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Differential fractional anisotropy abnormalities in adolescents with ADHD or schizophrenia

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Abstract

Schizophrenia and ADHD are associated with similar deficits in working memory, attention, and inhibition. Both disorders also involve abnormalities of white matter integrity, possibly reflecting neural communication disruptions. There are likely some regional white matter abnormalities that underlie the common cognitive impairment, though also some regional abnormalities unique to each disorder. We used diffusion tensor imaging (DTI) to compare white matter integrity, as indicated by fractional anisotropy (FA), in adolescents with schizophrenia (*n*=15) or ADHD (*n*=14) and healthy controls (*n*=26). Schizophrenia patients had uniquely low FA, relative to the other two groups, in bilateral cerebral peduncles, anterior and posterior corpus callosum, right anterior corona radiata, and right superior longitudinal fasciculus. ADHD patients had uniquely high FA in left inferior and right superior frontal regions. Both clinical groups had lower FA than controls in left posterior fornix. The two disorders generally demonstrated distinct patterns of abnormal connectivity suggesting that common cognitive and behavioral deficits derive from distinct sources, though the posterior fornix may be involved in both disorders. Schizophrenia was associated with abnormally low FA in widespread circuitry indicative of general connectivity disruptions, whereas ADHD was associated with abnormally *high* FA in frontal networks that may indicate impaired branching of fibers.

Keywords

diffusion tensor imaging; white matter; cognition; connectivity

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1. Introduction

Schizophrenia and Attention-Deficit/Hyperactivity Disorder (ADHD) are associated with similar cognitive and behavioral deficits, such as impairments in working memory, sustained attention, and response inhibition (Oie and Rund, 1999; Barr, 2001). There is also emerging neuroimaging evidence that disruptions of neural communication are involved in both ADHD (Durston, 2003; Casey et al., 2007; Makris et al., 2007; Castellanos et al., 2008) and schizophrenia (Friston and Frith, 1995; McGlashan and Hoffman, 2000; Ford et al., 2002; Douaud et al., 2007) and that measures of brain connectivity are related to cognitive skills in these groups (Nestor et al., 2004; Casey et al., 2007; Schlosser et al., 2007). It is plausible that some of these neural communication disruptions are associated with the shared cognitive and behavioral impairments and are therefore common to both disorders. However, it is also likely that there are regional connectivity abnormalities specific to each disorder that are associated with unique features, such as clinical symptoms.

Adolescence is a particularly critical time period for investigations of white matter due to the surge in myelination that occurs during this period of development (Giedd et al., 1999). Adolescence is also a time of emerging psychotic symptoms in schizophrenia and declining hyperactive/impulsive symptoms of ADHD, which may be related to maturation of frontal and frontostriatal circuitry (Durston, 2003; Woo and Crowell, 2005; Liston et al., 2006). Therefore, we have chosen to focus on adolescence to better characterize white matter abnormalities in these disorders during this critical time.

Previous studies of structural connectivity in clinical populations have used diffusion tensor imaging (DTI), and specifically fractional anisotropy (FA), to assess white matter integrity. In general, areas of densely packed, well-myelinated fibers that run in a consistent direction (i.e. “healthy” white matter) have higher FA than areas in which the fibers are sparse, poorly myelinated, or divergent (Beaulieu, 2002). Early DTI studies of adolescents with schizophrenia found lower FA in bilateral frontal regions (Kumra et al., 2004), left anterior cingulate (Kumra et al., 2005), and left posterior hippocampus (White et al., 2007). Two recent studies using white matter-specific registration, which provides better alignment of major tracts, have reported lower FA in adolescents (ages 13–19 years) with schizophrenia compared to healthy adolescents either limited to bilateral parietal and cerebellar regions (Kyriakopoulos et al., 2008) or encompassing several regions, including corticospinal/corticopontine tracts, superior thalamic radiations, left optic radiations, corpus callosum, left arcuate fasciculus, and the brainstem (Douaud et al., 2007). These results suggest that regions of abnormal FA reported in adolescents with schizophrenia are widespread, though they are similar to those reported in adult schizophrenia populations (White et al., 2008).

