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White matter fractional anisotropy over two time points in early onset schizophrenia and adolescent cannabis use disorder: A naturalistic diffusion tensor imaging study

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ABSTRACT

Recurrent exposure to cannabis in adolescence increases the risk for later development of psychosis, but there are sparse data regarding the impact of cannabis use on brain structure during adolescence. This pilot study investigated the effect of cannabis use disorder (CUD) upon white matter fractional anisotropy (WM FA) values in non-psychotic treatment-seeking adolescents relative to adolescents with early onset schizophrenia-spectrum disorders (EOSS) and to healthy control (HC) participants. Diffusion tensor imaging (DTI) and tractography methods were used to examine fractional anisotropy (FA) of the cingulum bundle, superior longitudinal fasciculus (SLF), corticospinal tract (CST), inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF) and uncinate fasciculus in adolescents with EOSS ($n=34$), CUD ($n=19$) and HC ($n=29$). Participants received DTI and substance use assessments at baseline and at 18-month follow-up. Using multivariate analysis of variance, a significant main effect of diagnostic group was observed. Post-hoc testing revealed that adolescents with CUD showed an altered change in FA values in the left ILF and in the left IFOF (trend level) compared with HC adolescents. Greater consumption of cannabis during the inter-scan interval predicted a greater decrease in left ILF FA in CUD. These preliminary longitudinal data suggest that heavy cannabis use during adolescence, or some factor associated with cannabis use, is associated with an altered change in WM FA values in a fiber bundle that has been implicated in the pathophysiology of EOSS (i.e., the left ILF). Additional studies are needed to clarify the clinical significance of these findings.

1. Introduction

Adolescent cannabis use increases the risk for later development of psychosis (Casadio et al., 2011), but the neurobiological mechanism underlying this increased risk remains poorly understood. The initiation of cannabis use during adolescence coincides with significant neurodevelopmental changes in white matter (WM). Diffusion tensor imaging (DTI) studies show that fractional anisotropy (FA), a parameter linked to axon packing and myelination, increases as major fiber tracts increase in integrity and coherence (Bava et al., 2010; Giorgio et al., 2010; Lebel and Beaulieu, 2011). In adolescence and young adulthood, cannabinoid receptor expression transiently increases on WM structures, indicating that adolescence may be a developmental period during which developing WM is particularly sensitive to the effects of exogenous cannabis (Zalesky et al., 2012). The purpose of this study was to examine the impact of recurrent exposure to cannabis on adolescent WM development using a longitudinal framework. This study may help provide a mechanism for understanding why adolescent cannabis use is associated with an increased risk for developing schizophrenia.

Preclinical and human studies demonstrate that developing WM is a sensitive target for exogenous cannabis exposure. Preclinical studies have demonstrated the existence of Cannabinoid-1 (CB-1) receptors in myelin precursors including astrocytes (Bouaboula et al., 1995; Sanchez et al., 1998), microglia (Waksman et al., 1999; Moldrich and Wenger, 2000; Rodriguez et al., 2001; Walter et al., 2003), and oligodendrocytes (Tamnes et al., 2010). CB-1 receptors are known to affect oligodendroglial development (Bourgeois and Rakic, 1993; Tamnes et al., 2010), and recurrent exposure to cannabis during adolescence may cause a down-regulation of CB-1 receptors and suppress oligodendrocyte function during neurodevelopment, leading to an altered trajectory of WM development (Kumra, 2007). In humans, adolescent cannabis use disorder (CUD) is associated with WM abnormalities. Cross-sectional DTI studies of FA have revealed alterations in the corpus callosum (Arnone et al., 2008), superior longitudinal fasciculus (SLF) (Ashtari et al., 2009), left inferior fronto-occipital fasciculus (IFOF) (Bava et al., 2009; Epstein et al., 2014), and

