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Research paper

Orbitofrontal connectivity is associated with depression and anxiety in marijuana-using adolescents

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ABSTRACT

Background: Prevalence of marijuana (MJ) use among adolescents has been on the rise. MJ use has been reported to impact several brain regions, including frontal regions such as the orbitofrontal cortex (OFC). The OFC is involved in emotion regulation and processing and has been associated with symptoms of depression and anxiety. Therefore, we hypothesized that adolescent MJ users would show disruptions in OFC connectivity compared with healthy adolescents (HC) which would be associated with symptoms of mood and anxiety.

Methods: 43 MJ-using and 31 HC adolescents completed clinical measures including the Hamilton Anxiety Scale (HAM-A) and Hamilton Depression Rating Scale (HAM-D). Resting-state functional magnetic resonance imaging data was also acquired for all participants.

Results: In MJ users, increased depressive symptoms were associated with increased connectivity between the left OFC and left parietal regions. In contrast, lower ratings of anxiety were associated with increased connectivity between right and left OFC and right occipital and temporal regions. These findings indicate significant differences in OFC connectivity in MJ-using adolescents, which correlated with mood/anxiety.

Limitations: Future studies with an increased number of female participants is required to address potential sex differences in connectivity patterns related to symptoms of depression and anxiety.

Conclusions: This study highlights the association between OFC connectivity, MJ use, and symptoms of depression and anxiety in adolescents. These findings provide further insight into understanding the neural correlates that modulate the relationship between comorbid MJ use and mood disorders and could potentially help us better develop preventive and treatment measures.

1. Introduction

In recent years, the prevalence of substance use among adolescents in the United States has increasingly become a cause for concern. According to the 2014 National Survey on Drug Use and Health, an estimated 2.3 million adolescents aged 12–17 are current illicit drug users. Estimates also suggest that 7.4% (1.8 million) are current marijuana (MJ) users indicating that MJ is one of the most commonly used illicit drugs among adolescents (Center for Behavioral Health Statistics and Quality, 2016). Additionally, with the recent legalization of MJ for both recreational and medical purposes, there has been an increase in the variability of MJ strains available as well as increased variability in concentration of Δ^9- tetrahydrocannabinol (THC), the key psychoactive ingredient in marijuana which could lead to potentially harmful effects in adolescents and adults (Hasin, 2018). Adolescent MJ use has been associated with decreased educational achievements (Silins et al., 2015), increased respiratory complications (Brook et al., 2008), as well as increased mental health problems such as psychosis, depression and anxiety and substance use disorders (Bagot et al., 2015; Brook et al., 2016; Guttmannova et al., 2017). This indicates an increased need to study and understand the associations between adolescent MJ use and behavioral and health outcomes.

Clinical studies have shown that adolescence is a period of increased vulnerability to maladaptive and addictive behaviors as well as to the onset of psychiatric disorders (Chambers et al., 2003; Paus et al., 2008; Steinberg, 2008). In addition, adolescence is a time during which

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critical neurodevelopmental and maturational processes occur that are related to behavioral control. It has been demonstrated that regions that underlie higher cognitive functions and emotional processing such as the prefrontal, parietal and temporal cortices continue to undergo developmental changes extending until approximately 25 years of age (Sowell et al., 2003; Sowell et al., 1999; Yurgelun-Todd, 2007). Consequently, brain regions associated with mood and cognition may be especially susceptible to the impact of MJ use during adolescence making it important to understand the implications of MJ use on the brain during this critical period of development.

