ORIGINAL ARTICLE

Compromised White Matter Tract Integrity in Schizophrenia Inferred From Diffusion Tensor Imaging

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Background: Current investigations suggest that brain white matter may be qualitatively altered in schizophrenia even in the face of normal white matter volume. Diffusion tensor imaging provides a new approach for quantifying the directional coherence and possibly connectivity of white matter fibers in vivo.

Methods: Ten men who were veterans of the US Armed Forces and met the *DSM-IV* criteria for schizophrenia and 10 healthy, age-matched control men were scanned using magnetic resonance diffusion tensor imaging and magnetic resonance structural imaging.

Results: Relative to controls, the patients with schizophrenia exhibited lower anisotropy in white matter, despite absence of a white matter volume deficit. In contrast to the white matter pattern, gray matter anisotropy did not distinguish the groups, even though the patients with schizophrenia had a significant gray matter volume deficit. The abnormal white matter anisotropy in patients with schizophrenia was present in both hemispheres and was widespread, extending from the frontal to occipital brain regions.

Conclusions: Despite the small sample size, diffusion tensor imaging was powerful enough to yield significant group differences, indicating widespread alteration in brain white matter integrity but not necessarily white matter volume in schizophrenia.

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THERE IS now little controversy regarding the claim that the brains of patients with schizophrenia are structurally and functionally compromised. Abnormalities occur in both gray matter and white matter. In vivo magnetic resonance imaging studies report volume deficits more often in cortical gray than white matter[1-4] and are consistent with neuropathologic observations of increased neuronal density and decreased neuropil[5] presence of smaller neurons in layer III of the prefrontal cortex and absence of glial cell enlargement.[6] There have also been reports of reduced prefrontal lobe white matter volume in patients with schizophrenia[7,8] and of patchy signal intensity differences between patients with schizophrenia and controls that affect white matter tracts.[9] Proton magnetic resonance spectroscopic imaging, which provides in vivo indices of some brain metabolites, has shown abnormally low white but not gray matter signals of *N*-acetyl (NAc) compounds, primarily *N*-acetyl aspartate, a putative marker for living mature neurons, in patients with schizophrenia who had abnormally small gray but not white matter volumes.[10] The low white matter NAc signal was interpreted as potentially reflecting compromised neuronal connectivity.[11-14] Evidence from postmortem studies supports the in vivo findings of anomalous white matter in schizophrenia, including selective displacement of interstitial white matter neurons in the prefrontal and temporal[15] cortex and delayed myelination in frontal white matter.[16,17] These neuropathologic signs may be reflected in measurements sensitive to directional coherence or connectivity of fiber tracts.

Findings of abnormal white matter integrity, together with the possibility that cortical gray matter volume deficit has a neurodevelopmental genesis, have led to the hypothesis that a cortical dysconnection syndrome plays a role in the pathophysiology of schizophrenia.[18-20] Perhaps the most current support for this speculation comes from diffusion tensor imaging (DTI), a relatively new magnetic resonance imaging method[21,22] that can be used to quantitate the magnitude and directionality of tissue water mobility (ie, self-diffusion) in 3 dimensions.

Self-diffusion (hereafter called diffusion) is caused by random Brownian move-

SUBJECTS AND METHODS

All subjects gave written informed consent for study participation and underwent physical and psychiatric examinations. The patients were 10 men, veterans of the US Armed Forces, who met the *DSM-IV* criteria for schizophrenia (**Table**). They were 47.7±7.8 (mean ±SD) years old (range, 32-64 years) and had 13.9±1.9 years of education. Exclusion factors were *DSM-IV* criteria for Alcohol or Substance Abuse or Dependence within 3 months prior to scanning; posttraumatic stress disorder; significant medical illness; or head injury resulting in loss of consciousness exceeding 30 minutes. *DSM-IV* diagnoses were determined by consensus between a psychiatrist or clinical psychologist, who conducted a clinical interview, and a trained research assistant, who administered the Structured Clinical Interview for Diagnosis. All patients were receiving antipsychotic medications. Clinical condition was evaluated using an average of the 18-item Brief Psychiatric Rating Scale score[32] (mean±SD, 33.6±6.2) obtained by 2 raters with established reliability. Premorbid intelligence was assessed using the National Adult Reading Test[33] (108.1±9.9), and parental socio-occupational status was determined using the Hollingshead 2-Factor Scale[34] (2.8±1.2).

The healthy control subjects were 10 men (41.9±8.3 years; range, 30-57 years), recruited from the local community.[35,36] Seven subjects were given the Structured Clinical Interview for Diagnosis and a physical examination; 3 completed a detailed questionnaire inquiring about current and past medical and psychiatric conditions, medications, and substance use.

