

Global White Matter Abnormalities in Schizophrenia: A Multisite Diffusion Tensor Imaging Study

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Background: Emerging evidence implicates white matter (WM) abnormalities in the pathophysiology of schizophrenia. However, there is considerable heterogeneity in the presentation of WM abnormalities in the existing studies. The object of this study was to evaluate WM integrity in a large sample of patients with first-episode (FE) and chronic schizophrenia in comparison to matched control groups. Our goal was to assess whether WM findings occurred early in the illness or whether these abnormalities developed with the illness over time. **Methods:** Participants included 114 patients with schizophrenia (31 FE and 83 chronic patients) and 138 matched controls. High-resolution structural and diffusion tensor images were obtained on all participants. Measures of fractional anisotropy (FA) were calculated for the 4 cortical lobes and the

cerebellum and brain stem. **Results:** FA was significant lower in patients vs controls in the whole brain and individually in the frontal, parietal, occipital, and temporal lobes. FA was not significantly different in the brain stem or cerebellum. FA differences were significant only in patients with chronic schizophrenia and not in the FE group. **Conclusions:** We found global differences in the WM microstructure in patients with chronic but not FE schizophrenia. These findings suggest progressive alterations in WM microstructure.

Key words: first-episode schizophrenia/fractional anisotropy/neuroimaging/DTI/microstructure

Introduction

Evidence from postmortem,^{1,2} magnetic resonance spectroscopy,³ and diffusion tensor imaging (DTI) studies^{4,5} implicates brain white matter (WM) abnormalities in the neurobiology of schizophrenia.⁶ WM forms the basis for high speed communication between brain regions, and disruption of WM pathways could potentially partially explain the vast array of clinical and cognitive symptoms associated with the illness.

There have now been more than 60 studies to date that have utilized DTI to evaluate the WM microstructure in patients with schizophrenia.⁵ One of the challenges in developing a unified understanding of the reported WM abnormalities is the variability in the reported locations of disrupted WM in schizophrenia. A review of DTI studies found an overrepresentation of fractional anisotropy (FA) reductions in the corpus callosum (CC), frontal WM, and the cingulum bundle.⁵ However, diverse abnormalities have also been identified in WM tracts in cortical, subcortical, and cerebellar regions. While the majority of these studies evaluate patients with chronic schizophrenia, studies of first-episode (FE) and early-onset schizophrenia (EOS) also have found lower FA in frontal and limbic regions. Finally, there is evidence for a worsening of WM abnormalities as individuals progress from FE to chronic schizophrenia,^{5,7} raising the question as to whether duration of illness (DOI), medication exposure, cohort effects, or illness-related environmental

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factors contribute to the greater differences in FA between patients and controls.

The majority of DTI studies utilize voxel-based (VB) techniques to study group differences between patients with schizophrenia and controls. The advantages of VB techniques include the ability to approach the data without a priori assumptions of the implicated regions of interest (ROIs) and greater efficiency of the analysis as compared with ROI analyses. The disadvantages of these techniques include the poor characterization of individual differences in the spatial location of specific brain regions, challenges associated with registration of the brains, and the multiple tests that require statistical correction. VB techniques are valuable and are continually being improved to address these challenges.

Because the majority of the DTI studies of schizophrenia utilize relatively small numbers of patients ($n = 20\text{--}30$), the purpose of this study was to utilize a multisite design to recruit a large number of subjects. The MIND Clinical Imaging Consortium was established as a collaborative multisite consortium that includes the Massachusetts General Hospital (MGH), the University of Iowa (Iowa), the University of Minnesota (Minn), and the University of New Mexico (NMex) and the MIND Research Network. Our goal was to include FE and chronic patients with schizophrenia, each with an associated matched control group in order to explore aberrant connectivity as a hypothesis in the pathogenesis of schizophrenia. In addition, because schizophrenia is associated with abnormalities that are not localized to any one brain region, our goal was to assess relatively large areas of the brain, including whole-brain FA and regional differences within each of the lobes, cerebellum, and the brain stem.

Methods

Participants

The participants consisted of 114 patients with schizophrenia and 138 controls matched by age, sex, and parental education level. Subjects were recruited from 4 sites: MGH, Iowa, Minn, and NMex. All subjects underwent an extensive clinical diagnostic assessment that included either the Structured Clinical Interview for the *DSM-IV* (SCID)⁸ or the Comprehensive Assessment of Symptoms and History (CASH).⁹ Both the SCID and CASH utilized *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria for the confirmation of diagnoses. Positive and negative symptoms were rated using the Scale for the Assessment of Positive Symptoms (SAPS)¹⁰ and the Scale for the Assessment of Negative Symptoms (SANS).¹¹ The consortium study included a total cohort of 385 subjects; however, we report on the subset of those for who had DTI data that could be analyzed. In the image processing methods, we indicate the criteria used for exclusion of imaging data. Importantly,

the cohort included (65% of the total) did not differ in any systematic way from the total cohort.

The clinical group consisted of patients characterized as either chronic or FE schizophrenia. The FE group consisted of patients in their first psychotic episode who had received fewer than 6 months of antipsychotic medications. The sample consisted of 31 FE and 83 chronic patients diagnosed with a schizophrenia spectrum disorder. The demographic information for the patient and control groups and the clinical characteristics of the patients at each site are provided in tables 1–2, respectively.

Healthy volunteers matched for age, sex, and handedness were recruited from the community through medical clinics and advertisements in local newspapers. The control subjects were excluded if they had a physical or neurological disorder affecting brain function (ie, head injury, seizure disorder) or a lifetime history of any Axis I psychiatric disorder, including substance abuse or dependence. A diagnosis of schizophrenia or bipolar disorder in a first-degree relative was also exclusionary. Recruitment into the study was performed only after written informed consent was obtained. The study was approved by the institutional review boards at each of the 4 sites.

