Published in final edited form as:

Psychopharmacology (Berl). 2015 August ; 232(16): 2939–2950. doi:10.1007/s00213-015-3931-0.

Effects of Marijuana Use on Prefrontal and Parietal Volumes and Cognition in Emerging Adults

Jenessa S. Price¹, Tim McQueeny², Skyler Shollenbarger³, Erin L. Browning³, Jon Wieser³, and Krista M. Lisdahl^{3,*}

¹Department of Psychiatry, Harvard Medical School – McLean Hospital, Belmont, MA

²Department of Psychology, University of Cincinnati, Cincinnati, Ohio

³Department of Psychology, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin

Abstract

Rationale—Chronic marijuana (MJ) use among adolescents has been associated with structural and functional abnormalities, particularly in developing regions responsible for higher order cognition.

Objectives—This study investigated prefrontal (PFC) and parietal volumes and executive function in emerging adult MJ users and explored potential gender differences.

Methods—Participants (ages 18–25) were 27 MJ users and 32 controls without neurologic or psychiatric disorders or heavy other drug use. A series of multiple regressions examined whether group status, past year MJ use, and their interactions with gender predicted ROI volumes. Post-hoc analyses consisted of brain-behavior correlations between volumes and cognitive variables and Fisher's z tests to assess group differences.

Results—MJ users demonstrated significantly smaller medial orbitofrontal (mOFC; $p=.004$, FDR $p=.024$) and inferior parietal volumes ($p=.04$, FDR $p=.12$); follow-up regressions found that increased past year MJ use did not significantly *dose-dependently* predict smaller mOFC volume in a sub-sample of individuals with at least one past year MJ use. There were no significant gender interactions. There was a significant brain-behavior difference by group, such that smaller mOFC volumes were associated with poorer complex attention for MJ users ($p<.05$).

Conclusions—Smaller mOFC volumes among MJ users suggest disruption of typical neurodevelopmental processes associated with regular MJ use for both genders. These results highlight the need for longitudinal, multi-modal imaging studies providing clearer information on timing of neurodevelopmental processes and neurocognitive impacts of youth MJ initiation.

Keywords

marijuana; prefrontal cortex; parietal lobe; executive function; gender; development

*Correspondence and reprint requests to: Krista M. Lisdahl, University of Wisconsin-Milwaukee, 2241 E. Hartford Avenue, Milwaukee, WI 53211. Telephone: 414-229-7159; Fax: 414-229-5219; krista.medina@gmail.com.

The authors have no conflicts of interest.

Rationale

Marijuana (MJ), containing delta⁹-tetrahydrocannabinol (THC), is the most popular illicit drug among adolescents and emerging adults (Martin et al., 1999; Johnston et al., 2013). According to the National Institute on Drug Abuse's (NIDA) Monitoring the Future survey, MJ has surpassed nicotine cigarette use among high school seniors, with 1 in 15 reporting daily or near daily use (Johnston et al., 2011; 2013). On balance, the Substance Abuse and Mental Health Services Administration (SAMHSA, 2013) reported MJ to have the highest rate of dependence or abuse of illicit drugs in 2012, affecting 4.3 million individuals.

Given that the average first MJ use occurs at age 17 (SAMHSA, 2013), effects of use on brain development and brain function is a major public health concern. Neuromaturation continues in several areas of the brain during adolescence and emerging adulthood, and anterior and superior regions, such as the prefrontal cortex (PFC) and parietal lobes, are among those last to develop (Sowell et al., 1999; Jernigan et al., 1991; Gogtay & Thompson, 2010). A significant amount of neural pruning, resulting in reduction in gray matter volume, and white matter proliferation occurs into emerging adulthood (Sowell et al., 2002; Jernigan et al., 1991; Pfefferbaum et al., 1994; Giedd et al., 1999), with females demonstrating earlier gray matter pruning while males have greater increases in myelination (Lenroot & Giedd, 2010). It has also been theorized that increased risk-taking during adolescence may be related to developmental trajectories of the PFC and the limbic system, such that as the PFC develops, it may impart increased top-down control of the limbic system (Galvan et al., 2006; Giedd et al., 1996). In turn, this is associated with optimized inhibitory control and affective processing (Lisdahl et al., 2013; Casey et al., 2008, 2005, 1997; Liston et al., 2006; Monk et al., 2003).

