

White Matter Abnormalities in Early-Onset Schizophrenia: A Voxel-Based Diffusion Tensor Imaging Study

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ABSTRACT

Objective: To investigate abnormalities in the structural integrity of brain white matter as suggested by diffusion tensor imaging in adolescents with early-onset schizophrenia (onset of psychosis by age 18). **Method:** Twenty-six patients with schizophrenia and 34 age- and gender-matched healthy volunteers received diffusion tensor imaging and structural magnetic resonance imaging examinations. Fractional anisotropy maps were compared between groups in the white matter using a voxelwise analysis after intersubject registration to Talairach space. **Results:** Compared with healthy volunteers, patients demonstrated lower fractional anisotropy values in the left anterior cingulate region in close proximity to the caudate nucleus (95% confidence interval of schizophrenic-healthy: -66 to -20). Using regression analysis, the rate of change in fractional anisotropy differed significantly between groups in this region across the age span examined (10–20 years), after adjusting for group differences in premorbid intellectual capacity and parental socioeconomic status. There were no areas of significantly higher fractional anisotropy in patients compared with healthy volunteers. **Conclusions:** These data suggest that early-onset schizophrenia is associated with a disruption in the structural integrity of white matter tracts in the anterior cingulate region. These structural abnormalities may contribute to the deficits in motivation, attention, memory, and higher executive functions in adolescents with schizophrenia. *J. Am. Acad. Child Adolesc. Psychiatry*, 2005;44(9): 934–941. **Key Words:** diffusion tensor imaging, schizophrenia, anterior cingulate, temporal lobes.

The structural maturation of the frontal lobe and its connecting pathways are essential for the successful development of cognitive functions. As summarized by Sowell et al. (2003), converging data from electrophys-

iological cerebral glucose metabolism, postmortem, animal, and structural magnetic resonance imaging (MRI) studies provide empirical evidence of ongoing maturation of the fiber projections to the frontal lobe during adolescence. Overall, these data suggest that the second decade of life may represent a particularly critical period in the structural maturation of fiber pathways connecting the frontal lobe to other brain regions.

There is increasing evidence that the pathophysiology of schizophrenia involves a white matter component and that elements of white matter—myelin and oligodendroglia—are abnormal in frontal regions, creating a physiological obstacle with functional consequences to corticocortical and corticosubcortical interaction (Davis et al., 2003). In support of this model, the clinical presentation of patients with metachromatic leukodystrophy frequently includes psychotic symptoms, particularly when there is involvement of frontal subcortical white matter in the disease process and

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the onset of the illness occurs during adolescence (Hyde et al., 1992). White matter provides the physical foundation for corticocortical and subcortical connectivity. Diffusion tensor imaging (DTI) is an MRI technique suited to the study of white matter because it can be used to provide an estimate of the orientation of fiber bundles in white matter based on the diffusion characteristics of water. Fractional anisotropy (FA), or the degree to which the diffusion of water follows one direction, is a commonly used scalar measure of anisotropy in diffusion tensor MRI. Decreases in white matter FA have been reported in disorders associated with changes in white matter tissue structure (e.g., demyelination, axonal disruption) such as multiple sclerosis (Horsfield et al., 1998). Using DTI, we have shown in an initial pilot study that adolescents with schizophrenia have decreased FA levels in frontal white matter regions (Kumra et al., 2004), similar to what has been reported in adult patients with schizophrenia (Ardekani et al., 2003; Buchsbaum et al., 1998; Hubl et al., 2004; Kubicki et al., 2003; Lim et al., 1999; Sun et al., 2003; Szeszko et al., in press; Wang et al., 2004). Based on these data, we have hypothesized that delays in the maturation of the frontal lobe and its connecting pathways may play an important role in the pathophysiology of early-onset schizophrenia (EOS; i.e., onset of psychotic symptoms by age 18).

To date, the results from DTI studies have not been entirely consistent, perhaps reflecting small sample size (e.g., Steel et al., 2001) and/or differences in methods of data acquisition and analysis across studies (i.e., region of interest versus voxelwise analysis methods). For example, using DTI, Foong et al. (2000) found differences in FA in the corpus callosum using a region of interest approach but failed to confirm these findings in a subsequent voxelwise analysis (Foong et al., 2002).