Of the 83 patients diagnosed with chronic schizophrenia at the time of scanning, 57 were on atypical antipsychotics only, 8 were on typical antipsychotic only, 3 were on both an atypical and typical antipsychotic, and 6 were not on medications at the time of scanning. Within the atypical antipsychotic group, 12 were on clozapine only and 5 were on clozapine in addition to another atypical. Twenty-three of those in the FE group were on atypical antipsychotics, and none were on either a typical antipsychotic or clozapine. Antipsychotic dose years (1 dose year = 100 chlorpromazine equivalents per day for 1 year¹²) for the patient groups are provided in table 2.

Image Acquisition and Processing

The image acquisition parameters for the high-resolution structural and diffusion tensor images are presented in table 3. The anatomical images were analyzed using BRAINS2.¹³ This produced a skull-stripped T_1 -weighted image and a WM mask. The skull-stripped T_1 -weighted image was coregistered with an AC-PC aligned atlas image using a rigid registration to a scaled version of the atlas image to account for linear stretching along each axis. The Talairach parameters were defined for the subject based on an affine registration of the atlas image into the raw subject space allowing the Talairach atlas to be warped onto each subject. The T_2 -weighted image was then coregistered with the AC-PC aligned T_1 -weighted image. Tissue classification was performed using a multimodal tissue classification.¹⁴

The diffusion weighted images were analyzed using the GTRACT program.¹⁵ The diffusion weighted images were first coregistered to the B0 image using a mutual

Table 1. Within-Site Demographics and Clinical Data of Patients With Schizophrenia and Controls

	Patients (<i>n</i> = 114)				Controls (<i>n</i> = 138)			
	MGH	Iowa	Minnesota	New Mexico	MGH	Iowa	Minnesota	New Mexico
Number	27	19	27	41	21	52	22	43
Age (y, SD)	36.3 (10.7)	31.5 (10.2)	31.3 (10.1)	33.1 (12.6)	40.1 (8.0)	30.8 (10.4)	28.9 (8.9)	28.7 (11.6)
Sex (M/F)	19/8	15/4	18/9	32/9	12/9	23/29	12/10	34/9
Hand (R/L/both)	26/1/1	17/0/2	22/2/2	35/3/2	19/1/0	49/2/1	21/0/1	38/5/0
WRAT3RT	45.5 (7.2)	49.1 (4.8)	46.0 (6.6)	47.4 (5.8)	53.2 (3.6)	50.2 (4.2)	50.9 (3.7)	49.7 (5.1)
Father's education	13.8 (3.9)	15.4 (3.2)	13.8 (3.5)	14.0 (3.9)	13.6 (3.4)	14.5 (2.8)	15.5 (2.5)	15.7 (3.9)
Mother's education	14.1 (3.0)	14.9 (3.4)	12.8 (3.0)	12.9 (4.0)	13.3 (3.2)	13.7 (2.0)	15.2 (2.5)	13.8 (3.2)
BMI	30.6 (6.3)	28.2 (4.2)	28.1 (7.0)	25.5 (5.6)	25.2 (4.2)	25.8 (5.7)	25.3 (5.3)	26.0 (4.8)

Note: MGH, Massachusetts General Hospital; WRAT3RT; Wide Range Achievement Test—3rd Edition, reading test; BMI, body mass index.

Demographics and Clinical Data of Patients With Schizophrenia and Controls Collapsed across Sites (Smaller Version of Table 1)

	Patients (<i>n</i> = 114)		Controls (<i>n</i> = 138)		<i>P</i>
	Chronic (<i>n</i> = 83)	FE (<i>n</i> = 31)	Chronic Controls (<i>n</i> = 95)	FE Controls (<i>n</i> = 43)	
Age (y, SD)	36.4 (11.0)	25.2 (6.7)	34.0 (11.3)	25.2 (6.6)	<.001 ^a
Sex (M/F)	62/21	22/9	57/38	24/19	<.05 ^b
Hand (R/L/both)	73/3/6	26/3/1	86/5/3	41/2/0	
WRAT3RT	46.8 (6.2)	47.1 (6.6)	50.8 (4.5)	50.2 (3.9)	<.001 ^b
Father's education	14.3 (3.3)	13.9 (4.7)	15.0 (3.7)	14.6 (2.3)	
Mother's education	13.3 (3.6)	14.1 (3.2)	13.8 (2.9)	14.1 (2.3)	

Note: FE, first episode; WRAT3RT; Wide Range Achievement Test—3rd Edition, reading test.

^aBetween chronic and FE patients.

^bBetween patients and controls.

$\tau P < .01$.

information image registration to correct for motion and distortions caused by eddy currents. The images were median filtered, and the diffusion tensor was estimated. Scalar measures for FA were calculated on the DTI images for all subjects.¹⁶

The B0 image was then coregistered with the skull-stripped T_1 -weighted anatomical image from BRAINS2 using a rigid body transformation and a mutual information metric similarity metric. Next, a B-spline transform was applied to remove distortion in the echo-planar images resulting from susceptibility changes at air tissue interfaces.¹⁵ The resulting transforms were applied to the scalar maps placing them into the space of the anatomical image.

Measurements of FA were obtained for the whole brain, cerebellum, and brain stem WM using the following equation:

$$FA = \sqrt{\frac{3\sqrt{(\lambda_1 - D)^2 + (\lambda_2 - D)^2 + (\lambda_3 - D)^2}}{2\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}}$$

where D is the diffusion tensor and the λ 's are the 3 eigenvalues.

In addition, FA measures were obtained for the frontal, temporal, parietal, and occipital lobes as well as lateralized measures for all regions utilizing Talairach parameters.¹⁷ The WM mask was defined for each individual as the intersection between the segmented WM obtained from the structural image and FA image with a threshold of 0.1. This combination of structural and DTI images eliminated regions of signal loss resulting from magnetic susceptibility differences. Regional brain measures were obtained using BRAINS2.

