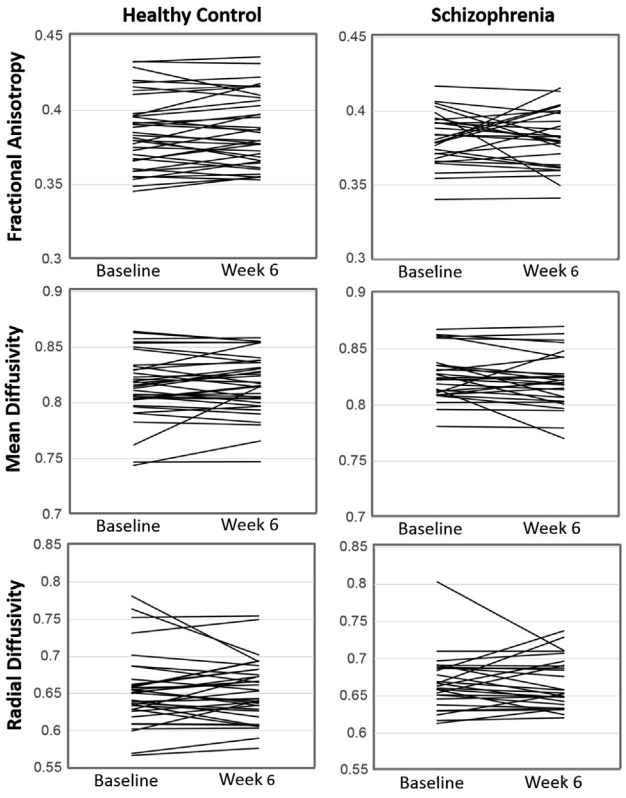

Figure 4. Individual changes in whole-brain white matter scalar diffusion indices in healthy control subjects (left column; n = 36) after 6 weeks and patients with schizophrenia (right column; n = 27) after 6 weeks of treatment with risperidone. We observed no significant changes in fractional anisotropy, mean diffusivity, or radial diffusivity.

cross-sectional study suggesting that whole-brain white matter integrity deficits are only found later in the illness (1). MD elevations in the fusiform/lingual gyrus white matter extending to the hippocampal part of the cingulum suggest a possible inflammatory process in this area. Consistent with this, a small positron emission tomography study reported evidence of hippocampal neuroinflammation accompanied by a nonsignificant increase of tracer binding potential in whole-brain white matter in patients recovering from a psychotic episode (44). Furthermore, postmortem studies in white matter revealed increased density (45) and activation (46) of microglia, the resident innate immune cells of the brain.

We did discern a modest positive relationship between positive symptom severity and MD abnormalities in the lingual/fusiform gyrus white matter extending to the hippocampal part of the cingulum bundle, but no such association was seen with FA deficits. Similarly, Filippi *et al.* reported a relationship (albeit a negative one) between MD, but not FA, and positive symptom severity in antipsychotic-naïve patients with schizophrenia (47). The lack of spatial overlap between decreased FA and increased MD and the dissimilar relationships between these indices and symptom severity in our study point toward a multifactorial contribution to white matter pathology in schizophrenia. Based on findings from a twin study and a study in patients with schizophrenia and first-degree relatives, Clark *et al.* argued that reduced FA may be related to genetic vulnerability for schizophrenia, while elevated MD may more directly be related to the disease processes (48). Pasternak *et al.* proposed neuroinflammation and axonal degeneration as two likely mechanisms of white matter alterations, with inflammation rather than degeneration as the predominant pathology at illness onset (49). This is further supported by a recent study showing widespread extracellular free water elevations, suggestive of neuroinflammation, but only limited FA abnormalities in minimally treated patients with first-episode psychosis (50).

We did not detect changes in white matter macrostructure associated with 6 weeks of risperidone treatment, which is consistent with the only other diffusion imaging study that has examined macrostructural integrity in this context (18). Using T1-weighted imaging, Emsley *et al.* reported no white matter volume changes after 1 year of treatment in a small group of antipsychotic-naïve patients (51), but others suggest that white matter volume trajectories in chronic patients differ based on the treatment received (52). Interestingly, higher antipsychotic doses were associated with white matter loss, and lower doses were associated with volume increase, even after accounting for illness severity (53). In a rare study of chronically ill, never-medicated patients, Xiao *et al.* found that these patients showed an accelerated and clinically relevant age-related reduction of FA in the genu of the corpus callosum compared with patients treated with antipsychotics, suggesting a potential beneficial medication effect on white matter integrity (54).

