White Matter Abnormalities and Cognitive Impairment in Early-Onset Schizophrenia-Spectrum Disorders

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Objective: To characterize white matter abnormalities in adolescents with early-onset schizophrenia (EOS) relative to 3 comparison groups (adolescents at clinical high risk for developing schizophrenia [CHR], adolescents with cannabis use disorder [CUD], and healthy controls [HC]), and to identify neurocognitive correlates of white matter abnormalities in EOS. **Method:** We used diffusion tensor imaging and tractography methods to examine fractional anisotropy (FA) of the cingulum bundle, superior longitudinal fasciculus, corticospinal tract (CST), inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), and uncinate fasciculus in adolescents with EOS (n = 55), CHR (n = 21), CUD (n = 31), and HC (n = 55). FA in tracts that were significantly altered in EOS was correlated with neurocognitive performance. **Results:** EOS and CHR groups had significantly lower FA than HC in 4 tracts, namely, bilateral CST, left ILF, and left IFOF. CUD had lower FA than HC in left IFOF. Lower FA in left IFOF and left ILF predicted worse neurocognitive performance in EOS. **Conclusions:** This study identified white matter abnormalities of the left ILF and left IFOF as possible biomarkers of vulnerability for developing schizophrenia. Lower FA in these tracts may disrupt functioning of ventral visual and language streams, producing domain-specific neurocognitive deficits that interfere with higher-order cognitive abilities. J. Am. Acad. Child Adolesc. Psychiatry, 2014;53(3):362–372. **Key Words:** diffusion tensor imaging (DTI), inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), schizophrenia

Schizophrenia is a disease characterized in part by white matter (WM) abnormalities that alter brain connectivity.[1] A large but variable body of literature exists on the topographic location of WM deficits in adult-onset schizophrenia.[2] Adolescents with early-onset schizophrenia (EOS) (onset by age 18 years) represent an ideal population to examine WM alterations, as these individuals may represent a subgroup with high genetic loading[3] that is less affected by chronic exposure to antipsychotic medication.[4]

Diffusion tensor imaging (DTI) is a magnetic resonance imaging technique that capitalizes on the propensity of water molecules to diffuse along, rather than across, WM tracts. Fractional anisotropy (FA) is a DTI measure that reflects tract integrity and coherence.[5] Region-of-interest (ROI) and voxel-based analyses have reported reduced FA in EOS across widespread brain regions and fiber tracts, including the left posterior hippocampus,[6] bilateral cerebral peduncles,[7] anterior and posterior corpus callosum,[7] right anterior corona radiata,[7] inferior frontal WM,[8] occipital WM,[8] corticospinal tracts,[9] parietal WM,[7,10] left anterior cingulate,[11] corpus callosum,[12] and left inferior longitudinal fasciculus (ILF).[13]

Several hypotheses have been proposed to explain the variable WM findings in EOS. First, underlying WM abnormalities may be subtle[2] and non–spatially overlapping,[14] making anomalies difficult to detect. However, a recent meta-analysis of adults with first-episode schizophrenia identified lower WM FA in the left deep temporal lobe, corresponding to left ILF and left IFOF.[15] In another study, these 2 major left hemisphere fiber tracts showed specific myelination deficits and FA

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reduction in adults with chronic schizophrenia, which correlated with reductions in processing speed,[16] a well-known cognitive abnormality in schizophrenia.

