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White matter integrity, language, and childhood onset schizophrenia

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Abstract

Background—The heterogeneity of symptoms and cognitive deficits in schizophrenia can be explained by abnormal connectivity between brain regions. Childhood-onset schizophrenia (COS) is a particularly severe form of schizophrenia, with an onset during a key time period for both cerebral pruning and myelination.

Methods—Diffusion tensor images were acquired from 18 children and adolescents with COS and 25 controls. The COS group was divided into two sub-groups—one with linguistic impairment (LI) and the other without (NLI). The fractional anisotropy (FA), axial (AD), and radial diffusivity (RD) data from the two COS sub-groups were compared to each other and to the controls using tract-based spatial statistics (TBSS) analyses, which is a voxel-based method used to identify regions of white matter abnormalities.

Results—TBSS identified several regions in the left hemisphere where the LI group had increased AD and RD relative to the NLI and the control groups. These areas primarily localized to linguistic tracts: left superior longitudinal fasciculus and left inferior longitudinal fasciculus/inferior fronto-occipital fasciculus. Regions of increased RD overlapped regions of increased AD, with the former showing more pronounced effects.

Conclusions—Studies of adult-onset schizophrenia typically identify areas of higher RD but unchanged AD; however, normal development studies have shown that while RD decreases are pronounced over this age range, smaller decreases in AD can also be detected. The observed increases in *both* RD and AD suggest that developmental disturbances affecting the structural

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Conflict of interest statement

All of the authors state that they have no conflict of interest in the current study.

Contributors

All authors contributed to and have approved the final manuscript.

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connectivity of these pathways are more severe in COS accompanied by severe linguistic impairments.

Keywords

Diffusion tensor imaging; Axial diffusivity; Radial diffusivity; Linguistic impairments; Neurodevelopment

1. Introduction

Childhood-onset schizophrenia (COS) is a rare, particularly severe form of schizophrenia that is associated with higher genetic load, increased treatment resistance, and a worse prognosis (Alaghband-Rad et al., 1997; Asarnow et al., 2001; Rapoport and Gogtay, 2010). COS is clinically continuous with adult onset schizophrenia consistent with models suggesting that alterations in neurodevelopmental processes contribute to the pathophysiology of the illness generally (Kinross and Frangou, 2010; Murray and Lewis, 1987; Nicolson et al., 2000a; Weinberger, 1987). Neurodevelopmental models of schizophrenia posit that, through a complex interaction of genes and environment, aberrations in brain development occur early in development. The consequences of these events are not typically evident until adolescence or early adulthood when brain maturation, particularly of the frontal lobes, is complete (Andreasen, 2010; Hoffman and McGlashan, 1997; Lewis and Levitt, 2002; Murray and Lewis, 1987; Weinberger, 1987). Dysconnectivity models posit that white matter abnormalities, and disturbances in myelination specifically, provide a parsimonious explanation for the heterogeneity of clinical symptoms and cognitive deficits frequently observed in schizophrenia (Davis et al., 2003; Karoutzou et al., 2008; Kubicki et al., 2007; Kubicki et al., 2005; Marengo and Radulescu, 2009; Peters et al., 2010). Together these models implicate disturbances in white matter development during childhood or adolescence as amongst the precipitating event(s) leading towards a clinical manifestation of schizophrenia.

Because COS is rare, affecting only about 1 in 40 000, compared to adult onset schizophrenia, affecting as many as 1 in 100, there are understandably few neuroimaging studies of COS. In fact most prior research has encompassed an ongoing, longitudinal study of COS, which was started at the National Institute of Mental Health (NIMH) in 1990 (Gogtay, 2008; Gordon et al., 1994). These landmark studies support the notion that COS is associated with early parietal gray matter loss followed by frontal and temporal gray matter reductions. Furthermore, these gray matter losses are more striking and robust than similar effects seen in adult onset schizophrenia (Gogtay et al., 2001; Gogtay, 2008; Thompson et al., 2001). Cortical thinning, particularly in the frontal and temporal cortices, has been reported in subjects at high-risk for schizophrenia (Lawrie et al., 2008), first-episode schizophrenia patients (Ho et al., 2003; Matsumoto et al., 2001), and chronic schizophrenia patients (Gogtay et al., 2008; Gogtay et al., 2004; Jacobsen et al., 1998; Rapoport et al., 1999; Sporn et al., 2003; Vidal et al., 2006).