Among teenage and young adult chronic MJ users, subtle cognitive deficits have been noted in attention, processing speed, executive ability (including cognitive disinhibition and perseveration), and learning and memory (Fried et al., 2005; Gonzalez et al., 2012; Grant et al., 2012; Hanson et al., 2007, 2010; Harvey et al., 2007; Medina et al., 2007a; Piechatzek et al., 2009; Scholes & Martin-Iverson, 2009; Schwartz et al., 1989; Tait et al., 2011; Tapert et al., 2002; Thoma et al., 2011). A review by Schweinsburg, Brown, and Tapert (2008a) suggests that while neuropsychological functioning may return after approximately one month of abstinence, adolescent users show deficits up to six weeks after last use. Our lab recently reported a dose-dependent association between past year MJ exposure and poorer sustained attention, psychomotor speed, and cognitive inhibition in emerging adult users ages 18–25 who had been abstinent for an average of 50 days (Lisdahl & Price, 2012).

Therefore, in youth it appears that MJ may have a particular impact on cortical areas associated with working memory/processing speed and executive function, such as the PFC and parietal cortex, as well as the cerebellum (Medina et al., 2010) and subcortical regions (including the amygdala and hippocampus). Indeed, adolescent and emerging adult MJ users demonstrate altered functional patterns compared to controls in cortical areas associated with complex, higher-order cognitive processes, including the dorsolateral PFC, left superior parietal lobe, parahippocampal gyrus, cingulate gyrus, and insular cortex (Jager et al., 2010; Tapert et al., 2007; Jacobus et al., 2012; Schweinsburg et al., 2008b; Becker et al., 2010;

Sneider et al., 2013; Hester et al., 2009; Brody et al., 2002; Naqvi & Bechara, 2009). Of note, there is evidence that activation patterns may resemble those of non-using youth following monitored abstinence (Jacobus et al., 2012) and that nicotine withdrawal may moderate findings (Jacobsen et al., 2007).

With respect to brain morphology, some studies have found no differences between adult MJ users or controls in regional or global gray matter volumes or cortical shape (Tzilos et al., 2005; Hannerz et al., 1983), while others have noted reduced volumes in the hippocampus, amygdala, and total gray matter (Lorenzetti et al., 2010; Yucel et al., 2008; Wilson et al., 2000). However, adult findings may not generalize to youth because of ongoing neurodevelopment. Our laboratory, utilizing hand-tracing methods, has found that adolescent MJ users demonstrate a disruption of the gray matter pruning process that may be exaggerated in females (Medina et al., 2010; Medina et al., 2009; McQueeney et al., 2011). Medina et al. (2009) found that gender marginally moderated the effects of MJ use on PFC structure in adolescents, such that female users had larger volumes compared to control females and this was in turn associated with poorer executive functioning; volumes were not significantly different between MJ users and controls. Lopez-Larson and colleagues (2011) reported reduced cortical thickness (semi-automated method) in PFC regions including the right caudal middle frontal, bilateral insular, and bilateral superior frontal cortices among daily adolescent MJ users compared to controls, although the study sample included primarily males and individuals with Axis I disorders and heavy other drug use (Kroes et al., 2011; Drevets et al., 2008; McQueeney & Medina, 2011). Churchwell et al. (2010) found decreased right medial orbitofrontal cortex volumes among adolescent MJ users compared to controls utilizing a semi-automated method; however, the majority of this sample was also male. A similar study examining cortical surface structure in a sample of early adult users and controls also found cortical abnormalities, including reduced concavity of sulci bilaterally, especially for the right frontal lobe, even when controlling for cortical thickness and gyrification (mean ages 25.7 and 25.8 years, respectively; Mata et al., 2010). A recent study by Gilman and colleagues (2014) utilizing VBM noted morphometric abnormalities among emerging adult MJ users as compared to controls, with respect to density, volume, and shape in reward regions including the left nucleus accumbens and bilateral amygdala. In addition, DTI studies have found smaller volumes associated with increased non-clinical depressive symptoms (Medina et al., 2007b), and reductions in fractional anisotropy (FA) and increased diffusivity linked with increased impulsivity (Gruber et al., 2011; 2014). Taken together, evidence from structural and DTI data suggest that alterations in brain morphology among MJ-using youth are associated with inefficiency in frontal and limbic pathways..