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white matter fractional anisotropy (WM FA) surrounding the hippocampus (Zalesky et al., 2012), while two studies found no effect of CUD on WM FA (Gruber and Yurgelun-Todd, 2005; Delisi et al., 2006). Two other studies have reported widespread WM FA alterations in adolescents with comorbid binge-drinking and cannabis use (Jacobus et al., 2009; Bava et al., 2010). To our knowledge, there has been only one longitudinal study that examined the effect of adolescent substance misuse on change in WM FA during development (Bava et al., 2013). Bava et al. (2013) revealed group differences in WM FA between adolescent cannabis users with comorbid binge drinking and healthy controls (HC) at study endpoint, but found no relationship between cannabis exposure during the interscan interval and change in WM FA over time. However, the study excluded adolescents with comorbid psychopathology and it is possible that cannabis misuse could affect WM development only in vulnerable subgroups (Rodriguez-Sanchez et al., 2010; van Os et al., 2010) (e.g., adolescent cannabis users with more severe mental health problems).

White matter abnormalities have been consistently observed in early onset schizophrenia-spectrum disorders (EOSS) (onset of psychotic symptoms by age 18 years) and may also indicate a risk factor for developing schizophrenia in the future (Epstein et al., 2014). Recent meta-analyses of DTI studies in adults with schizophrenia, including first episode patients, have identified lower WM FA in the left deep temporal lobe, corresponding to the left inferior longitudinal fasciculus (ILF) and left IFOF (Ellison–Wright and Bullmore, 2009; Palaniyappan et al., 2013; Yao et al., 2013). We have previously reported similar WM abnormalities in these two major left hemisphere fiber tracts in adolescents with EOSS that were associated with deficits in measures of executive function (Ashtari et al., 2007; Epstein et al., 2014). Similar abnormalities in these fiber tracts have also been observed in children and adolescents at clinical high risk (Jacobson et al., 2010; Epstein et al., 2014) and genetic high risk (Kikinis et al., 2013) for psychosis who had limited, if any, exposure to antipsychotic medications. Together, these data suggest that lower WM FA in the left ILF and left IFOF during adolescence may represent a biomarker for an increased risk for the development of psychosis.

To our knowledge, this is the first naturalistic study to examine WM FA in treatment-seeking adolescents with CUD relative to two comparison groups (adolescents with EOSS, healthy controls) for evidence of WM microstructural alterations associated with recurrent exposure to cannabis over an 18-month period. Our hypotheses were as follows: (1) healthy controls (HC) would show detectable increases in FA across several WM association fiber tracts (i.e., ILF, IFOF, SLF) during the 18-month inter-scan interval based on prior data suggesting that late adolescence is a period associated with ongoing WM maturation (Bava et al., 2010; Giorgio et al., 2010; Lebel and Beaulieu, 2011). (2) Adolescents with EOSS would show diminished FA in the left ILF and the left IFOF relative to HC based on data suggesting that WM abnormalities in these tracts represent a biomarker associated with psychosis in adolescents (Jacobson et al., 2010; Epstein et al., 2014). (3) FA in non-psychotic adolescents with CUD would decline during the inter-scan interval relative to findings in HC adolescents in those fiber bundles associated with WM abnormalities in EOSS (i.e., left ILF, left IFOF) based on our cross-sectional results (Epstein et al., 2014) and the previous literature (Bava et al., 2009; Jacobus et al., 2009; Baker et al., 2013). It was further hypothesized that more exposure to cannabis during the inter-scan interval would predict a greater decline in FA values during this time period.

2. Methods

2.1. Study participants

The methods of this study have been described in detail elsewhere (Kumra et al., 2012; Epstein et al., 2014). In brief, a sample of children and adolescents with EOSS ($n=76$) and CUD ($n=31$), as well as HC adolescents ($n=55$), between the ages of 10–23 years were recruited from the clinical programs at the University of Minnesota Medical Center in Minneapolis under an approved Institutional Review Board protocol. Baseline differences in FA values have been previously reported (Epstein et al., 2014). This cohort was followed for a period of 18 months to examine the relationship between brain morphology and substance misuse. Due to funding constraints, a subset (34 EOSS, 17 CUD, 31 HC) recruited during the initial phase of the study (first three years) completed both the baseline and 18-month follow-up DTI scans and corresponding clinical evaluations. However, during this time period, two HC participants initiated cannabis use and were diagnosed with CUD at follow-up. These two HC participants were included in the CUD group and were followed up as for other subjects with CUD per protocol.