IMAGE ACQUISITION AND PROCESSING

Anatomical Magnetic Resonance Imaging

An initial spin-echo sagittal scout image was collected (3-mm skip, 0 mm; repetition time [TR], 600 milliseconds; echo time [TE], 20 milliseconds; 256×256 pixel matrix; field of view, 24 cm). Using the midsagittal image, the line connecting the anterior and posterior commissures (AC-PC line) was identified. For tissue segmentation, a fast spin-echo (FSE) sequence was collected (TR, 2500 milliseconds; TE, 20/80 milliseconds; echo train length, 8; 5-mm skip, 0 mm; field of view, 24 cm; 256×256 pixel matrix; 18 slices beginning 2 cm below and aligned on the AC-PC line (**Figure 2**, A and B).

All analyses were performed blind to subject identity. Nonbrain tissue (dura, skull, and scalp) was stripped and the remaining tissue was segmented into gray matter, white matter, or cerebrospinal fluid (Figure 2, D) with a semiautomated procedure.[37,38] White-matter hyperintensities segmenting as gray matter were hand-edited for inclusion in the white matter compartment.

For regional analyses, 8 images were used for volumetric quantification and manually midlined along the interhemispheric fissure to separate the hemispheres and divided according to anatomical landmarks and a priori rules into 3 lobar regions: prefrontal, temporal-parietal, and parietal-occipital (**Figure 3**). A prefrontal region began at the anterior margin of the slice, with the posterior extent determined by the point where the anterior cingulate and adjacent white matter met at the interhemispheric fissure. Sulcal landmarks were also considered, such that on the inferior slices the posterior border fell at the juncture between the anterior-temporal pole and the frontal cortex. On superior slices, the prefrontal region included the 3 frontal-lateral gyri. A temporal-parietal region was formed by the posterior border of the prefrontal region and the anterior border of the parietal-occipital region. Included were the temporal lobes from the level of the insula and basal ganglia to the superior extents of the lateral ventricles. A parietal-occipital region had its anterior border determined by several landmarks, including the juncture at which the cortex joins white matter along the interhemispheric fissure, posterior to lateral ventricles, and the point at which the parietal sulci are horizontal (ie, perpendicular to the

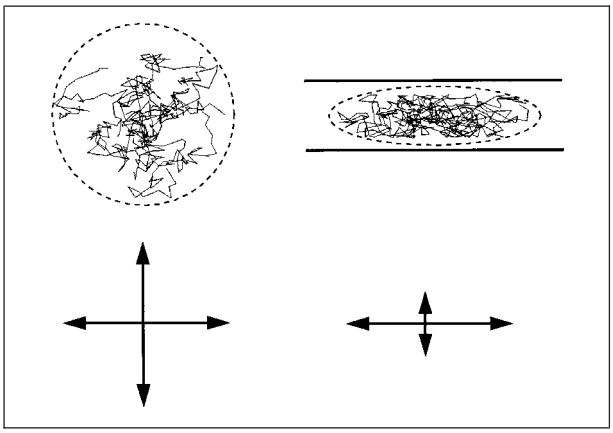

Figure 1. *A computer simulation of 2-dimensional Brownian motion. Left, Paths of 10 particles starting at the same position in a condition of no spatial constraint. The particles move randomly, with a chance of moving horizontally and vertically equally in all directions (arrows), resulting in a circular displacement profile (broken circle). This movement is termed* isotropic. *Right, Paths of 10 particles with a physical constraint in the vertical direction (solid lines). The particles move randomly, with a greater chance of moving horizontally than vertically (arrows), resulting in an ellipsoidal displacement profile. This movement is termed* anisotropic.

ment of molecules. Isotropic diffusion is characterized by identical diffusion properties in all directions, such that, after a period, a number of molecules originating at the same location would be spatially distributed over a circle in 2 dimensions (**Figure 1**, left) or a sphere in 3 dimensions. In brain tissue, the diffusion of water is impeded by structures such as cell membranes, myelin sheaths, and white matter tracts. When trapped, water molecules tend to move farther along paths that are parallel to fibers than ones that are perpendicular to fibers (Figure 1, right). The resulting distribution of water molecules becomes ellipsoid rather than circular, and the diffusion is termed *anisotropic*. The direction and shape of the ellipsoid is determined by the restricting fibers, and the degree of anisotropy can be thought of as the ratio of the long axis to the short axis of the diffusion ellipsoid.

Diffusion (expressed as the apparent diffusion coefficient) measured parallel to fiber tracts yields larger values than when measured perpendicular to tracts.[23] In heterogeneous tissue, such as the brain, it is not possible to choose diffusion directions perfectly aligned with the orientation of the fibers for all imaged voxels;

interhemispheric fissures). Region of interest determination was made by consensus of the 2 scorers (A.P. and E.V.S.).