Most patients with schizophrenia experience the onset of their disorder during adolescence and young adulthood (Hafner, 2004). In this study, we report a voxelwise analysis of DTI data in adolescents with EOS. The working model for this study is that, in schizophrenia, oligodendroglial dysfunction, with subsequent abnormalities in myelin maintenance and repair in frontal white matter, contributes to the schizophrenic syndrome (Davis et al., 2003). Based on this model, we hypothesized that patients would demonstrate lower white matter FA levels compared with healthy volunteers in frontal lobe white matter.

METHOD

Subjects

The recruitment and diagnostic procedures for this study have been described in detail elsewhere (Kumra et al., 2004). Twenty-six patients with EOS and 34 healthy comparison subjects were included in this analysis. There was no overlap in patients included in this report and our previous DTI study (Kumra et al., 2004). Thus, this study is an attempt to replicate our previous finding that schizophrenia is associated with a disruption in frontal white matter integrity using a more sophisticated analysis methodology that is more sensitive to subtle alterations in white matter microstructure. The demographic characteristics of the subjects are presented in Table 1.

The children and adolescents with schizophrenia were recruited from inpatient and outpatient units. Diagnoses were based on the Schedule for Affective Disorders and Schizophrenia for School Age Children—Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997). The Wide Range Achievement Test, Reading subtest, was used to estimate premorbid IQ (Wilkinson, 1993). All patients met criteria for schizophrenia ($n = 17$), schizoaffective disorder ($n = 8$), or schizophreniform disorder ($n = 1$). Median age at onset of psychotic symptoms was 12.0 years (range 6–17) and the median duration of illness at the time of MRI scan was 2.0 years (range 0.1–7). The median number of hospitalizations before MRI scans was one; thus, the majority of subjects were being scanned during their first psychiatric hospitalization. All but three patients were being treated with antipsychotic medication at the time of the scan. The median length of antipsychotic treatment was 12 months.

Healthy adolescent volunteers were recruited through advertisements and fliers distributed in libraries, doctors' offices, and community centers by a research coordinator. Comparison subjects were matched to patients based on age, gender, parental socioeconomic status, and ethnicity. Exclusion criteria for all subjects included a documented history of mental retardation, a history of substance abuse/dependence, and any history of neurological disorder that could produce psychotic-like symptoms.

The Institutional Review Board at the North Shore–Long Island Jewish Health System granted approval for this study. After the study was explained to subjects and their parents, written assent and informed consent were obtained.

Antipsychotic Medication History for Patients

Standing medications received by patients at time of testing are summarized in Table 1. Information regarding past antipsychotic treatment trials before the MRI scan was obtained from the medical chart, contact with previous treatment providers, and parent interview, and drug doses were converted into chlorpromazine equivalents (Hales and Yudofsky 2003; Woods 2003) to estimate previous exposure to antipsychotic medications.

MRI Procedures

The image acquisition (Ashtari et al., 2005) and processing methods (Ardekani et al., 2003; Szeszko et al., 2005) have been described in detail elsewhere. In brief, MRI examinations were conducted at the Long Island Jewish Medical Center on a 1.5-T GE Neuro Vascular Interactive (NV/i) system. This unit is equipped with high strength (50 mT/m) and a high-speed gradient system (slew rate = 150 T/m/s). An MR physicist (M.A.) acquired all of the scan data.

TABLE 1
Sample Characteristics

	Patients With Schizophrenia (<i>n</i> = 26)	Healthy Volunteers (<i>n</i> = 34)	<i>df</i>	Test Statistic	<i>p</i> Value
Age (yr)	15.2 (2.2)	15.4 (2.8)	58	<i>t</i> = -0.39	.70
Sex (male/female)	14/12	20/14		$\chi^2 = 0.46$.50 ^a
No. dextral, no. nondextral	24/2	33/1			.57 ^b
Socioeconomic status ^c					
High	7	18			.03 ^b
Low	19	13			
Ethnic distribution					
White	12	14			
Nonwhite	14	20		$\chi^2 = 0.15$.78 ^a
WRAT reading scores ^d	93.9 (19.1)	107.9 (6.1)	42	<i>t</i> = -3.23	.002*
No. of patients receiving antipsychotics on date of scan ^e					
Olanzapine	7				
Quetiapine	3				
Risperidone	9				
Clozapine	2				
Ziprasidone	3				
Aripiprazole	3				
Haloperidol	2				
None	3				

Note: SD in parentheses; WRAT = wide range achievement test.