Statistical Analyses

The evaluation of differences between patients and controls on demographic measures were initially performed using t -test and χ^2 analyses. Site by demographic differences were evaluated with a one-way analysis of variance (ANOVA). Within-site demographic variables of patients

Table 2. Clinical Characteristics of Patients With FE and Chronic Schizophrenia

Clinical Measures	Chronic Patients		FE Patients	
Years of Illness	13.6 (10.8) (<i>n</i> = 83)		2.1 (3.0) (<i>n</i> = 31)	
Dose years antipsychotics	294.5 (2044.6) CPE (<i>n</i> = 78)		0.64 (1.1) CPE (<i>n</i> = 31)	
Diagnostic subtypes	Iowa	MGH	UMinn	NMex
Paranoid	10	15	19	17
Disorganized	1	3	1	0
Undifferentiated	7	2	3	9
Residual	0	0	0	6
Schizoaffective disorder	1	1	1	2
Schizophreniform	0	1	3	2
SANS/SAPS scores				
Positive	4.4 (2.8)		5.6 (2.2)	
Negative	7.2 (3.7)		8.4 (4.1)	
Disorganized	1.5 (1.7)		1.8 (1.9)	

Note: FE, first episode; CPE, chlorpromazine equivalents (a CPE of 100 = 100 mg/day for 1 y).

vs controls were evaluated using χ^2 for discrete data or a one-way ANOVA for continuous data. To assess whether certain structures had greater variability, a coefficient of variability (CoV) was determined for each brain region. Because there were significant site-related differences in FA, site and age were both used

as a covariates in the analysis of covariance (ANCOVA). FA measures were also converted to *z* scores within site and combined to provide measures of effect sizes for the graphical representation of the findings. The evaluation of FA within the brain regions using an ANCOVA with site and age as a covariates was no different from using the *z*-transformed FA in an ANCOVA with age as a covariate.

Because differences were present in the number of patients and controls within each of the 4 sites, a secondary analysis was performed using a subset of the data that was closely matched within each site. Matching for this subset was performed using a minimum bipartite matching algorithm which minimizes the sum of edge weights between 2 sides of a bipartite graph.¹⁸ In our case, the 2 sides were represented by patients and controls and the weights were the age differences between a given patient and control. An independent bipartite graph was also created for each sex at each site, resulting in 2 matchings per site. Combining these matches results in age- and sex-matched subjects within each site. This matching algorithm resulted in 103 patients and an equal number of controls in which the above analyses were repeated.

Age-related differences were evaluated utilizing Pearson correlation coefficients. Due to nonlinearity in DOI and dose years of medication, Spearman rank correlations were used to assess the relationship between DOI, dose years of medication, and FA measures within

Table 3. High-Resolution Structural and DTI Parameters at Each of the 4 Sites

	Iowa	MGH	UMinn	NMex
High-resolution structural images				
Scanner	Siemens 1.5 T Sonata	Siemens 1.5 T Avanto	Siemens 3 T TRIO	Siemens 1.5 T Avanto
TR (ms)	20	12	2530	12
TE (ms)	6	4.76	3.79	4.76
TI (ms)	NA	NA	1100	NA
Flip angle (degrees)	20	20	7	20
In-plane voxel dimensions (mm)	0.625 × 0.625	0.625 × 0.625	0.625 × 0.625	0.625 × 0.625
Slice thickness (mm)	1.5	1.5	1.5	1.5
NEX	3	1, acquired 3 identical scans	1, acquired 3 identical scans	1, acquired 3 identical scans
Bandwidth (Hz/pixel)	122	110	181	110
Diffusion tensor images				
Scanner	Siemens 3T TRIO	Siemens 1.5 T Sonata	Siemens 3T TRIO	Siemens 1.5 T Sonata
TR (ms)	9500	8900	10 500	9800
TE (ms)	90	80	98	86
Voxel dimensions (mm)	2 × 2 × 2	2 × 2 × 2	2 × 2 × 2	2 × 2 × 2
Diffusion directions	6	60	12	12
<i>B</i> values (s/mm ²)	0/1000	0/700	0/1000	0/1000
NEX	4	1	2	4
Bandwidth (Hz/pixel)	1954	1860	1342	1502

Note: DTI, diffusion tensor imaging; TR, repetition time; TE, echo time; TI, inversion time; NEX, number of excitations; NA, not applicable.

brain regions. Finally, a localized regression analysis with an optimized smoothing parameter (localized regression [LOESS] procedure in SAS) was performed to obtain qualitative measures of the age-related trajectory of FA in both patients and controls. The LOESS procedure has the advantage of being more flexible and allowing for nonlinear registration. All statistical analyses were performed utilizing the SAS statistical package (Cary, NC).

Results

Demographic and Clinical Variables

The mean ages of the patients and controls were 33.3 (SD 11.2) and 31.2 (SD 10.9) years, respectively. There were no differences between the patients and controls in age, handedness, or in the educational level attained by the father or the mother (table 1). The patient group consisted of 84 males and 30 females (74% male), whereas the control group consisted of 81 males and 57 females (59% male). Thus, the patient group had a higher proportion of males compared with the control group (chi-square 6.2, $df = 1$, $P = .01$). These sex differences were evaluated by including sex as a covariate in the analyses and by repeating the analyses in a smaller age- and sex-matched sample.

There was a significant difference between patients and controls on the Wide Range Achievement Test—3rd Edition, reading test (WRAT3RT) ($t = 5.46$, $df = 246$, $P < .001$). The mean WRAT3RT for patients was 46.9 (SD 6.3) compared with 50.6 (SD 5.0) for the controls. Highest level of education obtained was also significantly different between the patient and control groups ($t = 7.1$, $df = 244$, $P < .0001$). The patients completed on average 13.6 (SD 2.6) years of education compared to 15.7 (SD 2.2) years completed by the controls.