Diffusion Tensor Imaging

A diffusion tensor data set was collected using a pulsed gradient spin-echo echo-planar imaging technique. The field of view was 24 cm; pixel matrix size, 128×128; 0 filled to 256×256 pixel matrix as required by scanner specifications; TE/TR, 106 milliseconds/6 seconds; and 18 oblique slices (5-mm skip, 0 mm) aligned with FSE slices. The duration of the diffusion gradient was 32 milliseconds, the maximum gradient strength was 1.4 G/cm, and the separation of the diffusion gradient pulses was maximized within the echo time (approximately 34 milliseconds). Gradients were always applied on 2 axes simultaneously, resulting in a total value of 860 s/mm^2. Diffusion was measured along 6 noncollinear directions: (Gx, Gy, Gz) = [(1,1,0), (0,1,1), (1,0,1), (–1,1,0), (0,–1,1), (1,0,–1)]. For each gradient direction, 4 diffusion-weighted images were acquired and averaged. Two additional images with no diffusion weighting were acquired and averaged. Averaging was performed after Fourier transformation. A set of cerebrospinal fluid–nulled inversion recovery images (TI ≈ 2100 milliseconds) was acquired with no diffusion weighting as a reference for unwarping eddy current effects in diffusion-weighted images, using the method of de Crespigny and Moseley.[39]

Using the averaged images with and without diffusion weighting, 6 maps of the apparent diffusion coefficient were calculated from which the 6 independent elements of the diffusion tensor were determined. Based on the eigenvalues, the degree of anisotropy can be calculated on a voxel-by-voxel basis. From the diffusion tensor, eigenvalues and eigenvectors were determined. Many scalar measures of anisotropy are derived from the tensor.[27] Fractional anisotropy (FA)[28] is a robust intravoxel measure that yields values between 0 (perfectly isotropic diffusion) and 1 (the hypothetical case of a cylinder infinitely long and infinitely thin). These values were plotted to produce an image (Figure 2, C) approximating the inverse of the anatomical FSE early-echo image (Figure 2, A).

According to simulation studies,[29] rotationally invariant measures of anisotropy are "reasonably accurate and precise for signal-to-noise ratio levels greater than 20."[29(p903)] Our current signal-to-noise ratio of about 30 in the non–diffusion-weighted image is thus well within the range of acceptable accuracy in fractional anisotropy measurement.

STRUCTURE/DIFFUSION ANALYSIS

This analysis used 8 contiguous slices of the FSE and corresponding FA images that began at the anterior commissure and proceeded superiorly 40 mm. This volume encompassed the largest extent of cerebral white matter across all subjects and included the corpus callosum and centrum semiovale. Segmented FSE images (Figure 2, D) were registered with FA images (Figure 2, C). Fractional anisotropy voxels were characterized according to their tissue type (white matter, gray matter, and cerebrospinal fluid) and allocated to the 3 cortical regions of interest. Echo-planar warping, present in DTI, has the potential to hamper registration between DTI and FSE images; however, such effects were apparent only in the most anterior regions (Figure 2, E) and were minimized by use of tissue segmentation contours.

STATISTICAL ANALYSIS

The unit of DTI analysis was median FA. Group differences in FA were examined with repeated-measures analysis of variance (ANOVA) and unpaired *t* tests. Group differences in total FA were further tested with 3 separate analyses of covariance that used gray matter volume, white matter volume, and age as covariates. The α level for all tests was .05 (2 tailed).

Characteristics of Patients With Schizophrenia*

Subject No./ Age at Scan, y	Education, y	Secondary Diagnosis	Past Substance Abuse/Dependence†	Age When Patient Last Met Diagnosis for Substance Abuse/Dependence, y‡	Global Assessment of Functioning Scale Score	Brief Psychiatric Rating Scale Score	Medication at Scan
1/32	14	Undifferentiated	Cannabis abuse	20 (12)	57	32.0	Risperidone, Prolixin
2/44	11	Disorganized	. . .	. . .	32	45.0	Clozapine
3/46	13	Undifferentiated	Cannabis dependence, hallucinogen abuse	26 (20)	37	39.0	Risperidone, Olanzapine
4/47	13	Undifferentiated	Cannabis dependence	20 (27)	52	32.6	Clozapine
5/47	12	Undifferentiated	Cocaine dependence	41 (6)	42	35.0	Risperidone
6/48	16	Residual	Cannabis abuse	43 (5)	60	23.0	Clozapine
7/49	15	Residual	Alcohol dependence, cannabis abuse, opiod abuse	38 (11)	60	29.6	Clozapine
8/50	14	Undifferentiated	. . .	. . .	45	38.6	Clozapine
9/50	11	Undifferentiated	Alcohol abuse	22 (32)	32	32.6	Olanzapine
10/64	16	Residual	. . .	. . .	57	28.0	Risperidone

**Schizophrenia was the* DSM-IV *diagnosis for all subjects.*
†*Ellipses indicate no substance use.*
‡*Numbers in parentheses indicate years since patient last met this diagnosis.*