To our knowledge, there have only been three studies comparing FA between individuals with a primary diagnosis of ADHD and healthy controls. In children (ages 7–11 years), ADHD was associated with lower FA in right premotor, right striatum, right cerebral peduncle, left cerebellar peduncle and cerebellum, and left parieto-occipital regions (Ashtari et al., 2005). In somewhat older children, ADHD was associated with lower FA in corticospinal and superior longitudinal fasciculus regions of interest (Hamilton et al., 2008). In adults (ages 37–46 years) who had ADHD as children, lower FA relative to control adults was reported in right cingulum and superior longitudinal fasciculus regions of interest, which are believed to underlie the attention and executive function abnormalities in ADHD (Makris et al., 2007). Comparison of these regions to those reported in adolescent schizophrenia populations reveals potentially common abnormalities in parietal tracts, the cerebral peduncles, and cerebellum. In contrast, abnormal FA in the corpus callosum, anterior cingulate, and hippocampal regions may be specific to schizophrenia.

Because adolescence is such a critical period in white matter development and in the clinical course of both ADHD and schizophrenia, the paucity of information about white matter integrity in adolescents with ADHD or schizophrenia, and specifically the lack of studies directly comparing these groups, limits our understanding of the role connectivity disruptions play in the cognitive, behavioral, and clinical features of these disorders. One goal of the current study was to determine whether there are areas in which schizophrenia and ADHD patients demonstrate *common* FA abnormalities, as these areas may reflect common neural communication disruptions that underlie cognitive or behavioral deficits. Based on previous studies, we expected these to be located in the brainstem and parietal regions. The other goal was to identify areas in which one of the clinical groups demonstrated *unique* FA abnormalities, which may be associated with cognitive or clinical features unique to that group. We expected schizophrenia to be associated with abnormal FA in the corpus callosum and limbic regions and ADHD to be associated with abnormal FA in frontal and frontostriatal tracts.

2. Methods

2.1 Participants

Participants consisted of 55 children and adolescents (age range 10–20 years) with either youth-onset schizophrenia (*n*=15), ADHD (*n*=14), or healthy volunteers (*n*=26). Table 1 summarizes demographic and clinical characteristics of these groups. In addition to the neuroimaging protocol described in this report, most of these participants were also administered computerized cognitive tasks. Results of these analyses are reported in other manuscripts (11 healthy and 9 ADHD participants were included in Karatekin, 2006; 20 healthy participants were included in Karatekin et al., 2007; and 14 healthy and 11 psychosis participants were included in White et al., 2007).

Participants with schizophrenia were recruited from child and adolescent psychiatric inpatient and outpatient clinics at the University of Minnesota, mental health professionals in the community, and flyers distributed at regional mental health conferences. ADHD participants were recruited from advertisements in the local community or from support groups for ADHD. Healthy volunteers were recruited through flyers posted in the community, through schools, via word of mouth from others who participated, or via advertisements in local newspapers.

Potential participants were excluded if they were not fluent in English, were color blind, had been premature by more than four weeks, had a history of significant neurological conditions, or had an IQ lower than 70. Potential participants were excluded from the ADHD and control groups if they had been adopted or had first-degree biological relatives with schizophrenia. Potential participants were excluded from the ADHD group if they were taking psychoactive medications other than psychostimulants, their parents were not willing to discontinue psychostimulants for cognitive testing, they had been diagnosed with or suspected of having a pervasive developmental disorder, or had never met criteria for the Combined subtype. Potential controls were excluded if they had ever taken psychoactive medications, had been diagnosed with a major psychiatric disorder or met criteria for a current disorder, had attention problems for which they had sought help, or had first-degree biological relatives with ADHD or schizophrenia. All participants were screened for the presence of implanted metal, medical devices, and other contraindications to MRI before entry into the study, and this screening was repeated immediately before the scan.

Diagnoses were made using DSM-IV criteria (American Psychiatric Association, 1994) and were based on semi-structured interviews conducted separately with participants and parents (Kiddie-Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version; Kaufman et al., 1996). Diagnoses of participants in the ADHD group were also based on developmental and medical history questionnaires completed by the parents, and ratings of

general behavioral symptoms completed by the parents and teachers [Child Behavior Checklist (CBCL) and Achenbach Teacher Report Form (Achenbach, 1991a; Achenbach, 1991b; Achenbach and Rescorla, 2001); Swanson, Nolan, and Pelham (SNAP-IV) Teacher and Parent Rating Scale (Swanson, 1992)] to ensure that the diagnoses were based on reports from multiple informants familiar with the participants' behavior in different settings. All ADHD participants had a history of treatment with stimulant medication, though three had been unmedicated for at least 2 weeks at the time of the scan.