Objectives

In summary, cortical abnormalities in PFC regions have been reported in MJ-using adolescents and emerging adults, but the effects of MJ use on structure in other cortical regions, such as the parietal cortex, have yet to be examined. The purpose of this study was to investigate the effects of chronic MJ use on frontal and parietal volumes and executive function in emerging adults (ages 18–25) with no current Axis I psychiatric diagnoses.

Additionally, we examined whether gender moderated these relationships (Giedd et al., 1996; Lenroot & Giedd, 2010; Burston et al., 2010; Lisdahl & Price, 2012).

Methods

The Institutional Review Board at the University of Cincinnati approved all aspects of the study. As part of a larger imaging genetics study (PI: Lisdahl, KM; 1R03 DA027457-01), participants were recruited from the community and local universities and screened by phone. Participants were required to be fluent in English, between the ages of 18–25 years, and right-handed. Exclusion criteria included MRI contraindications, history of chronic medical or neurologic illness or injury, history of a learning disability, known prenatal or perinatal concerns (including substance exposure), preexisting DSM-IV Axis I disorders independent of substance use, and refusal to remain abstinent from all drugs and alcohol for at least seven days prior to participation. Inclusion was based on whether they fit in one of two groups: current MJ users (≥ 25 past year MJ joints; >50 joints lifetime) or controls (<5 past year and <50 lifetime MJ joints) and balanced for gender. Please see prior publications (Lisdahl & Price, 2012 and Price et al., 2013) for greater detail regarding exclusionary criteria, subject screening, and protocol procedures. Relevant tasks for the present study are described below.

Following the phone screen, eligible participants completed either one or two sessions totaling five to seven hours, during which written informed consent was obtained, abstinence was verified via a urine drug screen and breathalyzer test, and study tasks were completed. Participants in the MJ group were permitted to continue the session with positive THC toxicology results. Those who tested positive for specimen adulteration or drugs and/or alcohol *other than* MJ were excluded. Height and weight were also collected to calculate body mass index (BMI; weight in kilograms/height in meters²) for inclusion as a covariate. Higher BMI has been associated with structural abnormalities in several regions, including frontal, in older adults (Ho et al., 2010; Gustafson et al., 2004; Pannaccuilli et al., 2006; Raji et al., 2010; Taki et al., 2008) and poorer executive ability in youth and adults (Bauer et al., 2010; Gunstad et al., 2007; Volkow & Wise, 2005; Hillman et al., 2006; Themanson & Hillman, 2006; Themanson et al., 2006; Lisdahl et al., under review); however, its relationship with MJ use remains unclear (Foltin et al., 1988; Smit & Crespo, 2001; Warren et al., 2005). Drug use frequency was recorded to exclude very heavy users as well as to control for possible variance in cognitive ability based on dosage. Semi-structured interviews, including a modified version of the Time-Line Follow-Back (Sobell et al., 1979), assessed *past year* and *lifetime* drug use frequencies. The Customary Drinking and Drug Use Record (CDDR) assessed withdrawal symptoms, DSM-IV abuse and dependence criteria, and substance-related difficulties (Brown et al., 1998; Stewart & Brown, 1995).

Consistent with findings from Lisdahl & Price (2012), the following tasks were administered. The Wide Range Achievement Test-4th edition (WRAT-4) Reading subtest (Wilkinson, 2006) estimates intelligence and quality of education for group comparison purposes (see Manly, 2002). Early-onset MJ users and current heavy users have been shown to have poorer Verbal IQ performances, and it was included in regression analyses as a potential confounding variable to control for this as well as educational differences that may