^a Chi-square test.

^b Fisher exact test.

^c Hollingshead scale (1975); high = levels 1, 2, 3 and low = levels 4 and 5.

^d Wide range achievement test III reading subtest (Wilkinson, 1993).

^e Six subjects were on multiple antipsychotics at the time of MRI scan.

**p* ≤ .01.

Routine clinical scans (T_1 , T_2 , and FLAIR) were acquired and reviewed by a neuroradiologist to rule out any pathological abnormalities. A fast spin-echo double-echo sequence was acquired for segmentation and a three-dimensional spoiled gradient recalled (SPGR) sequence with inversion prep pulse was also obtained. To clearly visualize the AC-PC landmarks, additional sagittal slices were acquired. All sequences, with the exception of the SPGR, were obtained in an orientation parallel to the AC-PC plane. A coronal orientation was used for the acquisition of the SPGR.

The diffusion tensor sequence used in this protocol included a total of 25 diffusion gradient directions for acquisition of 23 slices throughout the whole brain. Diffusion gradients were applied along noncollinear directions, with $b = 1,000$ s/mm² and NEX = 2, and one volume was acquired without diffusion weighting ($b = 0$; NEX = 2). There was no evidence of high frequency or Nyquist ghost as determined from a quantitative in-house quality control program and from visual inspection of the images at the time of scanning. An FA map was computed from the 26 DTI volumes for each subject after estimation of the eigenvalues of the diffusion tensor matrix for each voxel using previously described methods (Basser, 1995; Pierpaoli and Basser, 1996). FA levels ordinarily range from 0

(no directional dependence of diffusion coefficients) to 1 (diffusion along a single direction); however, for this analysis, these values were multiplied by 1,000 for ease of interpretation and efficient data storage.

Image Processing

Reliable inter- and intrasubject registration is an essential ingredient of a successful voxelwise analysis (Ashtari et al., 2005; Ardekani et al., 2005). The intrasubject image processing consisted of four essential steps: (1) skull stripping, which separates brain from nonbrain tissue; (2) distortion correction, which corrects for echo planar distortion; (3) rigid body registration, which corrects for any head motion during the scan and registers two differently acquired images to provide comparable images in the same orientation and dimension; (4) image segmentation, which classifies brain regions as white matter, gray matter, or cerebrospinal fluid. An average white matter mask was then used to exclude low signal-to-noise, cerebrospinal fluid, and gray matter voxels. Thus, only voxels classified as being in white matter were included in the FA analysis.

Intersubject registration was performed to coregister all images into common Talairach space. The subject with median brain

volume was selected as the template image and was then transformed into Talairach space. Subsequently, all other subjects were registered to this template. Intra- and intersubject registration produce transformation matrices or warp fields that are specific to each subject. One resultant transformation was then applied to the original FA map by a single interpolation operation. Thus, we obtained 60 FA maps (26 patients and 34 healthy volunteers) of matrix size $161 \times 191 \times 151$ and voxel size $1 \times 1 \times 1 \text{ mm}^3$ in common Talairach space.

Statistical Analyses

Group differences in demographic variables were examined using independent group *t* tests and/or Fisher exact test or χ^2 tests, as appropriate. Pearson or Spearman correlation coefficients were used based on the underlying distribution of the data.

To control for potential partial volume effects in our analysis, FA values for each voxel were adjusted for white matter intensity through linear regression. Two-sample *t* tests were performed at each voxel on the corrected FA values between patients and controls. For comparability with a previous study in adults with a first episode of schizophrenia at our center using the same MRI scanner and image analysis procedures (Szeszko et al., 2005), cluster of voxels that had a *t* statistic >3.47 ($p < .001$; uncorrected two tailed) and with an extent threshold of ≥ 100 contiguous voxels were considered significant. As a secondary analysis, we applied an extent threshold of 200 contiguous voxels criterion at $t = 2.00$ ($p < .05$, uncorrected two tailed) in the areas that we initially identified as being significant to examine the region(s) in more detail (Baudewig et al., 2003). Data were then examined for outliers, extreme values, and the normality of the distribution.