All individuals in the ADHD group met criteria for the Combined subtype at the time of participation except one participant who met criteria for the Inattentive subtype but who met full criteria for the Combined type in the past. Of the 15 individuals in the psychosis group, 12 had a primary diagnosis of schizophrenia of the paranoid (n=5), undifferentiated (n=5), or disorganized (n=2) subtypes. Two participants were given a diagnosis of schizoaffective disorder, and one was given a diagnosis of psychosis NOS but later converted to schizophrenia. The mean age of onset for the 11 schizophrenia patients for whom this information was available was 12.5 years (SD=2.16).

To estimate general intellectual ability, participants were administered the Vocabulary and Block Design subtests from the Wechsler Intelligence Scale, 3rd ed. (WISC-III; Wechsler, 1991), the WISC-IV (Wechsler, 2003), or the Wechsler Adult Intelligence Scale, 3rd ed. (Wechsler, 1997). IQs are reported in Table 1.

Families were provided with monetary compensation for their participation. Families with children in the clinical groups, and some families of controls, were provided with diagnostic reports. The study was approved by the University of Minnesota Institutional Review Board, and after complete description of the study to participants and their parents, written informed consent and assent were obtained.

2.2 Imaging data collection

Images were acquired on a 3T Siemens Trio (Erlangen, Germany) scanner using a standard birdcage coil. Head movement was minimized by placing cushions around the participant's head. A 3-plane localizer was used for orientation and prescription of 3D scans. DTI data were collected with a single-shot spin echo planar diffusion sequence of 64 axial slices covering the entire cerebrum and as much of the cerebellum as possible. Thirteen images were collected at each slice location, twelve of which had a diffusion gradient applied in one of 12 non-collinear directions with b=1000s/mm^2 and one had no diffusion gradient (b=0). Additional acquisition parameters for the diffusion sequence were TR/TE=11000/104msec, 128×128 matrix, 256mm FOV, 2mm thickness, 0 skip, GRAPPA=2. Acquisition voxel size was 2×2×2 mm^3.

2.3 Image processing

The diffusion-weighted images were corrected for eddy current distortions, and fractional anisotropy (FA) values were computed at each brain voxel using FSL software (Smith et al., 2004). The FA image from a control participant of median age (15 years) who had a full set of 64 images with good image quality was registered to the MNI (Montreal Neurologic Institute) standard reference brain with a 12-parameter affine transformation to create a template to which all other images were registered using a nonlinear algorithm (Rueckert et al., 1999). Following registration, all images were smoothed with a 4mm full-width-at-half-maximum Gaussian kernel to reduce measurement noise (Ashburner et al, 2000; White et al., 2001; Jones et al., 2005).

2.4 Statistical analysis

Demographic measures were compared across groups with one-way analyses of variance (ANOVAs) except for gender composition, which was compared with a chi-square test. Significant effects of ANOVAs were followed up using Tukey post-hoc tests.

A one-way ANOVA was conducted on a voxelwise basis to test for the effect of group after covarying for age. Only voxels that had FA > 0.25 in all subjects were included to ensure that analyses were conducted only at locations that were likely to include white matter in all subjects. Clusters were identified in which at least one voxel was significant at $P<0.005$, all voxels were significant at $P<0.05$, and the volume was greater than $200mm^3$. Regions were labeled according to a standard white matter atlas (Mori et al., 2005). To better examine how the groups differed at each significant location, the average value across all voxels within each cluster was calculated for each subject, and these cluster averages were imported into statistical software to test for group effects using one-way ANOVA. Tukey post-hoc tests were used to characterize significant group effects.

3. Results

3.1 Demographic results

As can be seen in Table 1, groups did not differ significantly on age. Although the ADHD group tended to have fewer females, differences in gender composition across groups did not reach statistical significance. The psychosis group had lower estimated IQ and parental SES than the ADHD and control groups, who did not differ from each other.

3.2 Imaging results

Table 2 summarizes the regions in which the groups differed on FA according to the initial voxelwise ANOVA and post hoc comparisons. Briefly, the schizophrenia patients had lower FA than the other two groups in the bilateral cerebral peduncles, genu and splenium of the corpus callosum, right anterior corona radiata, and right superior longitudinal fasciculus. The ADHD group demonstrated higher FA than the other two groups in left inferior and right superior prefrontal regions, which were considered to be in the anterior corona radiata. Both clinical groups had lower FA than the control group in the left posterior fornix. In the remaining clusters (left anterior limb of the internal capsule, left retrolenticular part of the internal capsule, and forceps minor), one group failed to differ from either of the other two.

