Developmental Cognitive Neuroscience 16 (2015) 16–22

Contents lists available at ScienceDirect

Developmental Cognitive Neuroscience

journal homepage: http://www.elsevier.com/locate/dcn

Preliminary findings demonstrating latent effects of early adolescent marijuana use onset on cortical architecture

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ARTICLE INFO

Article history:
Received 12 December 2014
Received in revised form 9 September 2015
Accepted 2 October 2015
Available online 9 October 2015

Keywords:
Adolescence
Marijuana
Cortical thickness
Gyrification
Morphology
FreeSurfer

ABSTRACT

Background: As the most commonly used illicit substance during early adolescence, long-term or latent effects of early adolescent marijuana use across adolescent developmental processes remain to be determined.
Methods: We examined cortical thickness, gray/white matter border contrast (GWR) and local gyrification index (LGI) in 42 marijuana (MJ) users. Voxelwise regressions assessed early-onset (age <16) vs. late-onset (≥16 years-old) differences and relationships to continued use while controlling for current age and alcohol use.
Results: Although groups did not differ by onset status, groups diverged in their correlations between cannabis use and cortical architecture. Among early-onset users, continued years of MJ use and current MJ consumption were associated with thicker cortex, increased GWR and decreased LGI. Late-onset users exhibited the opposite pattern. This divergence was observed in all three morphological measures in the anterior dorsolateral frontal cortex ($p < .05$, FWE-corrected).
Conclusions: Divergent patterns between current MJ use and elements of cortical architecture were associated with early MJ use onset. Considering brain development in early adolescence, findings are consistent with disruptions in pruning. However, divergence with continued use for many years thereafter suggests altered trajectories of brain maturation during late adolescence and beyond.

1. Introduction

With more than 25% of high school seniors reporting recent use and 6.5% of 12th graders being daily users (Johnston et al., 2014), marijuana (MJ) is the most frequently used illicit substance among adolescents. Across all age groups over 70% of new drug initiates start with using MJ at an average age of 18 years (SAMHSA, 2014). Indeed, the scope of MJ use prevalence is of great public interest, as MJ use in early adolescence is associated with increased risk of greater substance use, legal problems, disrupting education, injuries/medical problems, developing psychopathology, cognitive changes and chronic psychosocial struggles (CASA, 2011; Fergusson and Horwood, 1997; Fergusson et al., 1996; Patton et al., 2002). Taken together, rates of MJ use are suggestive of an epidemic based in adolescence, which is concerning not just due to societal cost, but also due to the potential to offset sensitive brain development during this period.

Despite its prevalence, the impact of MJ use on adolescent brain development is not fully known. Important neuromaturational processes during adolescence through young adulthood are believed to bring about improved higher-order cognition by refining neural systems locally and globally through white and gray matter development (Casey et al., 2005; Giedd, 2008; Paus, 2005). In general, gray matter reductions and cortical thinning coincide with increased white matter volume and organization through adolescence and young adulthood, suggestive of synaptic pruning and axonal myelination (Giorgio et al., 2010; Gogtay et al., 2004; Hasan et al., 2007; Lebel et al., 2010; Shaw et al., 2008). The endogenous cannabinoid (CB) system is also immature during adolescence (Anavi-Goffer and Mulder, 2009; Verdurand et al., 2011). In an animal model (Verdurand et al., 2011) imaged CB1 receptor binding using PET and found relatively lower activation of CB1 receptors in adolescent rats compared to adult rats in brain areas including those in the frontal cortex, temporal lobe (hippocampus and amygdala) and sub-cortical regions including striatal regions, thalamus, hypothalamus, superior colliculus. Thus, adolescence represents a

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http://dx.doi.org/10.1016/j.dcn.2015.10.001

developmental period with vulnerability to structural and functional changes due to exogenous MJ exposure.

Adolescent MJ use has the potential to cause structural and functional changes in the brain by altering cannabinoid signaling. One possible mechanism would be blunt neurotoxic influence. For example, delta9-tetrahydrocannabinol (THC), the primary psychoactive component in MJ that binds CB1 receptors, is reported to cause cell shrinkage and damage DNA strands in THC-treated neuron cultures (Chan et al., 1998). This may be the mechanism by which smaller volumes have been observed in individuals exposed to cannabis during adolescence (Battistella et al., 2014). However, it is more likely that MJ exerts its influence on brain development indirectly. The cannabinoid system plays a role in modulating other neurotransmitters, including gamma-aminobutyric acid (GABA), glutamate and monoamines (Lopez-Moreno et al., 2008). Specifically, activation of CB1 receptors is associated with down-regulating inhibitory GABAergic transmission in cortical interneurons during adolescence (Caballero and Tseng, 2012; Cass et al., 2014). In addition, CB signaling inhibits microglia function (Walter et al., 2003). These two points are important because cortical pruning processes involve glial-mediated synaptic elimination and altering the excitatory/inhibitory balance is liable to disrupt the selective tagging and preserving synapses (Selemon, 2013). The impact of this indirect influence on the developing brain may be in the observations of abnormal connectivity in those who began MJ use in adolescence (Jacobus et al., 2009). Evidence from human neuroimaging studies lends greater support to MJ-related disruptions to brain development.