Given the known associations between intelligence and parental socioeconomic status and brain volumes in healthy children (Wilke et al., 2003), a general linear regression was used to test whether there was an association among reading scores (Wilkinson, 1993), a measure of premorbid intelligence in adolescents with schizophrenia (Kumra et al., 2000), and parental socioeconomic status with FA levels in the anterior cingulate region in healthy children. In this model, FA values in the anterior cingulate region were entered as the dependent variable and reading scores and parental socioeconomic status were entered together as the independent variables. To further examine the question of whether the differences in brain structure seen in adolescents with schizophrenia could be explained by differences in intelligence, analysis of covariance was used to assess group differences in white matter microstructure in the anterior cingulate region, adjusting for differences in reading scores (Wilkinson, 1993) and parental socioeconomic status (Hollingshead, 1975).

To examine the effect of medication status and illness on FA levels in the anterior cingulate region, we conducted correlative analyses between FA levels and the number of previous antipsychotic trials, length of antipsychotic treatment, duration of psychosis, medication dose at time of scan, and total lifetime chlorpromazine equivalents. Chlorpromazine equivalents for each antipsychotic trial were calculated using published tables (Hales and Yudofsky, 2003; Woods, 2003).

To examine the relationship between FA levels in the left anterior cingulate region and age, multiple linear regression was used. We created a model in which FA levels in the anterior cingulate region was the dependent variable and age, group, and age-by-group interaction factor and socioeconomic status were the predictor variables.

RESULTS

Patients and healthy comparison subjects did not differ significantly in distributions of age, gender, ethnic distribution, or handedness (Table 1), but healthy volunteers had higher reading scores and higher parental socioeconomic status. Because of these differences, we included both reading scores (Wilkinson, 1993) and socioeconomic status as covariates in our analyses.

We obtained excellent intersubject registrations of the FA maps among subjects (Fig. 1). The cluster of significant voxels superimposed on the average normalized SPGR image of all 60 subjects is illustrated in Figure 1. Significantly decreased FA in patients compared with healthy volunteers was observed in the subcortical white matter in the left anterior cingulate region. When the threshold in this region was decreased to $p < .05$, this cluster of reduced FA extended into the left anterior cingulate gyrus (column 2). The Talairach coordinates for the centroid of this region were ($x = -17, y = 27, z = 13$). There were no areas of significantly higher FA in patients as compared with healthy volunteers.

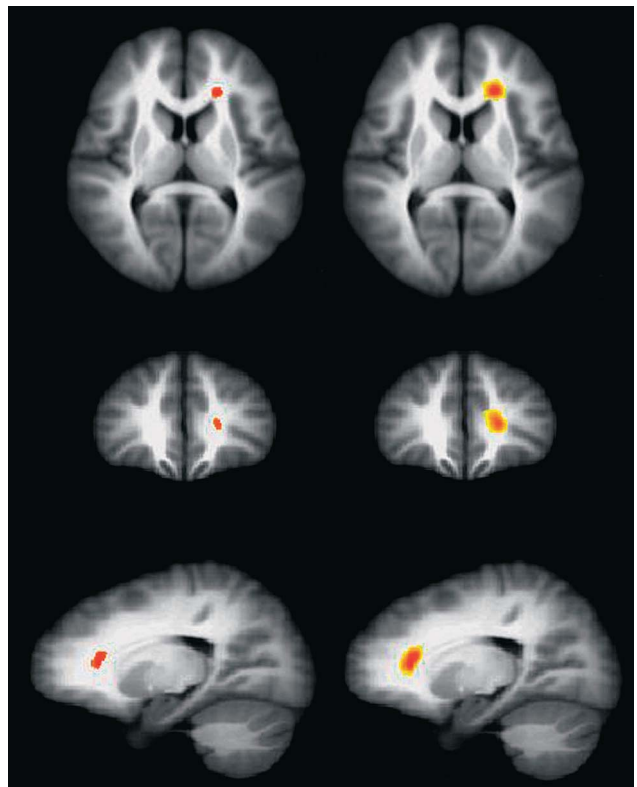


Fig. 1 Regions in patients in which FA was significantly lower than in healthy controls. Columns represent analyses of 100 voxels, $p < .001$ (left) and 200 voxels, $p < .05$ (right).