4. Discussion

In a study of adolescents with ADHD or schizophrenia, we used DTI to identify areas of white matter integrity abnormalities that were common to both disorders or unique to one disorder. The primary strength of this study is the direct comparison of two clinical syndromes, which provides information about the specificity of effects. An initial voxelwise ANOVA identified 12 areas in which FA differed among the three groups. According to post-hoc tests, six of these were regions in which schizophrenia patients had uniquely low FA, two were regions in which ADHD patients had uniquely high FA, and one was a region of abnormally low FA common to both clinical groups. In the remaining areas, one group failed to differ from the other two, meaning any difference in FA was neither unique to one clinical group nor common to both.

Despite the similarities of cognitive impairment between ADHD and schizophrenia and emerging evidence that these impairments involve disruptions of communication among brain regions, only one cluster was identified in which both clinical groups had lower FA than controls. That cluster was located in the left posterior fornix, which is similar to the area of abnormally low FA identified by our group in the same set of adolescent schizophrenia patients

compared to healthy adolescents (White et al., 2007). In that earlier report, we suggested that the observed effect could be a generalized finding associated with lower IQ; however, the observation of lower FA in ADHD subjects, whose average IQ was almost identical to that of the controls, reduces this possibility. Furthermore, the detection of this effect in both studies of these patients, despite using a higher quality non-linear registration and different analysis techniques, suggests that the finding is not due to an artifact or anomaly of image processing. The implicated region likely contains output fibers of the hippocampus in which disrupted communication may have widespread effects on cognitive processing through connections with prefrontal regions (Goldman-Rakic et al., 1984).

Areas of abnormal FA that were unique to schizophrenia are similar to those reported in previous studies of adolescent-onset schizophrenia using the same registration technique (Douaud et al., 2007; Kyriakopoulos et al., 2008). Lower FA in the cerebral peduncles, which includes the corticospinal/corticopontine tracts, may represent disruption of sensorimotor circuitry (Douaud et al., 2007) and further implicates dysfunction of the cortico-cerebellar-thalamo-cortical circuit, which has been suggested to be a primary trait of schizophrenia (Andreasen et al., 1996). The areas of abnormally low FA in the anterior and posterior portions of the corpus callosum are indicative of impaired interhemispheric communication in frontal and parietal regions, which is consistent with behavioral and electrophysiological evidence of increased functional lateralization in schizophrenia (Endrass et al., 2002). Abnormally low FA in areas identified as the right anterior corona radiata and superior longitudinal fasciculus further implicates disrupted cortical communication in frontal and parietal tracts. Together, these regions implicate a general deficit in intra- and interhemispheric communication among frontal, parietal, and brainstem regions. As mentioned in earlier work from our group (White et al., 2007), the possibility that these deficits are related to lower IQ or parental SES, rather than the disorder itself, cannot be ruled out with the current data.

Areas of abnormal FA that were unique to ADHD were remarkable in that they represented *higher* FA relative to the other groups, which has generally been interpreted as consistent with healthier white matter, including fibers that are more numerous, of greater density, more myelinated, and/or run in a more consistent direction (Beaulieu, 2002). However, a recent study of individuals with Williams syndrome found that higher FA in the superior longitudinal fasciculus was associated with higher cognitive impairment, possibly indicating that increased FA in this region is due to decreased dendritic branching (Hoeft et al., 2007). Both regions of abnormally high FA detected in the current study were located in the anterior corona radiata, which is composed of heavily branched frontostriatal connections (Mori et al., 2005). Although this may be further evidence that both higher and lower FA can be indicative of pathology (Tuch et al., 2005; Hoeft et al., 2007), it is also possible that these areas of increased FA represent compensatory mechanisms.