Nonpsychotic adolescents with CUD ($n=19$) who were seeking treatment for substance misuse were recruited from programs for chemical dependency. 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 (i.e., internalizing and externalizing disorders). Five of the 19 participants with CUD were taking antipsychotic medication at the time of baseline scanning. These subjects were carefully screened at baseline to ensure that they did not have psychotic symptoms. In this population, atypical antipsychotic medications were prescribed off-label and short-term to treat sleep disruption (Anderson and Vande Griend, 2014), mood disturbance, and aggression (Loy et al., 2012), all frequent problems in the early stages of sobriety. Participants were taking quetiapine at doses of 25 mg, 250 mg, and 300 mg, aripiprazole at 7.5 mg, and risperidone at 2.5 mg/day at the time of the baseline magnetic resonance imaging (MRI) scan. These medications had been discontinued in all but one participant at follow-up. At study completion, none of these patients were diagnosed as having a psychotic disorder.

Based on our previous cross-sectional data (Epstein et al., 2014) and the NIMH Research Domain Criteria (RDoC) (Casey et al., 2014), we did not differentiate among adolescents based on the severity and duration of their psychotic symptoms. Thus, adolescents with psychotic symptoms who met criteria for schizophrenia ($n=20$), schizoaffective disorder ($n=4$), schizophreniform disorder ($n=4$), or psychotic disorder not otherwise specified ($n=7$) and who reported an onset of psychotic symptoms before age 18 years at baseline were included in the EOSS group. Twenty-three participants with EOSS had no past or current *DSM-IV* diagnosis for a substance use disorder. Eleven of the 34 participants with EOSS met lifetime criteria for a co-occurring CUD of abuse or dependence. In EOSS, 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 based on information collected from structured interviews and collateral reports. Antipsychotic medications that were prescribed at time of scanning are shown in Table 1. Chlorpromazine-equivalent (CPZ) dose and lifetime exposure were calculated from the dose and duration of antipsychotics received using a standardized method (Andreasen et al., 2010).

A total of 29 HC adolescents were recruited from the same geographic area in response to flyers and by word of mouth to match the EOSS group on age, sex, and handedness. Controls were excluded if they had any current or past *DSM-IV* diagnosis (with the exception of subthreshold anxiety disorders), prior or current treatment with psychotropic medications, history of psychological counseling, reported history of more than five lifetime exposures to any illicit drug (with the exception of alcohol), and/or history of schizophrenia or psychosis in a first-degree relative.

General exclusion criteria for all participants included any contraindication to MRI, positive pregnancy test, history of a *DSM-IV* diagnosis of mental retardation, a neurological disorder, head injury with loss of consciousness for more than 30 s, or active medical illness that could potentially affect brain structure.

2.2. Clinical measures

Diagnoses of Axis I disorders including schizophrenia and substance use disorders were made using the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (in participants <18 years of age) or the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID) (in participants ≥ 18 years of age) using multiple data sources including school records and psychiatric records at baseline and follow-up. Handedness (Oldfield, 1971) and socioeconomic status (SES) (Hollingshead and Redlich, 2007) were assessed using standardized measures.

The Timeline Followback Method (Sobell and Sobell, 1992) assessed participants' chronicity and intensity of substance use by estimating cannabis use during the 18-month inter-scan interval as the number of days used. Urine toxicology tests were performed on the day of the MRI scan at both time points using the K012B 12 Panel Drug Screen Test (delta-9-tetrahydrocannabinol (THC) sensitivity 50 ng/ml) from Drug Test Systems (Dover, NH). The Wide-Range Achievement Test-3rd Edition (WRAT) Reading Subtest (Wilkinson, 1993) was administered to estimate premorbid intellectual functioning for all subjects.