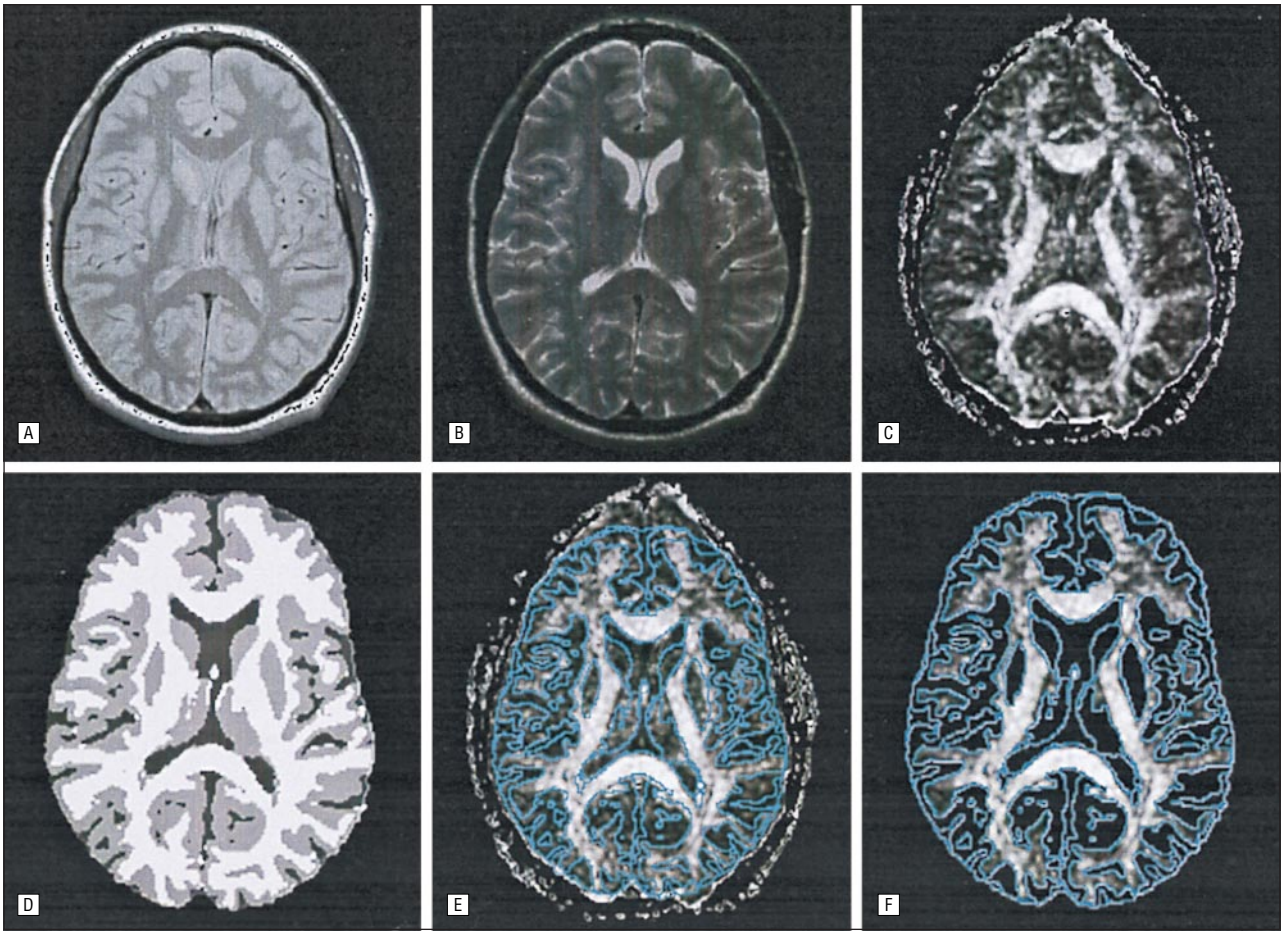

Figure 2. *Axial images from slice 3, 1.5 cm superior to the AC-PC line, from a single subject. A, Early echo. B, Late echo. C, Fractional anisotropy image. D, Fully processed image segmented into 3 tissue compartments (white matter=light gray, gray matter=dark gray, and cerebrospinal fluid=black). E, Fractional anisotropy image with segmentation contours overlaid to localize alignment and misalignment between anatomical and diffusion images. F, Fractional anisotropy voxels only for white matter, with segmentation contours overlaid. Note that the spatial distortion common to echo-planar imaging, especially at the frontal air-tissue boundaries (E), is confined primarily to cerebrospinal fluid and gray matter, with little distortion of white matter (F).*

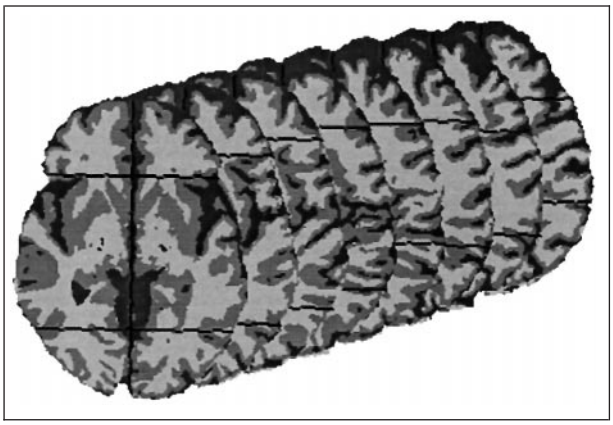

Figure 3. *Region-of-interest boundaries, marked in black lines, are superimposed on each of the 8 fast-spin echo segmented slices used in data analysis.*