Recently, many diffusion tensor imaging (DTI) studies of schizophrenia have provided support for the dysconnectivity model of schizophrenia. This is because DTI offers a unique opportunity to study white matter integrity in vivo. Most DTI studies report values of fractional anisotropy (FA), which has been shown to be sensitive to multiple biological processes including variations in myelination and the number and density of axons (Neil et al., 1998; Song et al., 2003; Takahashi et al., 2002; Takahashi et al., 2000). Several studies of adult onset schizophrenia have identified regions of decreased FA, particularly within the frontal and temporal lobes (Ardekani et al., 2005; Clark et al., 2011; DeLisi et al., 2006; Hao et al., 2006; Mori et al., 2007; Phillips et al., 2009; Rose et al., 2006; Shergill et al., 2007;

Shin et al., 2006; Szeszko et al., 2008; White et al., 2007). Additionally, several studies have correlated FA with clinical and cognitive features of schizophrenia, (Hubl et al., 2004; Karlsgodt et al., 2008; Peters et al., 2010; Shergill et al., 2007; Szeszko et al., 2008) and at least two studies have related FA to future clinical or cognitive outcomes (Karlsgodt et al., 2009; Mitelman et al., 2007).

Many of the core symptoms of schizophrenia, including auditory hallucinations and disorganized speech, implicate abnormalities in the language network in the pathophysiology of schizophrenia (Crow, 1997, 2008; DeLisi, 2001; Li et al., 2009). Several previous studies have found that schizophrenia patients have deficits in speech production and comprehension (for a review, see (DeLisi, 2001)). Additionally, studies have reported that adults with schizophrenia exhibit significant speech delays as children (Cannon et al., 2002; Jones et al., 1994; Nicolson et al., 2000a). However, to our knowledge, no previous studies have examined how these delays might be related to white matter integrity. In this study, we acquired DTI data to examine the white matter integrity of COS patients with respect to associations between structural dysconnectivity and linguistic impairments. Based on prior studies of adults and reports of pronounced structural deficits in children with schizophrenia, we predicted that COS patients would show marked disturbances in structural connectivity and that pathways associated with language development would be particularly affected in patients with linguistic impairment.

2. Materials and methods

2.1. Subjects

Data were acquired from eighteen children and adolescents with COS (9 females/9 males, age range at the time of testing: 8.5–17.8 years) and twenty-five normal controls (13 females/12 males, age range at the time of testing: 7.9–18.4 years) (Table 1). Written informed assent from each subject and consent from each subject's guardian was obtained prior to data acquisition according to the rules and regulations of the Institutional Review Board of UCLA.

Patients were recruited from the University of California—Los Angeles (UCLA) In-patient Adolescent Unit and community child psychiatry clinics. To be included in the study, children and adolescents met DSM-IV criteria for schizophrenia or schizoaffective disorder. A schizophrenia diagnosis was based on the Schedule for Affective Disorders and Schizophrenia for School-Age Children, Present and Lifetime Version (Kiddie-SADS) (Kaufman et al., 1997), administered separately to each child and parent as described in Caplan et al. (Caplan et al., 2000). Five subjects had premorbid autism spectrum symptoms and met past and current criteria for autism spectrum (ASD) diagnoses (one Autism, one Asperger's Disorder, two Pervasive Developmental Disorder) in addition to meeting DSM-IV criteria for schizophrenia, such as hallucinations and delusions. Past ASD diagnoses were clinically confirmed at entry into the study. The mean age of onset of schizophrenia was 10.9 ($\pm$ 2.6 standard deviation) years; three patients had an onset at 14 years; one patient had an onset at 15 years; age of onset data was missing for two patients. Antipsychotic drug doses were converted to the chlorpromazine equivalent dose (CPZ) (Woods, 2003). Exclusionary criteria included: neurological, metabolic, or hearing disorder; psychosis associated with a neurological disorder or substance abuse; bilingual speakers of American English who did not attend English speaking schools or speak English at home.