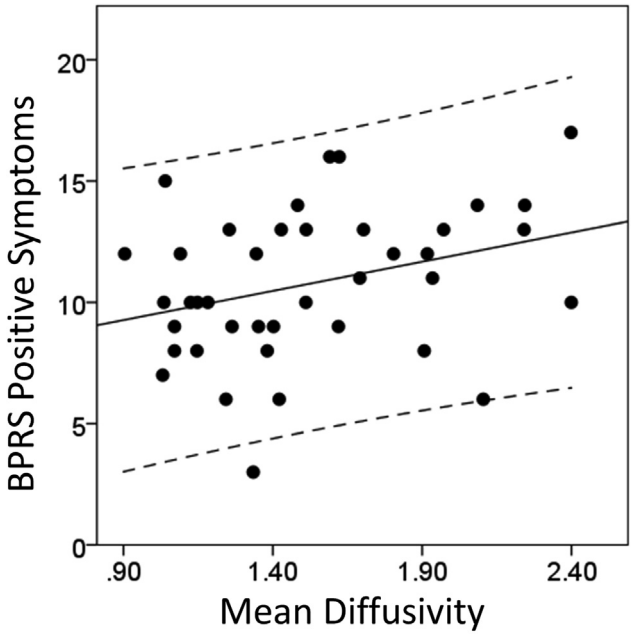

Figure 5. Relationship between mean diffusivity in the left fusiform/lingual gyrus white matter extending to the hippocampal part of the cingulum bundle (cluster extent: 185 voxels; Montreal Neurological Institute peak coordinates: x = −27, y = −49, z = 2) in never-treated and currently unmedicated patients with schizophrenia and Brief Psychiatric Rating Scale (BPRS) positive symptom severity.

Notably, we also observed no significant changes in microstructural diffusion indices after 6 weeks of treatment with risperidone at the voxel level and averaged across the whole brain. However, as seen in Figure 3, results were variable, especially in FA. Assuming a 4% FA change [the average decrease in FA reported by Szeszko *et al.* (17)] to be meaningful, a subset of patients showed either an increase (4 patients) or a decrease (5 patients) in FA after 6 weeks of treatment. These results could help to reconcile discrepancies in findings of prior studies investigating short-term antipsychotic medication effects on white matter microstructural integrity by demonstrating heterogeneity in changes with measurements on the individual subject level. However, a definitive attribution of this heterogeneity in changes in diffusion indices to differential, possibly even dose-related, medication effects rather than to divergence in disease progression between patients is impossible in human studies. Here, we did not observe any clinical correlates of change in diffusion images. It will be important for future large-scale studies to investigate the clinical correlates of this heterogeneity at the level of brain structural change in response to antipsychotic exposure in an effort to better inform our pathophysiological understanding of the illness. Another question that remains unanswered is whether different antipsychotic medications affect white matter structure differentially. A recent exploratory study in a small sample of patients directly compared effects of risperidone and aripiprazole on gray matter and white matter volumes as well as on neurometabolite levels and found a nonsignificant increase in prefrontal white matter volume in those treated with aripiprazole but not in those treated with risperidone, suggesting that these drugs may have differential effects (55). However, these results need to be considered preliminary at this time, and larger-scale studies making head-to-head comparisons of medication effects on not only macrostructural but also microstructural white matter integrity are direly needed in the field. Here, clozapine could be an especially interesting compound to compare with other drugs, given that it showed differential effects on FA compared with other typical antipsychotics and typical antipsychotics (56), and a small study reported a widespread increase in FA in patients that corresponded to improvement in semantic fluency after a 12-week trial of clozapine (57).

Our findings need to be seen in the context of a number of strengths and limitations. To minimize variance in data, we enrolled currently unmedicated SZs (many of them without any prior antipsychotic exposure), carefully matched groups on key demographic characteristics, and used a single antipsychotic medication in this prospective longitudinal study. We took a number of steps to ensure data quality, chose a nonlinear image registration algorithm, and carefully controlled for false-positive rates with state-of-the-art cluster thresholding methods (42). Ideally, we would have obtained a T2- weighted scan to aid coregistration, but we were not able to do so owing to time constraints. To assess for possible effects of time on diffusion indices, we included HCs who were scanned twice 6 weeks apart. It was not possible to follow medication-free or placebo-treated SZs longitudinally because it is not ethically permissible to withhold known effective treatments from patients. In addition, we did not have information available on prior nonresponse to risperidone in the 12 patients who had prior antipsychotic exposure, precluding us from assessing how medication history affected findings.

In summary, we demonstrated microstructural white matter integrity abnormalities in the absence of macrostructural impairment in never-treated and currently unmedicated patients with schizophrenia. Our data also empirically support a multifactorial model contributing to white matter pathology in this phenotypically heterogeneous syndrome, but the underlying mechanisms remain elusive. Importantly, we found no significant white matter changes after short-term treatment with risperidone in our data.

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ClinicalTrials.gov: Glutamate, Brain Connectivity and Duration of Untreated Psychosis; https://clinicaltrials.gov/ct2/show/NCT02034253?term=nct02034253&rank=1; NCT02034253.

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