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The impact of initiation: Early onset marijuana smokers demonstrate altered Stroop performance and brain activation☆

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ABSTRACT

Marijuana (MJ) use is on the rise, particularly among teens and emerging adults. This poses serious public health concern, given the potential deleterious effects of MJ on the developing brain. We examined 50 chronic MJ smokers divided into early onset (regular MJ use prior to age 16; $n = 24$) and late onset (age 16 or later; $n = 26$), and 34 healthy control participants (HCs). All completed a modified Stroop Color Word Test during fMRI. Results demonstrated that MJ smokers exhibited significantly poorer performance on the Interference subtest of the Stroop, as well as altered patterns of activation in the cingulate cortex relative to HCs. Further, early onset MJ smokers exhibited significantly poorer performance relative to both HCs and late onset smokers. Additionally, earlier age of MJ onset as well as increased frequency and magnitude (grams/week) of MJ use were predictive of poorer Stroop performance. fMRI results revealed that while late onset smokers demonstrated a more similar pattern of activation to the control group, a different pattern was evident in the early onset group. These findings underscore the importance of assessing age of onset and patterns of MJ use and support the need for widespread education and intervention efforts among youth.

1. Introduction

Marijuana (MJ) is predicted to become a multi-billion dollar industry within the next five years. Currently twenty-three states and the District of Columbia have legalized medical MJ, while four (Colorado, Washington, Oregon, and Alaska) have also approved recreational use. As voters say "yes" to MJ, benefits of use are often underscored, while negative effects may be overshadowed. This shift in national attitudes is occurring despite mounting evidence of the deleterious effects of MJ (Lisdahl et al., 2014; Lubman et al., 2014), particularly on the developing brain. Although once considered to be complete by early adolescence, longitudinal studies demonstrate that the brain continues to develop well into adulthood (Casey et al., 2005; Giedd et al., 1999; Gogtay et al., 2004), leaving adolescents and emerging adults particularly vulnerable to the potentially adverse effects of MJ on cognitive processes.

MJ continues to be the most widely used illicit substance and over the past several years, despite decreasing rates of use for other substances, rates of MJ use are climbing among youth (Johnston et al., 2014; Kann et al., 2014). According to the 2013 Monitoring the Future survey, more than 36% of 12th graders used MJ in the past year, and 6.5% used daily (Johnston et al., 2014). Moreover, survey data indicate that the perceived risk of MJ use is approaching historically low levels; less than half of high school students view MJ as harmful. Adolescents who perceive greater risk from MJ are less likely to try MJ, and as a result, the decrease in perception of harm is directly related to the recent increase in use. This trend also impacts public safety: the number of teens driving under the influence of MJ has surpassed the number of teens who drive drunk (Johnston et al., 2014). Youth are also initiating MJ use at alarmingly early ages; among those who began smoking during adolescence, the average age of onset was 16.3-years old (Substance Abuse and Mental Health Services Administration, 2013). This poses serious public health concerns given research findings demonstrating that MJ use is related to cognitive impairments particularly in those who initiate use during adolescence (Crane et al., 2013; Crean et al., 2011; Gruber et al., 2012a; Lisdahl et al., 2014; Solowij and Pesa,

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2010), and neuroimaging studies, which highlight the relationship between cognitive decrements and alterations in the brain (Batalla et al., 2013; Gruber et al., 2012b, 2013; Wrege et al., 2014).

Lisdahl et al. (2014) reported that MJ-smoking youth experience deficits in a variety of cognitive domains, including processing speed, attention, memory, and executive function. These findings support previous work, which revealed that MJ smokers exhibit processing deficits during frontally-mediated cognitive tasks, resulting in altered decision-making and behavioral inhibition (Gruber and Yurgelun-Todd, 2005), and that the deficits observed in MJ smokers were primarily attributable to those with early MJ onset (Gruber et al., 2012a). Additionally, Fontes et al. (2011) reported that early onset MJ smokers demonstrated significantly worse performance than both controls and late onset smokers on a neurocognitive battery designed to measure sustained attention, impulse control, and executive functioning. Neuroimaging studies have also revealed a relationship between age of MJ onset and functional alterations (Tapert et al., 2007), including work demonstrating a differential pattern of brain activation between early and late onset MJ smokers on the Multi-Source Interference Task (MSIT), a measure of inhibitory function (Gruber et al., 2012b). Several investigations have also reported a relationship between functional alterations and increased MJ use (Bolla et al., 2005; Hester et al., 2009; Nestor et al., 2010).