Fourteen of the controls were recruited specifically for this study from four public and two private schools in the Los Angeles community, while the other eleven controls were recruited contemporaneously as part of a large NIH-funded multi-site MRI study of normal brain development (Evans, 2006). Both sets of controls were scanned using the same

scanner with the same acquisition parameters during the same period of time. All controls were screened for psychiatric, neurological, language, and hearing disorders through a structured telephone interview with a parent. Children manifesting symptoms of these disorders in the past or after enrolling in the study were excluded, as well as bilingual speakers of American English who did not attend English-speaking schools or speak English at home. The only difference between the two groups of controls was that the fourteen controls recruited specifically for this study had: a) the language testing (described in the next section) and b) separate Kiddie-SADS interviews administered to both the subject and parent (about the child).

2.2. Cognitive and language testing

The Wechsler Intelligence Scale for Children-III (Wechsler, 1991) was administered to all forty-three subjects and used to compute Full Scale IQ (FSIQ) scores. All of the schizophrenia patients and fourteen of the healthy control subjects underwent testing with the Test of Language Development (TOLD)-2 (Newcomer and Hammill, 1978). The TOLD-2 Primary (TOLD-P), normed for children aged 4 – 8 years, was administered to 1 schizophrenia and 2 control subjects; the TOLD-2 Intermediate (TOLD-I), normed for children aged 8 – 12 years, was administered to 4 schizophrenia and 4 control subjects; and the Test of Adolescent and Adult Language (TOAL), normed for adolescents aged 12 – 18 years, was administered to 13 schizophrenia and 8 control subjects. The TOLD manual provides normative data and findings of studies indicating reliability and validity of the instruments (Newcomer and Hammill, 1978).

Given the relatively wide developmental age range of the subjects in our study, we used the age standardized Spoken Language Quotient (SLQ) derived from the TOLD-P, TOLD-I, and TOAL, as an independent variable for analysis. Higher SLQ values indicate higher basic linguistic skills. The schizophrenia patients were subdivided into linguistically impaired (LI) and non-linguistically impaired (NLI) sub-groups based on SLQ scores of above or below 1.5 standard deviations from the norm. These two sub-groups of schizophrenic patients were compared to the control group using a 3-group analysis of variance (ANOVA) design to detect white matter abnormalities that were specific to schizophrenia in the presence of significant linguistic impairments.

2.3. Image Acquisition and Preprocessing

Whole brain DTI ($b=0$, 1000 sec/mm²; voxel size: 3×3×3 mm³; 6 directions, 4 averages) and high-resolution T1-weighted structural MR were acquired on a Siemens 1.5T scanner (Erlangen, Germany). The diffusion-weighted images were acquired using a sequence that was optimized to minimize eddy current induced distortions (Reese et al., 2003). Any remaining eddy current induced distortions were corrected using a 2D nonlinear registration algorithm to align the diffusion-weighted images to each subject's first non-diffusion-weighted image (Woods et al., 1998b). The DTI data were corrected for motion artifacts using a 3D rigid body registration to each subject's first non-diffusion-weighted image, and the gradient table was corrected accordingly (Woods et al., 1998a). The diffusion tensor was computed at each voxel using a linear least squares method to fit the log-transformed data of the signal intensities (Basser et al., 1994). The resultant eigenvalues were used to compute the fractional anisotropy (FA), axial diffusivity (AD), and radial diffusivity (RD). All preprocessing of the DTI data was done using in-house software written in C (Clark et al., 2011), using the CLAPACK library (Anderson et al., 1999).

2.4. Tract based spatial statistics

Using the FMRIB software library (FSL 4.1; <http://www.fmrib.ox.ac.uk/fsl/>), the FA maps from all subjects ($n=43$) were first nonlinearly aligned to a high-resolution average FA map

in the MNI space (Smith et al., 2004). The resultant images were then used to generate a mean FA image, which was subsequently thinned to create a mean FA skeleton. This FA skeleton represents the centers of all tracts that are common to the group. Each subject's aligned FA, AD, and RD data was then projected onto the mean FA skeleton and used to compute tract-based spatial statistics (TBSS) (Smith et al., 2006).