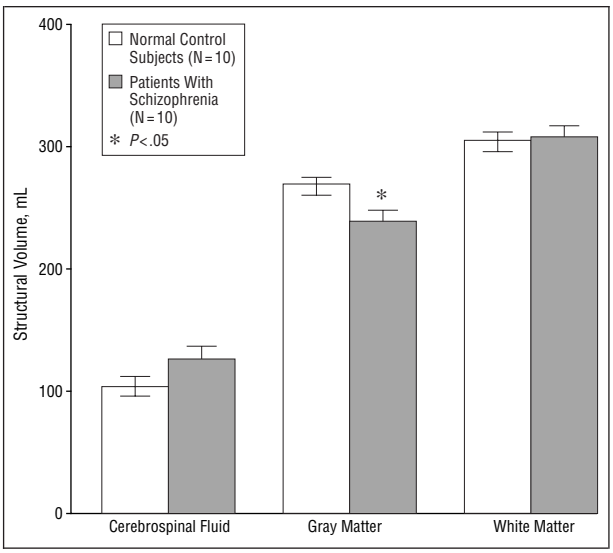

Figure 4. *Mean (SEM) cerebrospinal fluid, gray matter, and white matter volumes for the 10 normal control subjects and the 10 patients with schizophrenia.*

however, the so-called "diffusion tensor," first described by Basser et al,[24-26] contains information about the 3-dimensional geometry, orientation, and shape of the diffusion ellipsoid and thus fully characterizes the diffusion system. A tensor is a mathematical construct useful for describing multidimensional vector systems, and the diffusion tensor provides the apparent diffusion coefficient of a certain direction, degree of anisotropy, and primary fiber tract orientation.

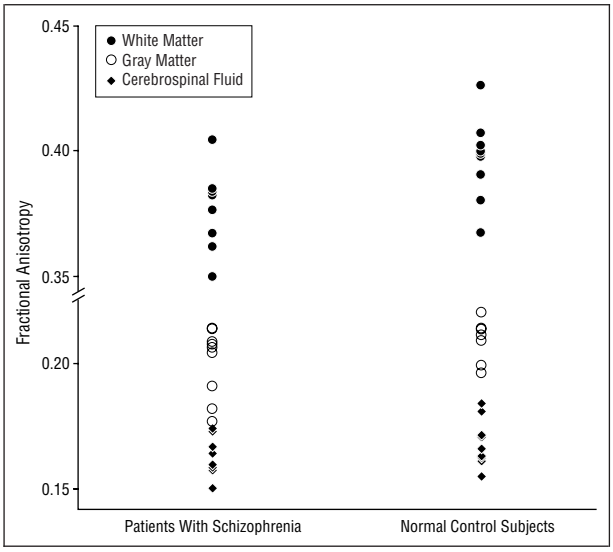

Figure 5. *Fractional anisotropy measures of cerebrospinal fluid, gray matter, and white matter for normal control subjects and patients with schizophrenia over all 8 slices analyzed.*

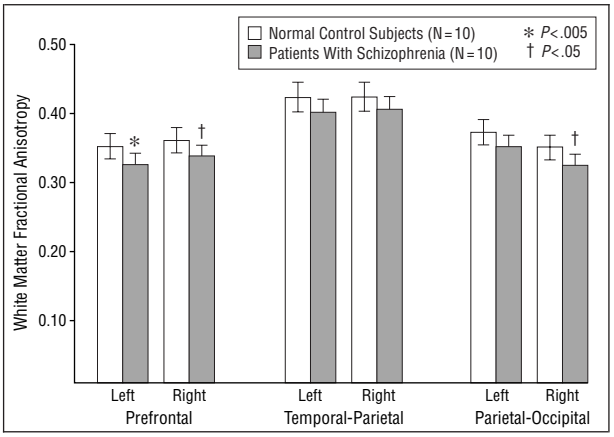

Figure 6. *White matter fractional anisotropy (mean and SEM) in the 3 regions of interest, in the left and right hemispheres, for 10 normal control subjects and 10 patients with schizophrenia.*

The degree of anisotropy in a voxel is determined by microstructural features of the tissue in that particular voxel, such as fiber diameter and density, as well as the degree of myelination,[27,28] and also by macrostructural features, such as intravoxel fiber-tract coherence.[29,30] At first glance, high anisotropy may seem to be evidence of a high degree of coherence and hence highly connected tissue (such as normal white matter), whereas low anisotropy would imply tissue with low connectivity (such as abnormal white matter); however, a high degree of connectivity with low anisotropy can be found at the junction of merging tracts,[29] where fibers with different orientations are found within the same voxel. Another example occurs in pons, where both descending and perpendicular fibers are found within a voxel. Wallerian degeneration of only the descending pathways reduces the amount of crossing fibers and increases the coherence of fibers within that particular voxel, such that the observed anisotropy increases.[30] Thus, the meaning of low anisotropy must always be interpreted in the context of the anisotropy in a corresponding normal region.