Scores on the SANS and SAPS in the patient group had a mean positive symptom score of 4.7 (SD 2.7), negative symptom of 7.5 (SD 3.8), and disorganized symptoms score of 1.6 (SD 1.8). There were no site differences for the patients on either positive, negative, or disorganized symptoms. The mean number of years since diagnosis and entry into the study was 10.7 (SD 10.7). There were no site-related differences in the log-transformed total number of years since diagnosis between sites. The mean number of years since diagnosis for each site is provided in table 2. To test whether there were site-related differences in diagnostic subtypes, we collapsed subtypes to compare with the paranoid subtype. We found no significant site-related differences between the paranoid subtype and the other subtypes of schizophrenia. The diagnostic subtypes for schizophrenia are presented in table 2. Finally, a one-way ANOVA revealed no site-related differences in total dose years of antipsychotic medications, atypical dose years, or typical dose years.

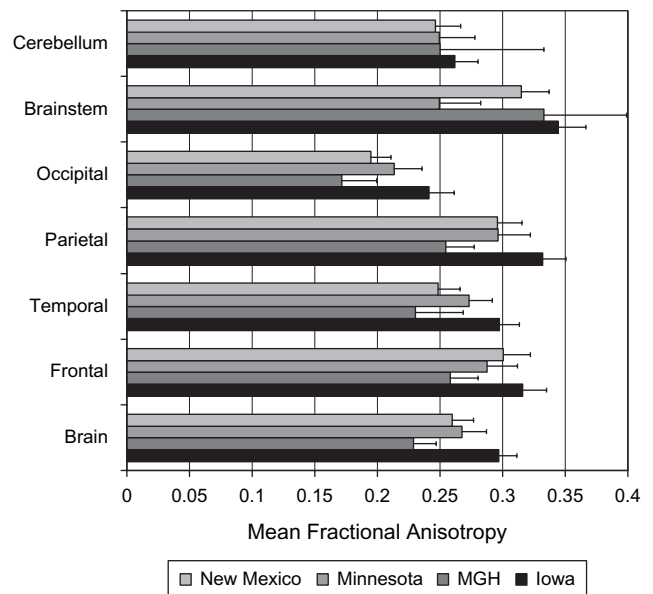


Fig. 1. Site-Related Differences in Mean Fractional Anisotropy Measures Within Specific White Matter Brain Regions in Entire Cohort.

Site Differences in Measures of FA

The mean FA values at the 4 sites for whole brain, the frontal, temporal, parietal, and occipital lobes, the cerebellum, and the brain stem are shown in figure 1. A one-way ANOVA revealed significant site differences in FA values in all brain regions (F 's between 12 and 180). The site differences remained highly significant when controlling for age and sex, and thus, site was used as a covariate in all analyses. To graphically represent the data, the FA measures were z-transformed within site to preserve the within-site patient control differences, while allowing for a standardization of the scanner platform-dependent differences. This provided for the visual representation of the effect sizes of the pooled data.

CoV in FA for each of the brain structures were similar between each of the 4 sites. The CoV was the lowest for the whole brain measure at Iowa (5.0), MGH (6.7), and NMex (6.5). The lowest CoV at UMinn was the temporal lobe (6.8), with the whole brain close at 7.2. The highest CoV was the occipital lobe for Iowa (7.1) and NMex (8.2); the brain stem at MGH (10.0) and UMinn (13.1).

FA Differences between Patients vs Controls

A one-way ANCOVA with site, age, and sex as covariates demonstrated that patients had significantly lower FA in the whole brain ($F_{1,244} = 20.5$, $P < .0001$) as well as in the frontal ($F_{1,244} = 23.2$, $P < .0001$), parietal ($F_{1,244} = 15.1$, $P < .0001$), occipital ($F_{1,244} = 13.7$, $P < .0003$), and temporal lobes ($F_{1,244} = 6.9$, $P < .009$). FA was not significantly different in either the brain stem ($F_{1,244} = 0.9$, $P = .35$) or the cerebellum ($F_{1,244} = 0$, $P = .98$). There was a small but significant negative correlation between

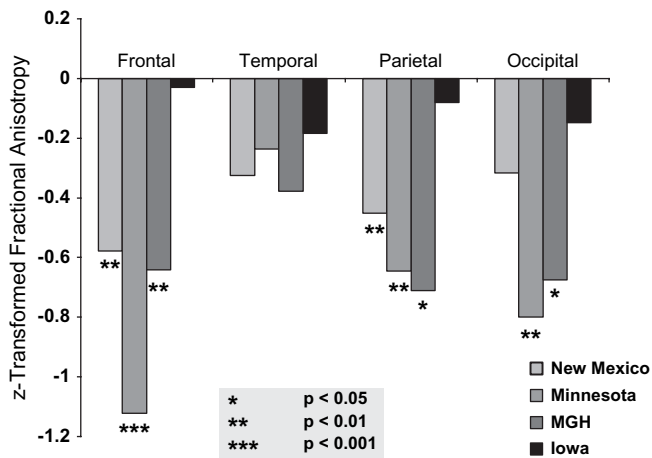


Fig. 2. Within-Site Differences in Fractional Anisotropy Measures on Cortical White Matter Between Patients With Schizophrenia and Controls. The z-transformed data are equivalent to effect sizes for the patient/control differences.

age and the whole-brain FA ($r = -.28, P < .0001$), as well as in the frontal ($r = -.28, P < .0001$), parietal ($r = -.29, P < .0001$), temporal ($r = -.24, P = .0001$), and occipital ($r = -.24, P = .0002$) lobes. This supports the use of age as a covariate, and age effects of FA have been described in the literature.¹⁹ Age and FA were not significantly correlated for either the cerebellum ($r = -.10$) and the brain stem ($r = -.07$).