Voxelwise statistics were conducted on each point of the white matter skeleton using FSL's randomise tool while correcting for multiple comparisons using the threshold-free cluster enhancement option (Hayasaka and Nichols, 2003; Nichols and Holmes, 2002; Salimi-Khorshidi et al., 2011). Three one-way between subject ANOVAs were computed to compare the overall main effect of group (control, LI, or NLI) on white matter integrity as measured with FA, AD, or RD data, respectively. Age was included as a covariate for all three ANOVAs. In regions that exhibited a statistically significant ($p < 0.05$, corrected) main effect of group, post-hoc t-tests were computed between each pair of groups (controls vs NLI, controls vs LI, and NLI vs LI). These post-hoc t-maps were then thresholded at family-wise error corrected p-values of < 0.05 , and intersected with the Johns Hopkins University (JHU) atlas (Mori et al., 2008) to generate Table 2. Since the JHU atlas does not identify any voxels as either the ILF or the IFO, this information was found from a complementary atlas developed by the same group (Hua et al., 2008).

3. Results

3.1. Demographics and clinical data

As shown from the demographic and clinical information provided in Table 1, groups did not differ significantly with respect to their age at the time of testing. Significant differences in CPZ equivalent dose between the two schizophrenia sub-groups were also absent ($p = 0.33$; Table 1). However, all three groups differed with respect to FSIQ with controls having the highest IQ, followed by NLI patients, and the LI patients showing the lowest IQ. The differences in the FSIQ between the controls and the NLI patients was driven by differences in the performance IQ (PIQ) sub-scores ($p < 0.001$) but not in the verbal IQ (VIQ) sub-scores ($p = 0.14$). Conversely, the differences in the FSIQ between the two patient sub-groups were driven by differences in the VIQ ($p < 0.001$) but not the PIQ ($p = 0.11$). The two patient sub-groups were identified using their SLQ means; as expected the LI group differed significantly from the NLI group as well as the controls. Notably, the control group did not differ from the NLI group with respect to mean SLQ scores ($p < 0.32$). Four of the five patients with COS-ASD were in the LI group, while one was in the NLI group.

3.2. TBSS results

There were no significant main effects of group observed in the FA data. However, numerous spatially significant main effects of group were identified in both the RD and AD data. Post-hoc t-tests revealed that the majority of these regions were ones in which the LI group exhibited higher AD and RD relative to the NLI and/or control groups. There was only one region in which the NLI group differed significantly from the control group, and that was a small region in the right posterior corona radiata (Table 2). Notably, this was the only region identified in any of the contrasts that localized to the right hemisphere, and in this area, the controls had a *higher* value of axial diffusivity relative to the NLI group.

In the AD data, the group main effects were generally driven by the LI group having significantly higher values than the NLI group. In the RD data, the majority of the effects were driven by the LI group having significantly higher values relative to the control group (Table 2, Figure 1). Specifically, relative to the control or NLI groups, the LI group was found to have increased AD and RD in the splenium of the corpus callosum, regions of the left superior and posterior corona radiata, and in the following long association tracts of the

left hemisphere: superior longitudinal fasciculus (SLF), inferior fronto-occipital and inferior longitudinal fasciculi (IFO and ILF, respectively) (Table 2, Figure 1). In general, RD effects were larger in spatial extent and of higher statistical significance than those observed for axial diffusivity. Moreover, the regions where the LI group exhibited increases in AD and RD were shown to spatially overlap (Figure 1).

All effects remained the same or larger when FSIQ was included as a covariate. One of the normal controls had an SLQ score that was in the range of the LI patients. When this subject was removed from the analysis, results remained the same. Additional analyses (not shown) that modeled the COS-ASD sub-group compared to COS alone and controls failed to identify any significant differences. Similarly, re-running the same analyses presented above while removing the COS-ASD subjects only produced null results. These last two analyses attempted (and failed) to disentangle the effects of linguistic impairment from ASD probably because nearly half of the LI group had comorbid ASD and cell sizes were not sufficient large to detect any such effect.