Using DTI, Buchsbaum et al[31] reported evidence of lower diffusion anisotropy in some inferior portions of prefrontal white matter in patients with schizophrenia (n=5) than in controls (n=6). Together with lower metabolic rates in the frontal cortex and striatum observed with positron emission tomographic scans in these same patients, these results were interpreted as diminished frontostriatal connectivity in schizophrenia.

Our controlled study of schizophrenia used DTI to quantify anisotropy determined from magnetic resonance images divided on the basis of tissue composition, hemisphere, and anatomically determined lobar regions. Our previous observations revealed gray but not white matter volume deficits, yet NAc concentration deficits occurred in white but not gray matter, suggesting compromised tissue composition in white matter.[10] Therefore, we hypothesized that patients with schizophrenia would exhibit gray but not white matter volume deficits in conjunction with decreased white but not necessarily gray matter anisotropy relative to age- and sex-matched controls. Given the results of Buchsbaum et al, we anticipated that the most notable deficits would be in inferior frontal white matter in the right hemisphere.

RESULTS

Based on the segmented FSE data, a repeated-measures ANOVA for total volume revealed a group × tissue-type interaction ($F_{1,18}$=13.125, $P<.002$), indicating a volume deficit in gray but not white matter in the patients with schizophrenia relative to the controls (**Figure 4**). The FA data for gray and white matter also yielded a significant interaction ($F_{1,18}$=10.521, $P<.005$), indicating lower FA in white but not gray matter in the patients with schizophrenia than in the controls (**Figure 5**). The effect size for the white matter FA group difference was 1.5 SD. The lower white matter FA persisted with 3 separate, 2-group analyses of covariance, controlling for gray matter volume, white matter volume, and age.

Regional effects between groups in white matter FA were tested with a repeated-measures ANOVA across the 3 lobar regions and across hemispheres (**Figure 6**), with the objective of testing for a group effect (patients vs controls) and interactions involving group. This 3-way ANOVA yielded a significant effect only for group ($F_{1,18}$=9.070, $P<.008$); none of the interactions involving group was significant.

The hypothesis that FA would be especially low in inferior frontal white matter in the right hemisphere of the schizophrenic group was tested by employing separate repeated-measures ANOVAs (2 groups × 2 hemispheres × 3 regions) for slice 2 (**Figure 7**; 0.5 cm superior to the AC-PC line, with inferior tips of the lateral ventricles, internal capsule, and some genu of the corpus callosum visible) and slice 3 (Figure 7; 1 cm superior to the AC-PC line, with genu and some splenium of the corpus callosum visible). For the frontal region of interest, these 2 slices appeared to correspond to those showing the greatest effects in the Buchsbaum et al[31] study. The ANOVAs yielded the same results for each slice, with significant effects only for group [slice 2: $F_{1,18}$ =9.843,