The subset of adolescents with a diagnosis of schizophrenia ($n = 17$, mean FA = 224, SD = 28.3) were noted to have lower FA values in the left anterior cingulate region at a trend level ($t = 2.0$, $df = 24$, $p = .06$) as compared with the remaining adolescents with a diagnosis of schizoaffective disorder or schizophreniform disorder ($n = 7$, mean FA = 254, SD = 48).

Medication Effects

Fractional anisotropy in the left anterior cingulate region in patients did not correlate significantly with medication use including total number of antipsychotic trials (Spearman $\rho = -0.12$, $p = .56$), chlorpromazine equivalents of antipsychotic medication at the time of scan (Spearman $\rho = -0.07$, $n = 26$, $p = .74$), duration of antipsychotic treatment (Spearman $\rho = -0.11$, $n = 26$, $p = .59$), lifetime chlorpromazine equivalents (Spearman $\rho = -0.01$, $n = 26$, $p = .96$) and/or illness-related factors, for example, duration of psychosis (Spearman $\rho = 0.19$, $n = 26$, $p = .35$) or number of hospitalizations (Spearman $\rho = 0.16$, $n = 26$, $p = .43$). Furthermore, when data for individuals who had significant previous exposure to antipsychotic medication (>12 weeks) were excluded, there was still a significant effect for group status ($F_{1,39} = 11.9$, $p < .0014$) after adjusting for differences in age and gender. Thus, medication use or illness-related factors did not seem to influence findings in any discernible way.

Effect of Premorbid Intelligence and Parental Socioeconomic Status

For healthy controls, we created a model in which FA levels in the anterior cingulate region were the dependent measure and reading scores and parental socioeconomic status were the predictor variables. The overall model in healthy controls was poor ($F_{2,23} = 1.48$, $p = .25$, adjusted $R^2 = 0.04$), and FA levels were not significantly predicted by reading scores ($p < .48$) or socioeconomic status ($p < .19$).

To further assess whether the findings of this study were related to differences in intellectual functioning rather than disease, we used analysis of covariance to assess for group differences in FA levels with reading scores and parental socioeconomic status as covariates. Based on visual inspection of the data and the test of normality, it was determined that data transformation was needed. The reciprocal transformation was applied.

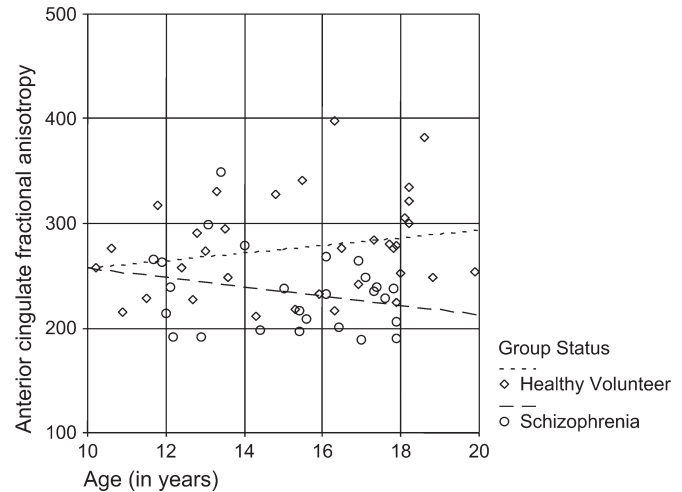


Fig. 2 Anterior cingulate FA ($\times 1000$) compared with age: patients versus healthy controls.

The main effect of group remained significant ($F_{1,45} = 21.4$, $p < .001$), and the effects of reading scores ($p < .74$) and parental socioeconomic status ($p < .24$) were not found to be statistically significant.

Effect of Age and Group Status

We examined the relationship between age and FA by group based on the hypothesis that there is ongoing development of afferent amygdalar fiber projections to the anterior cingulate cortex during adolescence (Fig. 2). A multiple linear regression was carried out to predict FA values in the white matter of the left anterior cingulate region where group status, age, a group-by-age interaction factor, and parental socioeconomic status were entered together. This model was based on the assumption that there may be a differential effect of age on FA measures depending on subject group. The overall model was significant ($F_{4,56} = 8.27$, $p < .001$, adjusted $R^2 = 0.34$). FA levels were predicted by age ($p < .04$) and the age-by-group interaction factor ($p < .045$) but not by group ($p < .19$) or socioeconomic status ($p < .10$; Table 2).