4. Discussion

The heterogeneity and complexity of psychiatric symptoms and cognitive deficits associated with schizophrenia can be explained as a fundamental disturbance in brain connectivity (Peters et al., 2010). Many studies have implicated myelin dysfunction and/or oligodendroglial abnormalities as a mechanism contributing towards schizophrenia, including the identification of genetic risk factors for schizophrenia that play a role in oligodendrocyte structure (Davis et al., 2003; McIntosh et al., 2008; Wang et al., 2009). Several previous DTI studies of adult onset schizophrenia have identified regions of decreased FA, increased RD and unchanged AD--a pattern which is consistent with decreased myelination (Levitt et al., 2011; Seal et al., 2008; Whitford et al., 2010). In our study, we found that LI patients had overlapping areas of increased AD and RD, relative to the NLI patients and controls, respectively, in the splenium of the corpus callosum, left superior and posterior corona radiata, left SLF, and left ILF/IFO.

The splenium, which is sometimes referred to as the forceps major, is located in the posterior region of the corpus callosum. Fibers that pass through this area connect the right and left occipitotemporal cortices (Catani et al., 2002) and have been shown to be one of the earliest pathways to develop (Lebel et al., 2008). A recent meta-analysis of DTI studies of the corpus callosum in schizophrenia identified a modest effect size of 0.527 for patients having a decreased FA value relative to healthy controls in the splenium, in contrast to a non-significant effect size of FA differences in the genu (Patel et al., 2011). Although the specific area of the FA skeleton in which the LI group exhibited increased diffusivities localized to the splenium, it is worth noting that the center of gravity was 17 mm to the left of midline and 14 mm or 24 mm above the midline; thus, the identified white matter abnormalities localized to the dorsal left hemispheric projections of the splenium. The dorsal projections of the splenium have been shown to primarily connect the parietal cortices (Park et al., 2008). Our findings of increased diffusivities in the posterior corona radiata also implicate abnormal connectivity with the parietal lobes, as axons in the posterior corona radiata have been shown to be primarily composed of cortico-thalamocortical axons that connect the thalamus with parietal and occipital cortices (Aralasmak et al., 2006). Such findings mirror early studies of COS demonstrating that the earliest gray matter deficits were found in parietal brain regions known to support visuospatial and associative thinking (Gogtay et al., 2001; Gogtay, 2008; Thompson et al., 2001). Together these findings suggest that when schizophrenia has an onset in childhood or early adolescence, the aberrations first occur in the parietal cortices. This is in contrast to schizophrenia with a later onset, in which the aberrations are more in the frontal lobes (Andreassen, 2010; Hoffman and McGlashan,

1997; Lewis and Levitt, 2002; Murray and Lewis, 1987; Weinberger, 1987). The frontal lobe changes are also evident in COS patients (Gogate et al., 2001; Gogtay, 2008; Thompson et al., 2001), but they occur later. This is in line with the normal developmental time course of white matter tracts, which has been shown to progress in a roughly inferior-posterior to superior-anterior direction (Colby et al., 2011). Such a pattern can explain why COS has a more severe clinical picture than adult onset schizophrenia.

Association pathways are those that connect intrahemispheric regions, and are typically classified as either short, i.e. U-fibers, or long (Aralasmak et al., 2006). In this study, LI patients had increased AD and RD in three of the six long association pathways in the left hemisphere: the superior longitudinal fasciculus (SLF), the inferior fronto-occipital and inferior longitudinal fasciculi (IFO and ILF, respectively). The left SLF is associated with language skills; thus, it was not surprising that white matter abnormalities were observed in this region. Deficits in this white matter tract, as well as the gray matter areas that it connects, have been reported in many studies of schizophrenia, particularly in association with verbal working memory deficits (Hubl et al., 2004; Karlsgodt et al., 2008; Seok et al., 2007; Shergill et al., 2007). The ILF and IFO are difficult to distinguish using DTI because of their close proximity and interindividual variability in spatial location, especially in the posterior part of the brain, which is where our effects were observed (Figure 1). Not only are the left ILF and IFO difficult to separate from each other, but they also both share considerable spatial overlap with both the optic radiations and with fibers that pass through the splenium of the corpus callosum. Several previous studies have identified decreases in white matter integrity, typically reduced FA, in the left posterior ILF/IFO that is associated with visual hallucinations, negative syndrome subscale scores of the Positive and Negative Syndrome Scale (PANSS), overall poor outcomes, and the development of psychosis (Ashtari et al., 2007; Mitelman et al., 2007; Walterfang et al., 2008). Decreases in FA in the ILF-IFO region have been associated with subclinical psychotic symptoms in children ages 11–13 (Jacobson et al., 2010). In one of our previous studies on adults with schizophrenia, we identified a significant genetic liability in the left ILF/IFO and left SLF (Clark et al., 2011).