Structural neuroimaging studies have indicated that volumes of several brain areas are smaller in heavy adult MJ users especially in areas enriched with cannabinoid 1 (CB1) receptors, such as medial temporal lobe, and prefrontal cortex (Lorenzetti et al., 2010). Studies of adult chronic MJ users note brain volume reductions in temporal lobe, insula, and prefrontal cortex, amygdala and hippocampus (Battistella et al., 2014; Cousijn et al., 2012; Filbey et al., 2014; Matochik et al., 2005; Yucel et al., 2008). Among different characteristics of MJ involvement (e.g., dependence symptoms, use frequency, consumption), the age of initial MJ use is a robust factor that has been associated with smaller brain volumes in users. For example, Battistella et al. (2014) observed left parahippocampal gyrus and right temporal pole structural differences in 25 regular MJ users compared to 22 occasional users, however, even the occasional users who began smoking MJ during adolescence (before age 18) demonstrated similar brain changes as the regular users. Our group has also found links with early MJ use onset (Bava et al., 2009) and structural connectivity with orbitofrontal cortex in a cohort of daily MJ users, suggesting complex neuroadaptive processes related to MJ use in the context of adolescent brain development (Filbey et al., 2014). These findings underscore the potential for significant heterogeneity in brain changes among adult MJ users, especially those who began using MJ during neurodevelopment.

Studies comparing early adolescent MJ use to users initiating MJ use in later adolescence provide further evidence for the potential of MJ to cause enduring change. The few studies that have directly investigated the timing of the effects of MJ during adolescence have noted divergent neurodevelopment effects. For example, in an fMRI study by Gruber and colleagues, functional and behavioral differences during an interference task were reported between early (before age 16) and late (after age 16) MJ users (Gruber et al., 2012) (Sagar et al., 2015). The same group also reported decreased white matter integrity in early onset vs. late onset MJ users (mean age 14.46 vs. 17.93) (Gruber et al., 2014). Similar differential effects have also been noted in parietal lobe activation between early and late adolescent binge drinkers during a spatial working memory task (Tapert et al., 2004). These studies highlight the importance of clarifying the differential neural effects of early- and late-adolescent onset use.

To that end, in the current study, we compared daily MJ users who were early onset users (<16 years old) versus late onset users (≥16 years old) on measures of cortical morphology that are sensitive to developmental changes. We aimed to characterize both the effect of early onset status on cortical morphology as well as assess for morphological patterns linked to the continued use of MJ after early and late adolescent MJ initiation. We expected early onset users to show a morphological pattern consistent with disruption of early adolescent brain development (e.g., increased cortical thickness, greater gray/white definition of the cortical ribbon via disruptions to adolescent pruning processes) that may be more consistent with indirect impact of MJ of brain development. While gray matter decline has been shown to be associated with marijuana use, particularly in areas rich in CB1 receptors, increased cortical thickness and greater gray/white definition in the cortical ribbon point to potential disruption in neurodevelopment (i.e. synaptic pruning) that may result from MJ use at key developmental stages (i.e. earlier as opposed to later in adolescent neuronal development). Such disruptions may extend to gyrification as well. While this process begins in utero, there is evidence that gyrification is ongoing into adolescence (Armstrong et al., 1995; Alemán-Gómez et al., 2013; Klein et al., 2014) and may also display aberrant developmental patterns in the presence of MJ use.

2. Methods

This study was approved by the University of Texas at Dallas (UTD) and University of Texas Southwestern Medical Center (UTSW) Institutional Review Boards. All participants were recruited from the Dallas-Ft.Worth metro area via flyers and advertisements. Following informed consent, MJ users completed two sessions – a baseline appointment for collecting demographic, psychosocial and behavioral measures and a thorough substance use history. Three days later the participants returned for a neuroimaging appointment. Prior to their scanning session, participants were asked to be abstinent from MJ use for 72 h, from alcohol for 24 h, and from caffeine and cigarettes for the preceding 2 h. These were confirmed by self-report (MJ, alcohol, caffeine and cigarettes), quantitative THC urinalysis (MJ), and by breath alcohol level of .000 (alcohol) at the start of their session.

2.1. Participants

We scanned 45 regular heavy MJ users as part of the parent project. Inclusion criteria were: right-handedness, English as the primary language and no histories of psychosis, traumatic brain injury, and MRI contraindications (e.g., pregnancy, non-removal metallic implants, claustrophobia). One subject reported a history of anxiety and depression and one other reported a history of ADHD as a child. Additional exclusions for the current study included: Axis I diagnosis (via SCID) other than cannabis use disorder, unusable sMRI due to motion artifact or poor signal-to-noise ratio that precluded accurate tissue segmentation ($n = 1$) and incomplete drug use histories ($n = 2$). Of the 42 remaining cases, 22 were early onset users (onset of first use before age 16). Group categorization using onset of regular use as opposed to onset of first use maintained the same grouping (mean early onset of regular use = 16.5, mean late onset of regular use = 19.0). Regular use was defined as at least one time per week. To determine how age of onset of regular MJ use influenced our reported effects, we performed these analyses while covarying for age of onset of regular use (see Supplement). Table 1 summarizes demographic and substance use information according to onset status. Table 2 summarizes the correlation between