To assess whether the regional brain FA differences between patients and controls were present within each site, we performed separate analyses with data within

each of the 4 sites. The effect sizes of the differences between patients and controls for each site are shown in figure 2. An ANCOVA using age and sex as covariates found significant within-site differences at MGH for the whole brain ($F_{1,44} = 5.4, P = .02$), frontal ($F_{1,44} = 4.5, P = .04$), parietal ($F_{1,44} = 6.3, P = .02$), and occipital ($F_{1,44} = 5.2, P = .03$). Similarly, UMinn had significant differences in the whole brain ($F_{1,45} = 10.3, P = .002$), frontal ($F_{1,45} = 19.7, P < .0001$), parietal ($F_{1,45} = 5.3, P = .03$), and occipital ($F_{1,45} = 8.5, P = .005$). NMex had significant FA differences in the whole brain ($F_{1,80} = 5.3, P = .02$) and in the frontal ($F_{1,80} = 8.3, P = .005$) and parietal ($F_{1,80} = 4.8, P = .03$) lobes but not in the occipital lobes. The Iowa site had no significant FA differences between patients and controls in any of the brain regions tested, although the data from Iowa trended in the same direction as from the other sites (figure 2).

FA Differences in FE Patients

A series of ANCOVAs were performed to evaluate differences between the chronic patients, FE patients, and their respective controls groups (Tables 4 and 5). FA differences were found in the comparison between the chronic patients and their matched control group (figure 3). The results paralleled the results seen with the combined FE and chronic comparison. Interestingly, none of the regions that were significant in the chronic patients were found to be significant in a comparison between the FE patient vs FE control groups (table 4). An ANCOVA comparing the chronic vs FE patients groups found no significant differences between the 2 groups, although there was a trend

Table 4. Measures of FA in Chronic and FE Patients and Controls

	Least-Square Mean FA Values				ANCOVA Results			
	Chronic Patients	Chronic Controls	FE Patients	FE Controls	Combined Patients vs Controls	Chronic Patients vs Chronic Controls	FE Patients vs FE Controls	FE Patients vs Chronic Patients
Brain	0.257	0.268	0.266	0.267	$F_{1,245} = 20.3$ $P < .0001$	$F_{1,171} = 18.7$ $P < .0001$	$F_{1,68} = 0.8$ NS	$F_{1,108} = 0.1$ NS
Cerebellum	0.249	0.249	0.252	0.246	$F_{1,245} = 0.2$ NS	$F_{1,171} = 0.2$ NS	$F_{1,68} = 1.5$ NS	$F_{1,108} = 1.0$ NS
Brain stem	0.304	0.310	0.316	0.308	$F_{1,245} = 0.4$ NS	$F_{1,171} = 0.4$ NS	$F_{1,68} = 1.6$ NS	$F_{1,108} = 2.4$ NS
Brain lobes								
Frontal	0.281	0.298	0.291	0.294	$F_{1,245} = 24.3$ $P < .0001$	$F_{1,171} = 27.7$ $P < .0001$	$F_{1,68} = 0.3$ NS	$F_{1,108} = 3.6$ $P = .06$
Parietal	0.289	0.300	0.292	0.299	$F_{1,245} = 14.9$ $P < .0001$	$F_{1,171} = 13.6$ $P = .0003$	$F_{1,68} = 0.7$ NS	$F_{1,108} = 0.3$ NS
Temporal	0.258	0.264	0.259	0.263	$F_{1,245} = 5.9$ $P < .02$	$F_{1,171} = 5.0$ $P < .03$	$F_{1,68} = 0.1$ NS	$F_{1,108} = 0.1$ NS
Occipital	0.199	0.208	0.202	0.209	$F_{1,245} = 13.7$ $P = .0003$	$F_{1,171} = 11.9$ $P = .0007$	$F_{1,68} = 1.2$ NS	$F_{1,108} = 0.3$ NS

Note: FA, fractional anisotropy; FE, first episode; ANCOVA, analysis of covariance; NS, nonsignificant. ANCOVA results used both site and age as covariates.

Table 5. Measures of Fractional Anisotropy in Chronic and FE Patients and Closely Matched Controls

	Least-Square Mean FA Values				ANCOVA Results			
	Chronic Patients	Chronic Controls	FE Patients	FE Controls	Combined Patients vs Controls	Chronic Patients vs Chronic Controls	FE Patients vs FE Controls	FE Patients vs Chronic Patients
Brain	0.257	0.270	0.263	0.265	$F_{1,200} = 18.4$ $P < .0001$	$F_{1,146} = 20.4$ $P < .0001$	$F_{1,48} = 0.5$ NS	$F_{1,97} = 2.1$ NS
Cerebellum	0.248	0.251	0.254	0.247	$F_{1,200} = 0$ NS	$F_{1,146} = 2.4$ $P < .0001$	$F_{1,48} = 1.4$ NS	$F_{1,97} = 2.1$ NS
Brain stem	0.303	0.310	0.320	0.311	$F_{1,200} = 0.5$ NS	$F_{1,146} = 20.4$ $P < .0001$	$F_{1,48} = 1.2$ NS	$F_{1,97} = 2.1$ NS
Brain lobes								
Frontal	0.281	0.300	0.293	0.296	$F_{1,200} = 24.9$ $P < .0001$	$F_{1,146} = 28.2$ $P < .0001$	$F_{1,48} = 0.4$ NS	$F_{1,97} = 4.9$ $P < .03$
Parietal	0.290	0.301	0.294	0.296	$F_{1,200} = 10.5$ $P = .001$	$F_{1,146} = 11.2$ $P = .001$	$F_{1,48} = 0.2$ NS	$F_{1,97} = 0.8$ NS
Temporal	0.258	0.266	0.262	0.261	$F_{1,200} = 6.4$ $P < .01$	$F_{1,146} = 9.0$ $P = .003$	$F_{1,48} = 0.1$ NS	$F_{1,97} = 1.0$ NS
Occipital	0.200	0.211	0.204	0.206	$F_{1,200} = 12.8$ $P = .0004$	$F_{1,146} = 14.7$ $P = .0002$	$F_{1,48} = 0.3$ NS	$F_{1,97} = 0.6$ NS

Note: FA, fractional anisotropy; FE, first episode; ANCOVA, analysis of covariance; NS, nonsignificant. ANCOVA results used both site and age as covariates.

for the chronics to have lower FA than the FE patients ($F_{1,107} = 3.6, P = .06$).