We did not identify any regions that decreased in FA; however the reason for this can be understood by considering that we did identify areas of increased AD in the LI patients in all of the regions that demonstrated increased RD. Because FA is correlated to the ratio of RD to AD, previous studies have shown that if RD and AD change in the same direction simultaneously, then the observed change in FA is less (or even absent) than if the RD changes without associated AD changes (Faria et al., 2010). Such a pattern is common in childhood and adolescence, as many studies have now shown that, over the course of normal neurodevelopment, the maturation of white matter tracts is associated with (in order of increasing magnitude): increased FA, decreased RD, and decreased AD (Faria et al., 2010; Kumar et al., 2012; Lebel et al., 2008). While the decreases in RD are largely attributed to myelination, the axonal pruning process has been shown to primarily cause a decrease in axial diffusivity (Bockhorst et al., 2008). Many of the early DTI studies in schizophrenia did not compute AD or RD, but only FA; however, two recent studies of schizophrenia, where the authors did measure AD and RD, found regions of increased AD (Lu et al., 2011; White et al., 2007). Notably, these two studies included younger subjects, with mean ages of 15.2 years (White et al., 2007) and 22 years (Lu et al., 2011), although Ashtari et al. failed to find differences in the AD of the ILF in their adolescent schizophrenia patients (Ashtari et al., 2007). If COS is attributable primarily to an alteration in normal neurodevelopmental processes, then our findings of increased AD and RD suggest *both* a decrease or delay in the myelination process *and* the normal pruning process. However, if COS also has a neurodegenerative component, then these findings could reflect fewer axons overall, such as is the case in neurodegenerative conditions that result in demyelination and axonal loss

(Kumar et al., 2010; Lowe et al., 2006; Pierpaoli et al., 2001). These two possibilities are not mutually exclusive.

There are several limitations to our study that should be noted. The main limitation is the relatively small sample sizes ($n=9$) for each of the two COS sub-groups; however, COS itself is rare and studying sub-groups within COS is valuable. Another limitation is that 5 of our COS patients met past and current criteria for ASD--4 in the LI group and 1 in the NLI group. However, abnormal language development and a history of ASD symptoms are reported in 44%–72% (Nicolson et al., 2000b; Watkins et al., 1988) and 25%–87% (Hollis, 1995; Kolvin et al., 1971; Sporn et al., 2004; Watkins et al., 1988) of COS patients respectively. Therefore, it is not surprising that most of the COS-ASD patients were in the LI group. Additional analyses that attempted to disentangle the effects of ASD from those of LI were unsuccessful, probably due to insufficient power. Nevertheless, our observations that patients with COS and linguistic deficits have additional white matter aberrations, whether due to COS with linguistic impairment or COS in conjunction with ASD, remain highly informative.

In conclusion, we have added evidence to both the neurodevelopmental and the dysconnectivity models of schizophrenia, particularly with respect to the role of developmental aberrations in the white matter. Furthermore, for the first time to our knowledge, we have shown that white matter integrity in language-related pathways as well as in other major white matter tracts reflect linguistic deficits in children with schizophrenia. We found that LI patients had increased RD in the splenium of the corpus callosum, left superior and posterior corona radiata, left SLF, and left ILF/IFO. These results are in support of previous studies implicating myelin dysfunction as a mechanism for the development of schizophrenia. In addition, we found that LI patients had increased AD in these same regions. The overlapping increases in both AD and RD suggest that COS patients with linguistic impairment have an even more severe deficit in these regions, either reflecting a decrease or delay in the normal pruning process or a neurodegenerative process leading to axonal loss.