Marijuana use has been associated with increased incidence of mental health conditions and a number of studies have reported a high incidence of comorbidity between MJ use and mood and anxiety disorders (Hayatbakhsh et al., 2007; Wittchen et al., 2007). A study of adult MJ smokers examining the relationship between MJ use, anxiety and mood disorders utilizing data collected as part of the Center for Addiction and Mental Health (CAMH) Monitor survey reported higher levels of anxiety and mood symptoms associated with MJ use using the 12-item version of the General Health Questionnaire. They examined heavy MJ users, classified as those who used MJ almost every day. Applying a logistic regression model, the authors also found that heavy and infrequent MJ use (MJ use of at least once in the past year but less than once a month) was associated with increased risk of anxiety and mood disorders, which was not observed among moderate users (MJ use of at least once per month to once per week) and non-users. These findings were interpreted as being indicative of a possible dose-response effect that needs to be studied further (Cheung et al., 2010). Lev-Ran et al. (2014) completed a systematic review examining the relationship between depression and MJ use based on longitudinal studies. They included investigations that controlled for baseline depressive symptoms and found that the risk for developing depression was significantly associated with MJ use that was initiated either during adolescence or adulthood. The relationship with depression was particularly strong for individuals with heavy MJ use defined as either weekly MJ use or those with a DSM-IV diagnosis of cannabis use disorder (Lev-Ran et al., 2014). Furthermore, in a separate review by Degenhardt and colleagues that included both cross-sectional and longitudinal studies, a similar association between heavy MJ use and depression was observed. The authors also found that the association was attenuated in infrequent users. The investigators reported that increased levels of depressive symptoms during adulthood were linked with earlier onset of MJ use suggesting that MJ exposure during adolescence may lead to increased risk for development and/or exacerbation of depressive symptoms (Degenhardt et al., 2003). A subsequent longitudinal study by Degenhardt et al. (2013) examined the relationship between MJ use in adolescence and the presence of depression and anxiety disorders at 29 years of age. Secondary school students were recruited in two separate waves of the study (Mean age at Wave 1: 14.9 years and Wave 2: 15.5 years). Participants were assessed for psychopathology and MJ use over the course of 15 years at seven different time points. Symptoms of depression and anxiety during adolescence were evaluated using the revised Clinical Interview Schedule and both major depressive disorder and anxiety disorder were defined using the Composite International Diagnostic Interview at 29 years. MJ use was assessed using self-report and participants were classified into non-users, occasional users and weekly or daily users. Findings indicated that daily MJ use during adolescence was associated with twice the risk of developing anxiety disorders during adulthood compared with less frequent use. However, no significant association was observed between adolescent MJ use and depression (Degenhardt et al., 2013). In contrast, more recent studies have reported that MJ use is not associated with depression and anxiety when data analyses adjust for confounding factors such as alcohol, other drug use, and socio-demographic factors (Danielsson et al., 2016; Grunberg et al., 2015). Although the relationship between MJ use and mood disorders including depression and anxiety have produced inconsistent results due to a number of methodological considerations including heterogeneity in study populations, variation in measures of depression and anxiety administered, as well as inconsistent definition of MJ use, there is strong evidence to suggest that MJ use, especially during adolescence, may be associated with depression and anxiety (Kedzior and Laeber, 2014; Rubino et al., 2012; van Laar et al., 2007).

Despite the ongoing debates surrounding the association between MJ use and mood and anxiety symptoms, no clear mechanism has been identified to underlie this relationship. Marijuana use has been associated with structural and functional alterations of a wide range of brain regions including prefrontal regions and the orbitofrontal cortex (OFC) (Battistella et al., 2014; Camchong et al., 2017; Price et al., 2015). The OFC has been implicated in various functional domains including sensory integration; higher order executive functions as well as reward-related behaviors (Kringelbach, 2005; Rolls, 2004b; Sescousse et al., 2010). Furthermore, the OFC is a region that has been shown to play a key role in the integration and processing of sensory and emotional stimuli (Rolls, 2004a). A number of studies to date have found that the OFC is impacted by MJ use. For instance, Volkow et al. (1996) used positron emission tomography methods to demonstrate that adult MJ users who met DSM-III-R criteria for cannabis dependence showed significantly increased metabolic response in the OFC. These investigators compared healthy controls and MJ users following administration of THC, and observed the differences in metabolic response (Volkow et al., 1996). Additionally, in a study examining structural alterations in adolescent MJ users, it was observed that right medial orbital prefrontal cortex volume was reduced in MJ-using subjects compared to healthy controls (Churchwell et al., 2010). Examination of structural and functional alterations associated with chronic MJ use in adults by Filbey et al. (2014) demonstrated that MJ users had significantly lower gray matter volume in the right middle and left superior orbitofrontal gyri. Furthermore, MJ users exhibited increased functional connectivity in the orbitofrontal network consisting of bilateral OFC and temporal gyri, which was associated with age of onset of MJ use and high lifetime MJ use (Filbey et al., 2014). Reduced OFC volume has been proposed to be a potential contributing factor to the initiation of MJ use as suggested by a longitudinal study by Cheetham et al. (2012). In this study, 12-year old participants were followed for 4 years and completed structural neuroimaging and MJ use assessments. At follow-up, 28 subjects had reported initiating MJ use. Moreover, study subjects who had smaller left and right OFC volumes at baseline were more likely to report using MJ, implicating smaller OFC volume as a possible predictor of MJ use (Cheetham et al., 2012).

A number of clinical investigators have also implicated the OFC in the pathophysiology of various psychiatric disorders including depression and anxiety (Drevets, 2007; Milad and Rauch, 2007; Webb et al., 2014). For instance, studies examining neural correlates of depression in adult and elderly patients have demonstrated significantly reduced OFC volume (Ballmaier et al., 2004; Bremner et al., 2002; Lai et al., 2000). Metabolic changes in the OFC region have also been associated with depression in adolescents. A study by Steingard et al. (2000) demonstrated that depressed adolescents had significantly increased choline/creatine and choline/N-acetyl aspartate ratios compared to healthy controls in the left OFC (Steingard et al., 2000). Alterations in the OFC have also been observed in several anxiety-related psychiatric disorders such as post-traumatic stress disorder, panic disorder and obsessive-compulsive disorder (Atmaca et al., 2012; Lagemann et al., 2012; Sekiguchi et al., 2013).

In summary, it has been demonstrated that the OFC region is altered in mood disorders as well as drug-related behavior. Nevertheless, no study has assessed the relationship between OFC connectivity and measures of depression and anxiety in MJ-using adolescents. Based on the findings reviewed above, we hypothesized that disruptions in OFC connectivity would be associated with symptoms of depression and anxiety in adolescent MJ users compared to healthy controls.