Paired *t*-tests were used to evaluate laterality in the measures of FA for each of the brain regions. The right cerebellum had significantly higher mean FA in all 4 groups: chronic patients ($t = 2.5, P = .01$), control group matched to the chronic patients ($t = 6.0, P < .0001$), FE patients ($t = 3.8, P < .0006$), and control group matched to the FE patients ($t = 4.8, P < .0006$). In addition, the FE patients ($t = 2.6, P = .01$), the FE controls ($t = 3.3, P =$

.002), and the chronic control ($t = 3.9, P = .0002$) groups had higher FA in the right occipital lobe. The chronic patient group had a similar finding in the occipital lobe at the trend level ($t = 1.9, P = .06$). Repeating the ANOVA on lateralized measures resulted in significant differences between patients and controls in all the same brain regions identified using the combined left and right brain regions.

Analyses between the full cohort of patients and controls and the additional analyses comparing the chronic patients and their matched controls, FE patients and their matched controls, and chronic vs FE patients were also performed in an age- and sex-matched subset of the larger sample. This sample included 76 patients with chronic schizophrenia and 27 FE patients with an equally matched number of controls corresponding to each group. Analyses performed on this closely matched sample did not differ significantly from the larger sample (table 5).

DOI and Medication Effects on FA

The high intercorrelation between age, DOI, and total dose years of antipsychotics (ADY) provides a challenge for teasing apart the contributions toward reduced FA for each of these variables. The Spearman rank correlation between the DOI and ADY for the chronic group was 0.69 ($P < .0001$). Subject age was highly correlated with both the DOI ($r = .80, P < .0001$) and ADY ($r = .59, P < .0001$).

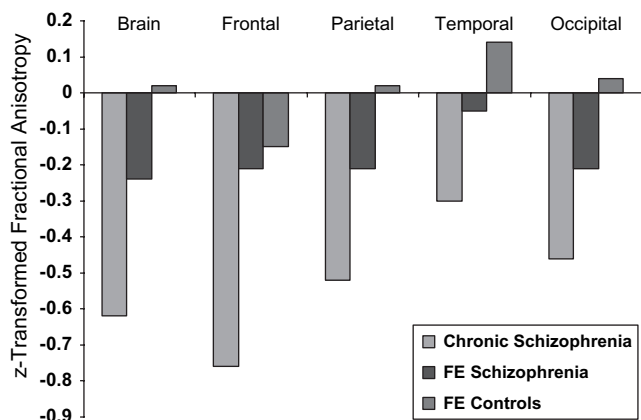


Fig. 3. Differences in *z*-Transformed Fractional Anisotropy Measures on Cortical White Matter Between FE and Chronic Patients With Schizophrenia and Controls. The *z* score for the chronic control group was set to zero.

Table 6. Spearman Rank Correlations Between FA in Specific Brain Regions and Age, Duration of Illness, and Dose Years of Antipsychotic Medications

	Age (<i>n</i> = 114)	DOI (<i>n</i> = 113)	DOI (Adjusting for Dose Years) (<i>n</i> = 113)	Dose Years of Medication (<i>n</i> = 113)	Dose Years of Medication (Adjusting for DOI) (<i>n</i> = 113)
Brain	<i>r</i> = $-.27$ <i>P</i> = .003	<i>r</i> = $-.15$ NS	<i>r</i> = $.02$ NS	<i>r</i> = $-.23$ <i>P</i> = .01	<i>r</i> = $-.19$ <i>P</i> = .05
Cerebellum	<i>r</i> = $.0$ NS	<i>r</i> = $.09$ NS	<i>r</i> = $.17$ NS	<i>r</i> = $-.06$ NS	<i>r</i> = $-.16$ NS
Brain stem	<i>r</i> = $-.01$ NS	<i>r</i> = $.02$ NS	<i>r</i> = $-.06$ NS	<i>r</i> = $.11$ NS	<i>r</i> = $.12$ NS
Brain lobes					
Frontal	<i>r</i> = $-.25$ <i>P</i> = .007	<i>r</i> = $-.19$ <i>P</i> = .05	<i>r</i> = $-.05$ NS	<i>r</i> = $-.22$ <i>P</i> = .02	<i>r</i> = $-.12$ NS
Parietal	<i>r</i> = $-.25$ <i>P</i> = .008	<i>r</i> = $-.13$ NS	<i>r</i> = $.02$ NS	<i>r</i> = $-.20$ <i>P</i> = .04	<i>r</i> = $-.16$ NS
Temporal	<i>r</i> = $-.23$ <i>P</i> = .01	<i>r</i> = $-.11$ NS	<i>r</i> = $.05$ NS	<i>r</i> = $-.21$ <i>P</i> = .03	<i>r</i> = $-.18$ <i>P</i> = .06
Occipital	<i>r</i> = $-.21$ <i>P</i> = .03	<i>r</i> = $-.07$ NS	<i>r</i> = $.09$ NS	<i>r</i> = $-.20$ <i>P</i> = .03	<i>r</i> = $-.21$ <i>P</i> = .03

Note: FA, fractional anisotropy; DOI, duration of illness.