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Figure 1. Tract-based spatial statistics (TBSS) revealed increases in white matter diffusivity in patients with childhood onset schizophrenia (COS) and significant linguistic impairment

A. The LI group showed increased axial diffusivity relative to the NLI group in both the left SLF (black circle) and a more inferior region that localizes to the ILF/IFO (gray arrow). B. In these same regions, the LI group showed larger areas of increases in the radial diffusivity relative to the control group. Red values indicate significant differences $p < 0.05$, TFCE corrected for multiple comparisons.

LI group=linguistically impaired COS patients, NLI group=non-linguistically impaired patients with COS, TFCE=threshold-free cluster enhancement, SLF=superior longitudinal fasciculus, ILF=inferior longitudinal fasciculus, IFO=inferior fronto-occipital fasciculus

Table 1

Demographic and clinical characteristics of subjects

Demographic	Control (n=25) Mean (SD)	NLI (n=9) Mean (SD)	LI (n=9) Mean (SD)	Statistic	p
Age at time of testing, years	14.2 (3.1)	15.2 (2.9)	13.4 (2.4)	F(2,40)=0.8	0.45
Gender	13F, 12M	4F, 5M	5F, 4M		
Ethnicity	8H, 17N	1H, 8N	3H, 6N		
Race	3A, 2B, 1I, 19W	1A, 1B, 7W	1B, 8W		
Met ASD criteria	0	1	4		
FSIQ	112 (11)	99 (13)	80 (19)	F(2,40)=19.7 ^{###†††***}	<0.001
VIQ	113 (11)	105 (16)	82 (17)	F(2,40)=17.4 ^{†††***}	<0.001
PIQ	109 (11)	93 (12)	81 (24)	F(2,40)=20.0 ^{###†††}	<0.001
CPZ, mg	N/A	140 (119) ^a	225 (276)	t(17)=1.0	0.33
SLQ	105 (14) ^b	99 (12)	68 (13)	F(2,29)=22.3 ^{†††***}	<0.001

NLI=non-linguistically impaired patients with childhood-onset schizophrenia (COS); LI=linguistically impaired COS patients; SD=standard deviation; M=male; F=female; H=Hispanic or Latino; N=Not Hispanic or Latino; A=Asian; B=Black or African American; I=Native Hawaiian or Other Pacific Islander; W=White or Caucasian; ASD=autism spectrum disorder; FSIQ=Full-scale intelligence quotient (IQ); VIQ=verbal IQ; PIQ=performance IQ; CPZ=chlorpromazine equivalent; SLQ=spoken language quotient;

^aData missing for one patient;

^bData was only available for 14 controls

p<0.05, ^{##}0.01, ^{###}0.001 significant post-hoc test between Control and NLI groups;

p<[†]0.05, ^{††}0.01, ^{†††}0.001 significant post-hoc test between Control and LI groups

p<*0.05, **0.01, ***0.001 significant post-hoc test between NLI and LI groups

Table 2

TBSS significant post-hocs in regions with a significant main effect of group

	Cluster size (voxels)	Mean t-stat	Center of gravity coordinates (mm)
<i>Axial diffusivity</i>			
<i>Control > NLI</i>			
R Post. corona radiata	31	2.60	(-21, -40, 38)
<i>LI > NLI</i>			
L Sup. corona radiata	67	1.88	(22, -18, 38)
L Post. corona radiata	268	2.10	(24, -46, 28)
L SLF	175	2.11	(33, -45, 23)
L ILF/IFO	64	2.11	(30, -55, 17)
Splenium	35	1.92	(17, -45, 14)
<i>Radial diffusivity</i>			
<i>LI > NLI</i>			
L Sup. corona radiata	31	2.83	(26, -2, 31)
<i>LI > Control</i>			
L Post. corona radiata	278	3.25	(22, -45, 29)
L SLF	258	3.13	(36, -35, 27)
L ILF/IFO	154	3.21	(32, -61, 8.5)
Splenium	83	3.09	(17, -45, 24)

NLI=non-linguistically impaired patients with childhood-onset schizophrenia (COS); LI=linguistically impaired COS patients; Post=posterior; Sup=superior; SLF=superior longitudinal fasciculus; ILF=inferior longitudinal fasciculus; IFO=inferior fronto-occipital fasciculus