In healthy comparison subjects, there was a subtle nonsignificant increase in FA values with age (Spearman $\rho = 0.23$, $n = 34$, $p = .19$), whereas in adolescents with schizophrenia, there was a subtle decrease in FA values with age (Spearman $\rho = -.24$, $n = 26$, $p = .25$).

DISCUSSION

This study investigated the structural integrity of brain white matter using DTI in adolescents with

TABLE 2

Multiple Linear Regression of Anterior Cingulate Fractional Anisotropy Controlling for Group Status, Parental Socioeconomic Status, Age, and Age-by-Group Status Interaction

Variable	B	SE	<i>t</i>	<i>p</i>
Group status	0.00081	0.00061	1.34	.19
SES	0.00016	0.00010	1.66	.103
Age	0.00014	0.00007	2.12	.038
Age-by-group interaction	-0.00008	0.00004	-2.05	.045

Note: Overall model $F_{4,52} = 8.27$, adjusted $R^2 = 0.34$. SES = socioeconomic status.

EOS and age- and gender-matched healthy controls. Using a rigorous voxelwise method and after adjusting for differences in parental socioeconomic status and pre-morbid intellectual ability, we found reductions in FA in adolescents with EOS relative to healthy comparison subjects in the left anterior cingulate region. These data are compatible with a disruption in the orientation or organization of fiber bundles in the anterior cingulate region, as previously reported by four other groups using different methods in adult patients with schizophrenia (Hubl et al., 2004; Kubicki et al., 2003; Sun et al., 2003; Wang et al., 2004). It has been suggested that the pathophysiology of schizophrenia may involve significant changes at the level of interconnections between the anterior cingulate cortex and other parts of the neuronal network (Benes, 2000), for example, the amygdala (Benes, 2003). As summarized by Kubicki et al. (2003), functional, metabolic, anatomical, and histopathological studies have provided strong evidence regarding the relevance of the anterior cingulate cortex in the pathophysiology of schizophrenia. Lesions of the anterior cingulate cortex have been associated with apathy and lack of drive (Bush et al., 2000), which are characteristic early negative symptoms in adolescents with schizophrenia.

Although the results of this study support previously reported findings of anterior cingulate abnormalities in adult patients with schizophrenia using DTI (Hubl et al., 2004; Kubicki et al., 2003; Sun et al., 2003; Wang et al., 2004), there has been a lack of agreement across published studies to date regarding the regional localization of white matter abnormalities in schizophrenia (Burns et al., 2003). The data reported herein are also broadly consistent with our previous pilot study of 21 subjects (12 patients with EOS, 9 healthy controls

[Kumra et al., 2004]), which revealed an overall reduction in FA in the frontal white matter (Cohen's effect size = 0.51) but only a small effect size difference (e.g., Cohen's effect size = 0.33) in the left anterior cingulate region using a manual region of interest placement. The use of region-of-interest methodology may not be the best technique, however, for examining the structural integrity of frontal white matter given the variability of the directionality of fiber tracts in this region (Wakana et al., 2004). Furthermore, it should be noted that in our present study, we used a 25-direction DTI imaging procedure to generate FA values and a distortion correction program as opposed to our previous study, in which we used a six-direction DTI sequence. It has been shown that at least 20 unique sampling orientations are necessary for a robust estimation of anisotropy (Papadakis et al., 2000); hence, this may account for the discrepancy in findings in the present study versus our previous DTI studies (Kumra et al., 2004; Szeszko et al., 2005).

The time period of brain maturation between adolescence and young adulthood represents a critical period of ongoing maturation of white matter tracts and provides a unique opportunity to examine regional and disease-specific abnormal brain development in the disorder (Benes et al., 1994). It is also when most patients experience the onset of a schizophrenic illness (Hafner, 2004). With respect to the relationship of FA levels in the left anterior cingulate region and age, we found that a group-by-age interaction factor predicted DTI measures in subjects. As seen in Figure 2, we observed a differential relationship between age and FA in patients relative to healthy comparison subjects. In healthy comparison subjects, the developmental trajectory suggested a subtle increase in FA levels in the anterior cingulate region during adolescence. In contrast, we did not find a statistically significant relationship between duration of psychosis and FA. These data would suggest that the decreases in white matter FA in adolescents with schizophrenia may reflect a developmental effect (Schmithorst et al., 2002) rather than a secondary effect of the disease process. These data are also potentially compatible with animal data that suggest throughout postnatal development, extending into the adolescent years, there is ongoing development of amygdalar fibers that project to the anterior cingulate cortex (Benes, 2003). This development may increase the ability of the amygdalar fibers to regulate emotional and attentional responses in the