Overall, correlations between the brain FA measures with age, DOI, and dose years of antipsychotic medications were small (table 6). These analyses were also performed while adjusting for the ADY and DOI, respectively. There was a negative correlation between DOI and frontal lobe FA ($r = -.19$, $P = .05$). Controlling for ADY, there was no longer a significant correlation between the frontal lobe FA and DOI. There was a negative correlation between ADY and FA in multiple brain regions, including the whole brain ($r = -.23$, $P = .01$) and in all 4 lobes (table 6).

The FE group included 23 patients who were on medication and 8 patients who were not on medications at the time of scanning. A 4 (site) by 2 (naive/nonnaive) ANCOVA with age as a covariate found no differences between those who were neuroleptic naive compared with those who were not.

The large number of subjects coupled with the variability in ADY and DOI allowed for an alternative approach to tease apart DOI and medication exposure on global and regional brain FA measures. To assess the effects of medications on brain FA measures, we further analyzed the data from a subgroup of 22 patients who had a DOI between 20 and 40 years. The mean age for this group was 46.3 years (SD 5.3), the range of ADY was between 6.4 and 1023, and the correlation between the DOI and ADY was 0.07. The Spearman rank correlations were generally low with the cerebellum ($r = -.23$) having the highest absolute correlation, which was nonsignificant.

A subgroup of 45 patients with similar ADY but with considerable variability in DOI was selected for addi-

tional analyses. The mean age of this group was 40.1 years (SD 10.0) and the DOI ranged between 0 and 42 years and the ADY was between 17.9 and 145.9. This patient subgroup had a nonsignificant correlation between the DOI and ADY ($r = .14$, $P = .36$). A Spearman rank correlation resulted in no significant correlations between DOI and FA, although the frontal lobe had the highest negative correlation ($r = -.24$, $P = .10$).

Relationship Between Clinical Variables and FA

Because there were site-related FA differences in findings between patients and controls, exploratory analyses were performed to evaluate the role of clinical variables. To limit multiple testing, this was performed in a 2-stage process. First, either a chi-square for categorical data or an ANOVA for continuous data was performed to assess for site differences in that clinic variable. Those measures that had significant differences in site underwent subsequent analyses to determine if they influenced FA.

A history of alcohol abuse, but not alcohol dependence, had a significant effect of site ($\chi^2 = 8.2$, $df = 3$, $P = .04$). Iowa and NMex both had lower rates (21% and 17%, respectively) compared with MGH and UMinn, who had rates of 44% and 41%, respectively). A 4 (site) by 2 (alcohol abuse) ANCOVA with age as a covariate found those who did not have a history of alcohol abuse had significantly higher FA in the whole brain ($F_{1,108} = 4.5$, $P = .04$), frontal lobe ($F_{1,108} = 5.7$, $P = .02$), and parietal lobe ($F_{1,108} = 5.1$, $P = .03$).

Both a history of cannabis abuse ($\chi^2 = 10.5$, $df = 3$, $P = .02$) and cannabis dependence ($\chi^2 = 15.4$, $df = 3$, $P = .001$)

had a significant effects of site. For cannabis abuse, once again Iowa and NMex both had lower rates (16% and 23%, respectively) compared with MGH and UMin, who both had rates of 44%). For cannabis dependence, Iowa had none, whereas NMex had a rate of 10%, MGH had a rate of 41%, and UMin had a rate of 22%. However, neither cannabis abuse or dependence showed a significant effect on any of the brain measures.

Discussion

We demonstrate global WM differences in FA in a large sample of patients with schizophrenia. Differences were present in the whole brain, and individually in the frontal, temporal, parietal, and occipital lobes, but were not present in either the brain stem or the cerebellum. The abnormalities were more pronounced in patients with chronic schizophrenia in contrast to the FE patients. The differences in chronic patients also had larger effect sizes compared with the FE patients, lessening the chance that the difference is a result of the larger sample size for the chronic patients. We found that only frontal lobe WM demonstrated a significant difference between the FE and chronic patients.

Disrupted connectivity between brain regions is a potential hypothesis that may explain the global nature and diversity of deficits in schizophrenia.^{6,20} Alterations in distributed neural networks, evidenced by abnormalities in WM, could account for the global nature of the clinical, cognitive, and social cognitive symptoms that are a hallmark of the illness. WM disruptions have been supported by the over 60 DTI papers that report aberrant WM microstructure in the pathophysiology of schizophrenia.⁵ While, there is considerable heterogeneity in the results of these studies, taken together, they provide strong support for WM abnormalities in the pathophysiology of schizophrenia. This is especially notable for pathways involving interhemispheric connections and frontal and limbic WM.

The neuropathological changes responsible for lower FA in patients with schizophrenia are yet unknown. It has been postulated to reflect abnormalities in myelination, oligodendrocytes, neuronal loss, disruption of the integrity of the cell membrane, or alterations in fiber orientation. Perhaps one of the more interesting findings of the current study is the reduced likelihood that altered fiber orientation, such as crossing fibers, would account for the decreases in FA. It is likely that differences as a result of crossing fibers would be equally present in the FE and chronic groups. Although better studied using longitudinal designs, our findings suggest a progressive decrease in FA as patients progress from FE into chronic schizophrenia. Such a progression is also supported in a review of the DTI literature in schizophrenia,⁵ a recent DTI study comparing FE and chronic patients,⁷ and is consistent with a number of structural imaging studies.^{21–25}

Longitudinal magnetic resonance imaging studies early in the illness have documented progression of volume loss in the frontal regions after 2.5 years,²⁶ both cerebral hemispheres after 4 years,²² parietal, frontal, temporal gray matter, and hippocampus after 4 years,^{23,25} frontal WM after 3 years,²¹ and ventricular enlargement after 2.5 years in patients with persistent symptoms.²⁴ It has been proposed that this early brain volume reduction stabilizes in early adulthood²⁷; however, a recent review suggests that progressive atrophy occurs even later in the illness.²⁸