A strength of this study is that we have attempted to equate groups on factors that are unrelated to the disorders but may affect FA, such as age. Factors that are related to the disorders, such as clinical variables (e.g. symptom severity, duration of illness, and medication exposure), could not be equated, and continued investigation is required to determine whether FA abnormalities in schizophrenia and ADHD are directly related to the presence of the disorder itself or are instead related to intrinsic features of the disorder, such as individual symptoms. Based on studies of adults with schizophrenia, neuroleptic medication exposure has not been shown to have a substantial effect on FA (Christensen et al., 2004) and there is currently no information about the effects of psychostimulants on FA in ADHD patients. There is potentially a recruitment bias created by using clinical sources for the schizophrenia patients but a community-based approach for the other two groups. However, the very low prevalence of adolescent-onset schizophrenia makes community-based recruitment difficult. Similarly, the overrepresentation of males in the ADHD group and lower IQ and parental SES in the

schizophrenia group may also limit the results of this study, though it is unlikely that the groups are unrepresentative of their respective populations because these are factors often associated with these disorders and to equalize groups on these factors may also limit the generalizability of results. However, future studies that are able to recruit larger groups may benefit from determining whether the results change when SES is matched or when only males are included in analyses. Another potential limitation is the assumption, inherent to using age as a covariate, that age-related changes during adolescence are similar across these three groups. This limitation may be confounded by the wide age range used in this study that was required to obtain a sufficient sample size. Future studies of FA in ADHD and schizophrenia during adolescence are necessary to better characterize the appropriateness of this assumption. Finally, a limitation present for all voxel-based studies is that of the potential for systematic registration error to confound comparisons of FA. This concern is reduced by the use of a custom template, though we also visually inspected the overlay of group averages to verify that there were no obvious registration differences across groups. In addition, studies that have attempted to control for this confound have found that it accounts for a minority of effects if any at all (Ardekani et al. 2003; Burns et al. 2003; Vangberg et al., 2006; Seok et al., 2007)

In summary, both clinical groups had abnormally low FA in the left posterior fornix, which may be associated with the common cognitive and/or behavioral impairments. The schizophrenia patients had widespread areas of uniquely low FA that suggest deficits of neural communication in multiple networks. The unique abnormalities seen in the ADHD patients were of higher FA in bilateral frontostriatal tracts. The majority of areas represented FA abnormalities unique to one of the clinical groups, suggesting that the cognitive and behavioral deficits shared by the two disorders likely arise from different sources.

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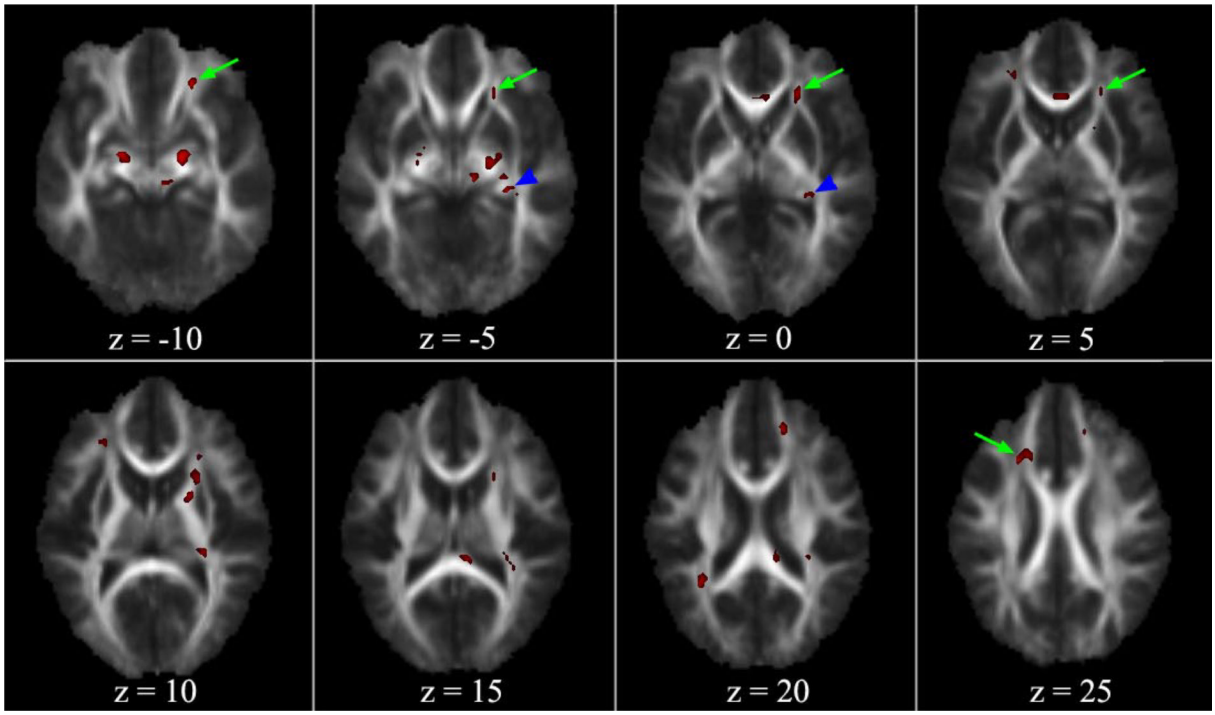