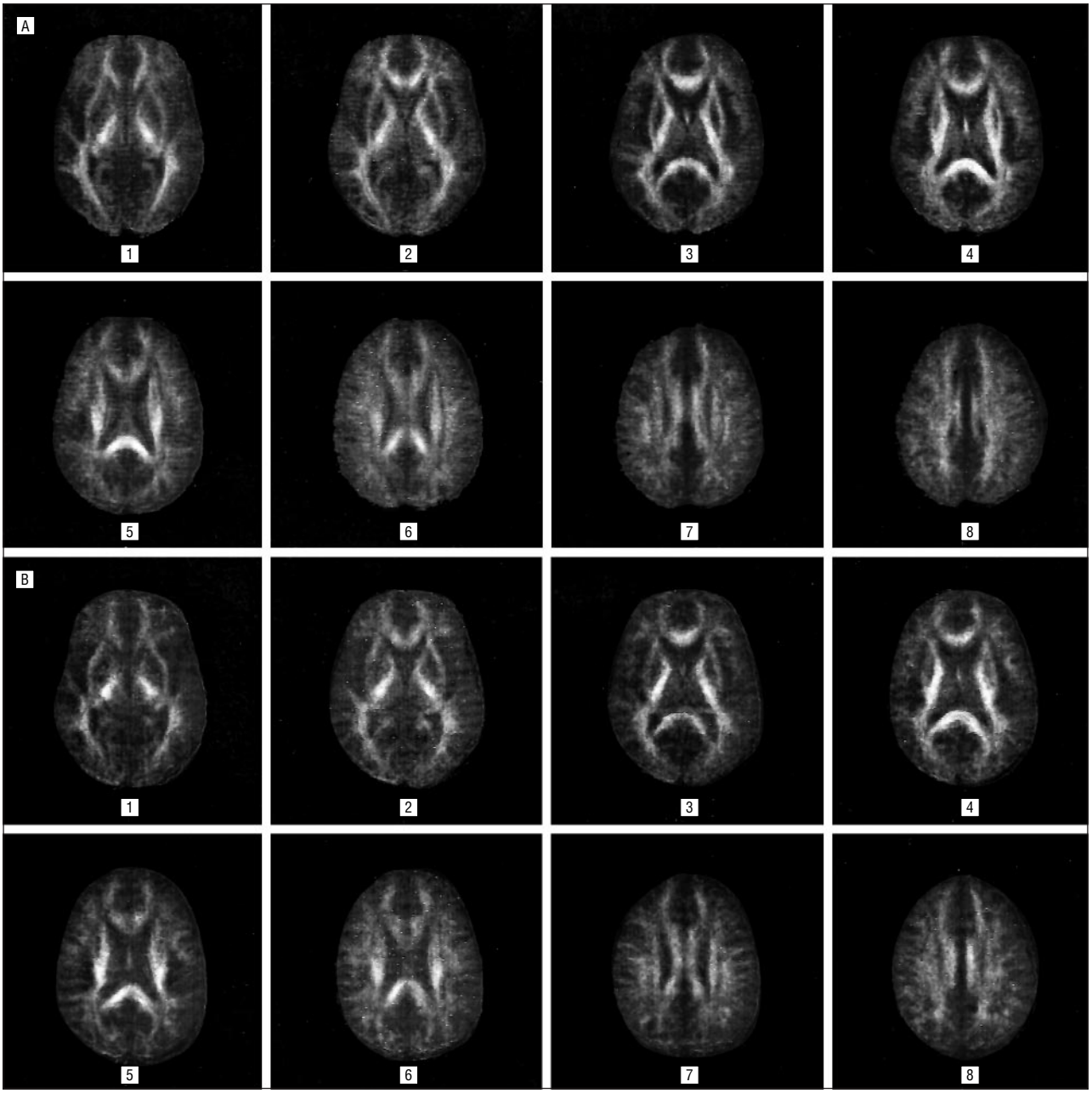

Figure 7. *Grand average images (each slice was warped to a standard size and rotation) of fractional anisotropy for 8 slices for the 10 normal control subjects (A) and the 10 patients with schizophrenia (B).*

$P<.006$; slice 3: $F_{1,18}=11.824$, $P<.003$], region [slice 2: $F_{2,36}=27.418$, $P<.001$; slice 3: $F_{2,36}=98.559$, $P<.001$], and region × hemisphere [slice 2: $F_{2,36}=5.168$, $P<.02$; slice 3: $F_{2,36}=7.155$, $P<.003$]. **Figure 8** plots the FA for each slice within each region of interest.

COMMENT

We compared anisotropy and volumes of equivalent regions of white and gray matter in patients with schizophrenia and controls and observed the following double dissociation. Although patients with schizophrenia and controls had an equivalent volume of white matter, this white matter exhibited lower anisotropy among patients with schizophrenia. By contrast, gray matter anisotropy did not distinguish the groups even though the schizophrenic group had a significant gray matter volume deficit. Furthermore, the abnormal white matter anisotropy in the patients with schizophrenia was present in both hemispheres and was widespread, extending from the frontal to occipital brain regions. A similar double dissociation was observed in our previous comparison[10] of tissue volume and tissue composition of the brain metabolite NAc; patients with schizophrenia had decreased gray matter but not white matter volume and decreased white matter but not gray matter NAc concentration.

There is no convention for a DTI outcome, and the appropriateness of traditional statistical tests in the analysis of DTI data has yet to be decided. The information

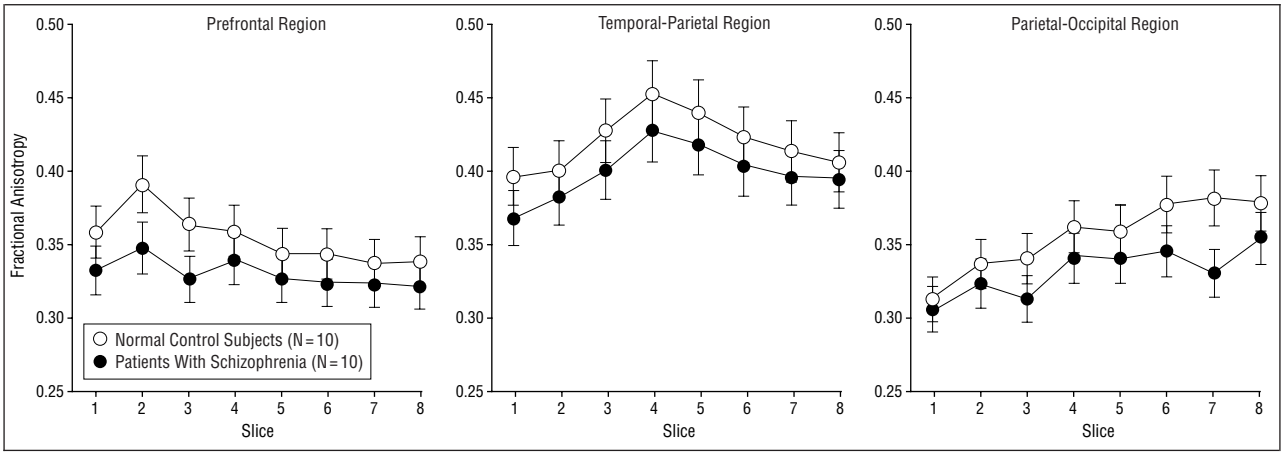

Figure 8. *White matter fractional anisotropy (mean and SEM) in the 3 regions of interest (frontal, temporal-parietal, and parietal-occipital) for each of the 8 analyzed slices from the 10 normal control subjects and the 10 patients with schizophrenia.*