Second, exposure to antipsychotic medication could potentially affect the pattern of WM alterations in EOS. To address this problem, the study of adolescents with subthreshold psychotic symptoms (CHR) could be informative: these adolescents are at elevated risk for conversion to psychosis in adulthood, but tend to have no or very limited exposure to antipsychotic medications.[4] Also, prior history of cannabis misuse[17] may affect the pattern of WM alterations within EOS. Adolescent cannabis exposure also increases the risk of developing a psychotic disorder,[18] and is associated with cognitive deficits.[19] Finally, data from adults with first-episode schizophrenia indicate that patterns of WM alterations may be affected by cognitive function.[20]

In the present study, we investigated WM integrity in adolescents with EOS relative to 3 other comparison groups: CHR; nonpsychotic adolescents with cannabis use disorders (CUD); and healthy comparison participants (HC). We used probabilistic tractography, a methodological refinement compared to previous DTI studies in EOS, which localizes FA variations to specific fiber tracts as compared to brain regions. We also investigated the relationship between FA and neurocognitive performance in EOS.[21] Based on recent studies in adults with schizophrenia[15,16,22] and previous studies in EOS, we hypothesized the following: patients with EOS would have lower FA than HC in the left temporal lobe, specifically in left ILF[8,13] and left IFOF; patients with CHR and CUD would have some shared WM abnormalities with EOS, based on nonspecific phenotypic characteristics; and deficits in executive function and motor skills would be related to FA in fiber tracts that were aberrant in EOS.[20]

METHOD

Study Participants

The details of the clinical protocol have been described in detail elsewhere.[23] In brief, 162 participants ranging in age from 10 to 23 years were recruited from clinical programs at the University of Minnesota under an Institutional Review Board–approved protocol. For participants less than 18 years of age, informed consent was obtained from parents, and assent was obtained from the child. Participants more than 18 years of age provided their own consent, and their parents were consented for a collateral interview. These parents were consented so that they could provide information about pertinent family psychiatric history and collateral data to aid in the diagnostic formulation and assessment of premorbid function[24] of their children.

Participants with EOS met criteria for schizophrenia (n = 43), schizoaffective (n = 5), or schizophreniform disorder (n = 7), and reported an onset of psychotic symptoms before age 18 years. Thirty-four participants with EOS had no past or current *DSM-IV* diagnosis for substance or alcohol use disorders. Twenty-one of the 55 participants with EOS met lifetime criteria for a co-occurring cannabis use disorder (CUD) of abuse or dependence. In EOS, participants with co-occurring CUD were included if a history of psychotic symptoms was present when there was no evidence of substance misuse or withdrawal. Forty-five of the 55 participants with EOS were taking second-generation antipsychotic medications (SGAs) at the time of scanning, which included risperidone (n = 14), aripiprazole (n = 11), quetiapine (n = 11), olanzapine (n = 4), clozapine (n = 3), ziprasidone (n = 1), and paliperidone (n = 1). Two participants with EOS were taking first-generation antipsychotics at the time of scanning, including haloperidol (n = 1) and perphenazine (n = 1). Chlorpromazine equivalent (CPZ) dose and lifetime exposure were calculated from the dose and duration of antipsychotic medications received using a standardized method.[25]

Nonpsychotic adolescents with CUD (n = 31) were recruited from programs for chemical dependency. As many of the adolescents with schizophrenia-spectrum disorders tested positive for cannabis at the time of the scan, the CUD group allowed for examination of the effect of repeated exposure to cannabis on white matter microstructure in the absence of psychosis. Adolescents were selected who reported cannabis as their drug of choice with significant cannabis exposure by age 17 years (>50 exposures to cannabis), and who did not meet lifetime criteria for abuse of or dependence on other illicit drugs with the exception of alcohol or nicotine dependence. Exclusion criteria for the CUD group included a lifetime diagnosis of bipolar disorder or schizophrenia-spectrum disorder. However, as this was a treatment-seeking clinical population, the presence of other psychopathology was permitted. Fourteen of the 31 participants with CUD were taking psychotropic medication at the time of scanning, which included stimulants (n = 1), antidepressants (n = 13), mood stabilizers (n = 2), and SGAs (n = 6). SGAs were prescribed in this group to target sleep disturbance (n = 4) and irritability (n = 2), both frequent problems in this group during the early stages of sobriety, to enhance program retention.

Treatment-seeking adolescents at clinical high risk for developing schizophrenia (CHR; n = 21) were recruited from an outpatient university clinic developed to evaluate youth who might be at risk for developing