Figure 1.

Regional Fractional Anisotropy Differences across Groups. Significant clusters identified by voxelwise ANOVA are overlaid on the average FA map. The left side of the brain is represented on the right side of the image. Both clinical groups had lower FA in the left posterior fornix (arrowheads in B and C). ADHD patients had uniquely high FA in the left (arrows in A–D) and right (arrow in H) anterior corona radiata. Schizophrenia patients had uniquely low FA in bilateral cerebral peduncles (visible on A and B), anterior (C, D) and posterior (F, G) corpus callosum, right anterior corona radiata (D, E), and right superior longitudinal fasciculus (G).

Table 1

Demographic and Clinical Characteristics of the Participants

	Control	Schizophrenia	ADHD	Statistical Tests
N	26	15	14	
M:F	16:12	8:7	12:2	ns
Age in years (*SD*)	14.8 (2.41)	15.2 (2.42)	15.0 (2.34)	ns
Range	11–20	10–19	12–18	
Estimated IQ (*SD*)*	114.2 (10.4)	93.2 (14.4)	113.1 (15.7)	$F_{2,46} = 10.13$, $p < 0.001$; (CTRL = ADHD) > SCHZ
Parental SES (*SD*)**	51.0 (9.65)	38.4 (14.61)	54.4 (8.32)	$F_{2,48} = 8.65$, $p < 0.001$; (CTRL = ADHD) > SCHZ

Notes. ns = not significant; CTRL = controls; SCHZ = schizophrenia patients

* Based on 25 controls, 10 schizophrenia patients, and 14 ADHD patients

** Based on 23 controls, 15 schizophrenia patients, and 13 ADHD patients

Table 2

Regional Fractional Anisotropy Differences across Groups.

Location	Volume mm^3 (voxels)	Center (x, y, z)	F(2,52)	P	Tukey	Schiz	ADHD	Control
L cerebral peduncle	1480 (185)	(−14, −18, −8)	13.27	<0.001	S<A=C	0.4651	0.5083	0.5124
R cerebral peduncle	416 (52)	(22, −12, −8)	7.78	0.001	S<A=C	0.4459	0.4830	0.4892
L anterior corona radiata	632 (79)	(−22, 28, −4)	5.45	0.007	A>S=C	0.4456	0.4841	0.4455
L posterior fornix	240 (30)	(−30, −34, −2)	6.98	0.002	S=A<C	0.4151	0.4144	0.4553
Anterior corpus callosum	272 (34)	(0, 24, 4)	5.63	0.006	S<A=C	0.5384	0.6030	0.5871
L anterior limb of the internal capsule	496 (62)	(−22, 8, 4)	7.28	0.002	A>C	0.4829	0.5072	0.4657
R anterior corona radiata	208 (26)	(32, 34, 8)	5.21	0.009	S<A=C	0.3476	0.3788	0.3820
L retrolenticular part of the internal capsule	336 (42)	(−28, −34, 14)	6.74	0.002	S>C	0.5336	0.5093	0.4928
L splenium of the corpus callosum	280 (35)	(−6, −36, 18)	5.32	0.008	S<A=C	0.5426	0.5897	0.5922
R superior longitudinal fasciculus	224 (28)	(36, −50, 20)	6.57	0.003	S<A=C	0.4377	0.4777	0.4690
L forceps minor	200 (25)	(−14, 42, 22)	8.07	0.001	S>A	0.4939	0.4324	0.4604
R anterior corona radiata	424 (53)	(24, 24, 26)	6.05	0.004	A>S=C	0.3835	0.4165	0.3761

L = left; R = right; A = ADHD group; C = control group; S = schizophrenia group

Clusters are ordered from inferior to superior based on the center, which is given in MNI coordinates.