Schizophrenia Research 162 (2015) 143–152

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Altered cortical maturation in adolescent cannabis users with and without schizophrenia

Katherine A. Epstein, Sanjiv Kumra *

Division of Child and Adolescent Psychiatry, University of Minnesota, Minneapolis, MN, United States

ARTICLE INFO

Article history:
Received 20 June 2014
Received in revised form 19 November 2014
Accepted 21 November 2014
Available online 15 January 2015

Keywords:
Structural imaging
Schizophrenia
Critical period
Endocannabinoid
Cortical
Gray matter

ABSTRACT

During late adolescence, progressive cortical thinning occurs in heteromodal association cortex (HASC) that is thought to subserve cognitive development. However, the impact of cannabis use disorder (CUD) upon cortical gray matter development in both healthy adolescents and adolescents with early-onset schizophrenia (EOS) is unclear. T1-weighted magnetic resonance images were acquired from 79 adolescents at baseline and after an 18-month follow-up: 17 with EOS, 17 with CUD, 11 with EOS + CUD, and 34 healthy controls (HC). Mean age at baseline was 16.4 years (CUD+) and 17.0 years (CUD−). Using FreeSurfer, measures of cortical thickness for ROIs within HASC were obtained. A 2 (EOS versus no EOS) × 2 (CUD versus no CUD) multivariate analysis of covariance was applied to change scores from baseline to follow-up to test for main effects of EOS and CUD and an interaction effect. After adjusting for covariates, a significant main effect of CUD was observed. Adolescents with CUD showed an attenuated loss of cortical thickness in the left and right supramarginal, left and right inferior parietal, right pars triangularis, left pars opercularis, left superior frontal, and left superior temporal regions compared to non-using subjects. Stepwise linear regression analysis indicated that greater cumulative cannabis exposure predicted greater cortical thickness in both the left ($p = .008$) and right ($p = .04$) superior frontal gyri at study endpoint after adjusting for baseline cortical thickness for the entire sample. These preliminary longitudinal data demonstrate an atypical pattern of cortical development in HASC in adolescents with CUD relative to non-using subjects, across diagnostic groups. Additional studies are needed to replicate these data and to clarify the clinical significance of these findings.

1. Introduction

Adolescent brain development is characterized by ongoing molding of cortical gray matter (GM) (Sowell et al., 2001). During typical development, cortical maturation occurs in a back-to-front direction with the heteromodal association cortex (HASC) maturing last, during late adolescence and into early adulthood (Gogtay et al., 2004). The HASC comprises the prefrontal, superior temporal, and inferior parietal cortices and supports the highest integrative functions of the brain, including attention, language, working memory, and executive function (Ross and Pearlson, 1996). Within the HASC, the protracted maturation of the superior frontal cortex during adolescence is thought to subserve the development of executive functions (Luciana et al., 2009), including working memory and planning, that are important for the development of self-organized behavior and emotional regulation.

Cannabis is one of the most commonly used illicit substances among adolescents and young adults (SAMHSA, 2014). There are increasing data suggesting that the effects of delta-9-tetrahydrocannabinol (THC) may be more deleterious in adolescents, whose cognitive development and brain maturation are still ongoing, than in adults (Lisdahl et al., 2013). Recently, a primate study found that exposure to THC for six months during adolescence selectively impaired development of a spatial working memory task that preferentially activates the still-developing superior frontal cortex (Verrico et al., 2014). The primary target of exogenous cannabinoids in the brain is the cannabinoid-1 (CB-1) receptor. CB-1 receptors are located throughout the brain including the HASC and are part of the endocannibinoid system, which regulates synaptic plasticity and other fundamental neuromaturational processes (Harkany et al., 2008). To date, very little is known about the relationship between regular cannabis use during adolescence and cortical GM development in late-developing brain regions such as the HASC. Data from cross-sectional studies suggest that regular cannabis use during adolescence may disrupt GM pruning processes in both typical

* Corresponding author at: Division of Child and Adolescent Psychiatry, University of Minnesota, F256/2B West, 2450 Riverside Ave., Minneapolis, MN 55454, United States. Tel.: +1 612 273 9775; fax: +1 612 273 9779.
E-mail address: kumra002@umn.edu (S. Kumra).

http://dx.doi.org/10.1016/j.schres.2014.11.029
0920-9964/

(Cousijn et al., 2012; Squeglia et al., 2009) and atypical development (Jarvis et al., 2008). Specifically, a study of adolescent cannabis users (mean age = 17.8) found reduced cortical thickness in prefrontal and insular regions, and increased cortical thickness in temporal and parietal regions, compared to healthy controls (HC) (Lopez-Larson et al., 2011). In contrast, a study in young adult cannabis users (mean age = 25.7) found no differences in cortical thickness between cannabis users and HC (Mata et al., 2010). However, in the latter study, HC participants were noted to have decreasing cortical thickness with age, while this pattern was not observed in cannabis users (Mata et al., 2010). These data support a working hypothesis that recurrent exposure to cannabis during adolescence could alter the maturation of cortical GM (Bossong and Niesink, 2010) within the HASC leading to an ostensible normalization of cortical structural abnormalities in adulthood.