cingulate cortex (Benes, 2003). Alternatively, it is also theoretically possible that excessive synaptic pruning in the left anterior cingulate area in this group of adolescents with schizophrenia could result in secondary changes in the structural integrity of the underlying subcortical white matter.

Because the cingulate region is a limbic brain area implicated in the pathophysiology of schizophrenia, it has been suggested that any change in the amygdalocingulate pathway during the late adolescent years may influence the development of schizophrenic symptoms (Benes, 2003). In adolescents with schizophrenia, we observed a slight decrease in FA levels during the same time period in the anterior cingulate pathway that would potentially include fibers in the amygdalocingulate pathway. The mechanism underlying the reduction in FA levels in patients with schizophrenia remains unknown. The reduction in FA levels in the left anterior cingulate cluster in patients with EOS could reflect a decreased number or density of axons, decreased degree of myelination of the axons, decreased coherence of the fiber tracts, and/or increased number or density of tracts perpendicular to white matter fiber tracts (Davis et al., 2003; Kubicki et al., 2003).

Limitations

We found a differential relationship between age and FA in patients relative to healthy comparison subjects. Because of the cross-sectional nature of this analysis, we do not know whether this finding is related to the diagnosis per se or perhaps to treatment variables or the factors secondary to this illness such as differences in environmental stimulation. We did not find a relationship between FA levels and duration of psychosis and/or number of hospitalizations that we would have expected to see if these findings were largely driven by factors secondary to illness.

To date, there are no available data examining the effect of antipsychotic medications on diffusion measures in either healthy people or animals. There is some evidence suggesting that antipsychotic medications may affect DTI measures in patients with schizophrenia, and most of the patients included in this analysis were being treated with antipsychotic medication. Although we cannot discount the possibility that medications contributed to our findings, our group (Szeszko et al., 2005) and others (Bagary et al., 2003) have reported

alterations of white matter fiber tracts in adult patients with a first episode of schizophrenia and minimal previous exposure to antipsychotic medications in frontal regions close to our findings. Second, although data from nonhuman primates suggest that glial proliferation is associated with chronic antipsychotic drug exposure with typical and atypical antipsychotic drugs (Selemon et al., 1999), a postmortem study reported glial cell loss, not proliferation, in the anterior cingulate cortex in human subjects with schizophrenia (Stark et al., 2004). Third, although in some studies, higher FA was significantly correlated with a higher dose of neuroleptics in patients with schizophrenia in the left middle cerebral peduncle (Okugawa et al., 2003) and left frontal white matter (Minami et al., 2003), we did not find any significant/suggestive relationships between FA levels in the anterior cingulate and several parameters related to antipsychotic exposure at the time of MRI.

The cross-sectional design of this study precludes a definitive assessment of developmental effects on white matter microstructure in adolescents with schizophrenia. It is possible that time-of-measurement effects or cohort effects (Kraemer et al., 2000) could potentially confound the age-related findings. Thus, the findings of this study will need to be replicated in a larger sample using a longitudinal design.

Clinical Implications

Although the present findings contribute to the growing body of evidence regarding white matter pathology in schizophrenia, they do not directly influence the diagnosis and treatment of the disorder at this time. Understanding the significance of white matter pathology in the anterior cingulate region in adolescents with schizophrenia will help to improve our understanding of the phenotype and point to new intervention strategies for the disorder. Should future studies confirm the presence of white matter abnormalities in the anterior cingulate in adolescents with schizophrenia early in the course of illness before medication exposure, DTI could ultimately be used with other clinical and neurocognitive correlates of EOS to create a profile of risk factors that could help identify adolescents who may be at risk for developing the illness. Accurate identification of adolescents in the earliest phase of the illness would open up the possibility of intervening earlier in the disease process,

which could potentially lead to prevention of the disorder or amelioration of the disability associated with it.

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