contained in the tensor comprises complex 3-dimensional directionality, which by its very nature is difficult to condense into a scalar measure. The most quoted measure, however, is the degree of diffusion anisotropy, the simplest being the ratios between diffusivities along different directions. Such ratios are highly sensitive to noise and have small deviations in the eigenvalues.[29] Fractional anisotropy, used in our study, and relative anisotropy (RA),[27] used in the Buchsbaum study, are more robust measures that are normalized and thus appropriate for between-group comparisons. The physiologically relevant range of anisotropy is FA of 0.2 to 0.8, corresponding to a ratio of about 1:4 between the largest and smallest diffusivities in a symmetrical cylinder. In this anisotropy range, RA and FA are comparable; however, RA is the ratio of the anisotropic component of the tensor to the isotropic component; as one goes up, the other goes down, rendering RA more sensitive to variations for large degrees of anisotropy but not as sensitive in the midrange. Fractional anisotropy, on the other hand, is the ratio of the anisotropic component to the entire tensor, which is independent of the degree of anisotropy; the anisotropy that we observed in white matter (approximately 0.3 to 0.4) is in the range where FA is more sensitive than RA.

Buchsbaum et al[31] reported lower RA in frontal white matter, including the anterior limb of the external capsule only in the right hemisphere. Our study observed abnormalities in these frontal regions in both hemispheres as well as in nonfrontal regions. These 2 studies differed in the analysis approach and the anisotropy measure: Buchsbaum et al used RA, whereas we used FA. They also employed a spatial normalization method to standardized coordinates,[40] which involved stretching each slice of each subject to a common size, followed by pixel-by-pixel *t* tests corrected for multiple observations. We analyzed large regions of interest that were inherently less anatomically specific but more robust to noise and statistically more conservative. Nonetheless, the results of both studies converge on the possibility of compromised frontostriatal connectivity or directional coherence of white matter fibers in schizophrenia, although our study also points to abnormalities in other regions.

The possibility of compromised white matter connectivity suggested by our study must be considered within the context of cortical gray matter pathology noted in schizophrenia. The gray matter volume deficit is especially prominent in the heteromodal cortex,[1,4,41] which has extensive corticocortical and subcorticocortical interconnections.[42] Disruption of these interconnections could arise from several sources: abnormally small size or number of neurons producing commensurately fewer than normal arbors, disturbances in the white matter structure arising from displaced interstitial neurons, or aberrant myelination. These white matter anomalies could disrupt fiber coherence or might even result in compromised connections. Considering neuropathologic reports, either or both of these possibilities could occur in schizophrenia. White matter growth and restructuring occur from late prenatal development through late adolescence. The cortical targets—prefrontal, superior temporal, and parietal—in the heteromodal system putatively disrupted in schizophrenia are critical to higher-order cognitive functions of problem solving, working memory, sequencing, language, and spatial orientation, many of which are commonly impaired in patients with schizophrenia.[43,44] Our results note a potential substrate for functional disconnection[18,20] or for a less dramatic disruption in brain structural organization in the form of decreased fiber coherence. Decreased anisotropy could, therefore, arise from underdevelopment of these otherwise highly integrated neural networks, possibly from incomplete organization of target sites during development, and could result in decreased directional coherence of white matter fibers or vulnerability from neurotoxic sources, including neuroleptic exposure or symptom exacerbation.[45]

Limitations of our study arise from the fact that the echo-planar acquisition used in DTI introduces warping in the images due to magnetic field inhomogeneity, particularly at borders between tissue and air and especially prominent at the most inferior frontal margins of the brain. The structural images used for defining anatomical structures and tissue types for regions of FA measurement were acquired with an FSE protocol. This echo-planar warping is not present in FSE images, therefore

precluding perfect registration of the 2 image types. In our study, however, the misregistration appeared to be minimal except for the most anterior regions (Figure 2, E). Consequently, we used tissue segmentation as a basis for defining anatomical borders for regional FA measurements (Figure 2, F). A preferred approach may involve unwarping the DTI images,[46] which requires the acquisition of a magnetic field map at the time of data acquisition; however, such data were not available for our analysis. Despite the limitations of our study, including its restrictions in sample size and sex, the method was powerful enough to yield group differences with a 1.5-SD effect size, indicating widespread alteration in brain white matter integrity but not necessarily white matter volume in schizophrenia.

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