Impulsive personality traits have been identified as a risk factor and predictor of substance use (Brady et al., 1998; Guy et al., 1994; Heil et al., 2006; Vitaro et al., 1998). Impulsivity is characterized by weak executive control that compromises higher-order cognitive processes including inhibition, set-shifting, and utilizing feedback (Wrege et al., 2014). Higher levels of self-reported impulsivity, as measured by the Barratt Impulsiveness Scale (BIS), and risk taking have been reported in substance abusers (Lejuez et al., 2002, 2003; Gruber and Yurgelun-Todd, 2005). One study suggests that MJ smokers with higher levels of impulsivity held fewer negative expectancies related to MJ, and used MJ more often than those reporting lower levels of impulsivity (Vangsness et al., 2005). Further, Squeglia and colleagues (2014) found that poorer performance on tasks of cognitive inhibition/interference prior to initiation of substance use during early adolescence predicted increased frequency of MJ use in late adolescence. In combination with the neuroimaging findings that report alterations in response inhibition and decision-making (Gruber and Yurgelun-Todd, 2005; Gruber et al., 2012b; Hester et al., 2009; Jacobus et al., 2009; Schweinsburg et al., 2008; Tapert et al., 2007), impulsivity may reflect a stable trait which precedes substance use in MJ smokers and which may predict increased MJ use. In addition, recent work has demonstrated not only that MJ smokers reported higher levels of impulsivity than non-MJ smoking individuals, but that within early onset MJ smokers (regular use prior to age 16), higher levels of impulsivity were correlated with lower levels of white matter organization and coherence (Gruber et al., 2013). This suggests that MJ is related to both impulsivity and, particularly in early onset MJ smokers, alterations of white matter, critical for efficient communication between brain regions.

Overall, research has demonstrated that MJ smokers exhibit altered frontal function and suggests that cognitive deficits may compromise function, impairing the ability to make good decisions and inhibit inappropriate actions. Given these findings, we hypothesized that MJ smokers would perform more poorly on the Interference condition of the Stroop Color Word Test and would exhibit significantly different patterns of brain activation relative to healthy controls (HC). We also predicted that performance deficits in the MJ smokers would be specifically related to early onset of MJ use, and that these performance differences would correspond with a markedly different pattern of activation than the late onset smokers. Further, we expected that these results would be influenced by heavier patterns of MJ use in terms of frequency (smokes/week) and magnitude (grams/week).

2. Materials and methods

2.1. Participants

Participants were recruited from the Greater Boston Area community and included 50 chronic, heavy MJ smokers (age range: 17–46), divided into those with early onset (initiation of *regular* MJ use prior to age 16; $n = 24$) and late onset (regular MJ use at age 16 or later; $n = 26$). Thirty-four non-MJ-smoking, HCs (age range: 18–48) were also included. Participants were excluded if they met criteria for any *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) Axis I pathology (with the exception of MJ abuse/dependence in the smoking group), as assessed by the Structured Clinical Interview for DSM-IV, Patient Edition (SCID-P; First et al., 1994). Individuals were also excluded if they reported any significant head injury with loss of consciousness, history of a neurological disorder or serious medical problem, previous and/or current use of psychotropic medications, or were non-native English speakers. Further, no participant was enrolled if they reported more than 15 lifetime uses of any illicit drugs (except MJ for the smoking group) or recreational use of prescription or over-the-counter (OTC) medications. While a number of participants had completed other studies which have previously been published (Gruber et al., 2012a,b), approximately 30% of the participant pool was newly recruited and had not participated in lab-based clinical research prior to the current study. Further, cognitive and fMRI data collected for the current study has not previously been reported.

All MJ smokers were well-characterized as chronic MJ smokers. In order to qualify for study enrollment, MJ smokers had to have reported smoking a minimum of 2500 times in their lives, used MJ at least five out of the last seven days, tested positive for urinary cannabinoids, and met DSM-IV criteria for MJ abuse or dependence. In addition, in order to ensure that performance on measures of cognitive tasks was not impacted by acute intoxication, MJ smokers were required to abstain from smoking at least 12 h prior to their study visit. All participants were required to provide a urine sample upon arrival at the laboratory to assess for the presence of illicit substances, and in order to ensure adherence to the required 12-h abstinence, MJ participants were led to believe that our researchers could use this sample to detect MJ use within this time frame, a method we have successfully utilized in the past (Gruber et al., 2011, 2012a,b, 2013). Study participants who reported MJ use that violated the abstinence schedule or who appeared intoxicated were assessed for recent use and rescheduled for a later date. Individuals who tested positive for any illicit substance other than MJ were disqualified.

MJ use was quantified using a modified timeline follow-back procedure (Sobell et al., 1998). Participants provided information regarding history of MJ use, including age of onset, and duration of use (years), as well as current frequency (smokes/week), magnitude (grams/week), and mode of use using guided interview questions (i.e., *When did you first try MJ? Who were you with? How did you use it?*), which significantly facilitated recall. Lifetime use was also determined via the SCID-P. As previously mentioned, MJ smokers were further divided into two groups based on age of onset of regular MJ use in order to determine the potential differential impact of age of onset on cognitive function. For this study, age of 'regular' use of MJ was defined as the age at which subjects began using MJ on a routine, expected and consistent basis, and not the age at which they tried MJ for the first time. Although no uniform definition of early and late onset exists, these parameters have been utilized in several studies (Ehrenreich et al., 1999; Gruber et al., 2011, 2012a,b, 2013; Kempel et al., 2003; Pope et al., 2003).