What mechanism may account for progressive FA reduction as well as white and gray matter volume losses previously described in adults with schizophrenia? Hypofunction of N-methyl-D-aspartic acid receptors in gamma-aminobutyric acid interneurons resulting in a paradoxical downstream glutamatergic excitotoxic process has been proposed.^{29–31} Consistently, cortical neuropil reductions without neuronal loss or gliosis have been found in postmortem studies.^{32,33} Hence, excessive cortical synaptic pruning with neuropil contractions and subsequent axonal microstructural dysfunction may account for the greater FA reductions in chronically treated compared with the FE patients in our study. However, other possible explanations include a neuroplastic adaptation to psychosocial impoverishment or treatment effects.³⁴

With the suggestion of a progression of WM changes, we explored underlying factors contributing to these observed group differences. While it was somewhat difficult to tease apart whether lower FA was associated with DOI from the effects of medication, there is evidence that it is more associated with medication effects, although it is difficult to parse out the effects of multicollinear variables. Mori *et al.*³⁵ reported an age-dependent decline in FA in schizophrenia that was correlated with DOI rather than medication; however, the variable of ‘current dose of antipsychotic medication’ was used and this does not provide information about the cumulative dose of antipsychotic exposure.

Studies tend to lump the different antipsychotics into 1 or 2 categories to increase power. However, different atypical antipsychotics will have different effects on the neurochemistry. These neurochemical differences may decrease associations seen between FA and ADY. Overall, we report relatively low correlations between FA measures and DOI and total dose years of medications, although the variability in FA in cross-sectional studies likely considerably impacts the correlation. Thus, the question of a progressive decrease in FA and the underlying cause is best addressed in a longitudinal study of FA in schizophrenia.

Interestingly, by including both an FE and chronic sample, we were able identify FA differences in the frontal lobe between these 2 groups. The differences in DOI in the current literature may account for some of the heterogeneity of findings. Studies have reported lower FA in the frontal, parietal, temporal, and occipital lobes in patients with

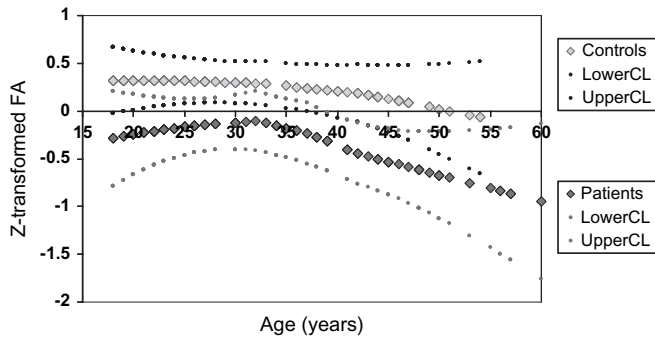


Fig. 4. Age-Related Trajectories of z-Transformed Fractional Anisotropy Measures in Patients With Chronic Schizophrenia and Controls.

schizophrenia.⁵ The frontal lobe tends to have a larger number of studies identifying abnormalities, although this may be a result of it being a target for a number of ROI studies. Alternatively, because frontal WM development tends to progress into early adulthood, greater frontal WM deficits in chronic patients may correspond with a cessation or failure to maintain typical developmental trajectories, rather than WM pathophysiologic changes. Future cross-sectional and longitudinal studies using DTI in schizophrenia will need to consider the stage of the illness and development of the participants.

There are several limitations to the study. We performed a number of different statistical analyses adjusting for multiple comparisons in the initial analysis but not in the post hoc tests. Adjusting for multiple comparisons would allow the findings of lower FA in the frontal, parietal, and occipital lobe, but the finding in the temporal lobe in chronic patients would not survive Bonferroni correction. In addition, the finding of lower frontal FA in the chronic compared with the FE patients would also not survive Bonferroni correction. We would expect that random error would affect the patients and controls equally, and we found no brain regions showing higher FA in the controls compared with the patients. Cross-sectional studies of individuals with large age ranges may be susceptible to cohort effects. The patients had a matched control group, which may help reduce some of the cohort effects. The LOESS curve for cortical FA between patients and controls is shown in figure 4. As can be seen, the trajectory for FA in patients is lower but parallels the trajectory for FA in controls.

Data collected from multiple sites, using scanners with different field strengths, head coils, and sequence parameters may induce artifacts and increase the variance of the FA measures. While these site-related differences cannot be completely removed, we corrected for these differences by using site as a covariate and through the use of relatively large ROIs. In addition, post-processing was performed at one site using the same image processing algorithms. Differences in scanner noise could increase

the variance in the measures, resulting in a lowering of the effects sizes and significant findings. The CoV was higher in the occipital lobe and brain stem; thus, the higher noise in these smaller structures may have limited smaller effects. Finally, we evaluated differences between patients and controls at each site and found overlapping patterns in 3 of the 4 sites. The differences at the Iowa site may be related to a cohort effect, smaller sample size of patients, a more rural setting, or greater variability due to scanner differences such as obtaining only 6 directions.

Despite these limitations, we report global differences in WM microstructure in patients compared with controls in a large, multicenter study of FE and chronic schizophrenia. Regional FA differences are only observed in the cerebrum but involve all 4 lobes. The frontal lobe is the only region that is significantly different between the FE and chronic patient groups, with the lower FA being more pronounced in the chronic cohort. Finally, lower FA appears to be more related to antipsychotic medications; however, due to multicollinearities, it is difficult to separate ADY from DOI. Longitudinal studies of WM microstructure will be important to better understand whether these FA differences are a result of the DOI, medication, environmental effects, or adaptive processes within the brain as an attempt to compensate for the illness. Future studies should also assess the functional consequences and prognostic indicators associated with lower cerebral FA.

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