Cannabis use disorder (CUD) is frequently diagnosed in patients with schizophrenia (SZ) (Koskinen et al., 2010). Schizophrenia is characterized by cortical abnormalities within the HASC (Buchanan et al., 2004), and the presence of CUD may be a moderating factor contributing to gray matter alterations in SZ. There is increasing evidence suggesting that patients with SZ and comorbid CUD may represent a clinically distinct subgroup of SZ patients with better premorbid adjustment (Dixon et al., 1991), superior cognitive abilities (Rabin et al., 2011; Yucel et al., 2012), and a less severe pattern of brain dysmorphology (Kumra et al., 2012) within the HASC compared to non-using SZ patients. In our previous cross-sectional data, we observed that early-onset schizophrenia (onset by age 18) (EOS) + CUD was associated with a larger brain volume in the right superior frontal cortex compared to non-using EOS patients. Previous longitudinal studies have found that there is an exaggerated pattern of cortical thinning in the HASC in adolescents with treatment-refractory childhood-onset schizophrenia (onset by age 12) (Sporn et al., 2003; Thompson et al., 2001), and in less severely ill adolescents with EOS (Arango et al., 2012), relative to HC. There has been one cross-sectional study suggesting that the presence of CUD is associated with more exaggerated cortical gray matter deficits in adolescents with EOS (James et al., 2011). To our knowledge, there have been no longitudinal studies conducted in adolescents with CUD, with or without comorbid EOS. Characterizing the effects of CUD on adolescent brain development in EOS is important: (1) to identify potential differences in pathophysiology between EOS and EOS + CUD; and (2) to determine whether the effects of CUD on brain morphology are dependent on diagnostic grouping.

To date, there have been no longitudinal studies that have examined the impact of CUD on adolescent cortical GM development. The present study aimed to examine the impact of CUD on cortical development in HASC over an 18-month period in both nonpsychotic and psychotic adolescents. On the basis of our cross-sectional data (Kumra et al., 2012) and the existing literature, we hypothesized that: (1) The magnitude of cortical thinning would be altered for CUD (+) compared to CUD (−) across HASC regions, based on preclinical data suggesting that adolescent exposure to cannabis could disrupt cortical GM development (Bossong and Niesink, 2010), and prior morphometric data demonstrating differences in cortical thickness and brain volumes associated with CUD in both typical (Lopez-Larson et al., 2011) and atypical development (Jarvis et al., 2008; Kumra et al., 2012); and (2) The magnitude of these alterations would be related to the amount of cannabis consumed. As an exploratory aim, we examined the relationship between neurocognitive performance and change in cortical thickness within the HASC. Here we hypothesized that greater loss of cortical thickness in the superior frontal gyrus (SFG) in HC would be related to improvement on a test of planning and problem solving (the Delis–Kaplan Executive Function System (D-KEFS) Tower Test (Delis et al., 2001)), as the slow development of planning performance during adolescence (Luciana et al., 2009) may be related to GM structural changes in the SFG (Burgaleta et al., 2014).

2. Methods and materials

2.1. Study participants

The methods of this study have been described in detail elsewhere (Kumra et al., 2012). In brief, a sample of children and adolescents with EOS (n = 55), CUD (n = 31), and HC (n = 55) between the ages of 10 to 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 volume measurements have been previously reported (Kumra et al., 2012). A subgroup (28 EOS, 17 CUD, 34 HC) of participants recruited during the initial phase of the study (first three years) completed both baseline and 18-month follow-up Magnetic Resonance Imaging (MRI) and corresponding clinical evaluations. The time interval of 18 months was chosen based on issues of feasibility and grant funding for this project.

At baseline, adolescents with EOS met criteria for schizophrenia (n = 20), schizoaffective (n = 4), or schizophreniform disorder (n = 4), and reported an onset of psychotic symptoms prior to age 18 years. Seventeen participants with EOS had no past or current *DSM-IV* diagnosis for substance or alcohol-use disorders. Eleven of the 28 participants with EOS met lifetime criteria for a co-occurring 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 based on evaluation from a structured interview and collateral reports. Antipsychotic medications that were prescribed at the time of scanning at baseline and follow-up are shown in Table 1. Chlorpromazine equivalent (CPZ) dose and lifetime exposure were calculated using a standardized method (Andreasen et al., 2010).

Nonpsychotic adolescents with CUD (n = 17) who were seeking treatment for substance misuse were recruited from programs for chemical dependency. Thus, all subjects met criteria for cannabis use disorder at the time of study entry. However, a proportion of subjects with CUD were scanned after they had been stabilized in a drug treatment program and thus had negative drug screens at the time of their baseline MRI scan. Adolescents 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 abuse or nicotine dependence were selected. The 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).

A total of 34 HC were recruited from the same geographic area in response to flyers and by word of mouth to match the EOS group on age, sex, and handedness. Controls were excluded if they had any current or past *DSM-IV* diagnosis (with the exception of minor anxiety disorders), treatment with psychotropic medications, 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 of substance use disorders were made using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version (<18 years of age) or the Structured Clinical Interview for