account for differences in cognitive performance (Pope et al., 2003; Fried et al., 2002; Fontes et al., 2011; Meier et al., 2012; Manly, 2002). The Wechsler Adult Intelligence Scale – Third Edition (WAIS-III) Letter Number Sequencing (LNS) total correct and the Paced Auditory Serial Attention Test (PASAT) total correct assessed complex attention. The LNS contributes to the WAIS-III Working Memory Index and requires the participant to hold auditory information in mind and accurately manipulate it in correct order (Wechsler, 1997). The examiner reads aloud jumbled groupings of numbers and letters ranging from two to eight items, and the participant is asked to immediately order the information numerically then alphabetically over a series of several trials (maximum 21). The PASAT is a working memory task in which single digit numbers are presented at the rate of one every two seconds (Gronwall, 1977). Participants must add each number to the preceding one, providing totals for the last two numbers presented across the presentation of 60 numbers. The D-KEFS Color Word Interference Test Inhibition total time to complete task assessed this domain. During the Inhibition condition, color words are printed in different colored ink (i.e., “red” is printed in green ink), and the participant must correctly name the color of the ink as quickly as possible without making mistakes (Delis et al., 2001).

High-resolution anatomical images were optimized on a 4T Varian MRI scanner. A T1-weighted, 3-D anatomical brain scan was obtained using a modified driven equilibrium Fourier transform (MDEFT) sequence ($T_{MD}=1.1$ s, $TR=13$ ms, $TE=6$ ms, $FOV=25.6 \times 19.2 \times 19.2$ cm, matrix $256 \times 192 \times 96$ pixels, flip angle=20 degrees; 15 min; Lee, et al., 1995). No participants with neurologic abnormalities on their scans were included in this sample.

All T-1 weighted 3D anatomical datasets underwent automatic alignment, removal of non-brain materials, and skull-stripping using the FreeSurfer software program, followed by whole brain segmentation of white and gray matter as well as registration of anatomical brain regions (see Fischl et al., 2002). Regional cortex volumes in mm^3 included in this analysis were: lateral orbitofrontal, medial orbitofrontal, superior frontal, rostral middle frontal, and inferior parietal. Left and right hemispheres were combined for increased power. All automated steps were checked for processing errors, and the author, blind to participant group status and gender and utilizing a randomized subject list, inspected automatic segmentation/parcellation masks, and manually edited the mask using the FreeSurfer editing program to ensure accurate segmentation for each case, using visual inspection in multiple views.

Preliminary analyses included ANOVAs and Chi-square tests to examine potential demographic differences as well as differences in past year drug use histories between MJ users and controls by gender. In order to test whether MJ impacts PFC and inferior parietal brain structure, one series of regressions was run as primary analysis with two post-hoc analyses. Data was analyzed to determine whether the assumptions of multiple regressions were met. The first regression examined whether *MJ group status* predicted ROI volume after controlling for gender, WRAT-4 Reading Standard Score, intracranial volume (ICV), body mass index (BMI), and past year alcohol, nicotine and hallucinogen use. The interaction term (MJ group-by-gender) was entered in the second block. Findings of primary analyses were similar when age was included as a covariate in the regression models, and thus it was excluded in these analyses to conserve degrees of freedom. Correction for False

Discovery Rate (FDR), using Benjamini and Hochberg method (1995), was conducted on the MJ group results.

In order to examine whether dose-dependent relationships existed between past year MJ use and ROIs that significantly differed by group, follow-up regressions were run to assess whether *past year frequency of MJ use* was significantly associated with ROI volume after controlling for the same covariates within a smaller subset of participants with at least one past year MJ use, including 6 controls (n=33). Although the continuous variable of past year MJ use was negatively skewed, ordinary least squares regression is robust to non-normality in the predictor variables as long as the dependent variables are normally distributed (which was confirmed). Further, prior literature has found that past year *raw* MJ use serves as predictors of *a priori* defined neurocognitive variables (Medina et al., 2009; Lisdahl & Price, 2012; Churchwell et al., 2010). Thus, the predictor variables were not transformed. Examination of DFBETAS (Cohen and colleagues, 2003) for the past year MJ regression coefficient for each case yielded two individuals above the recommended cut-off (.348, n=33), suggesting that they demonstrated undue influence on the analysis. As such, these two MJ users were removed from the analysis (final n=31). For all regressions, interpretations about statistical significance were made if $p < .05$. Additionally, f^2 was used to examine effect sizes for multiple regression analyses, defined as: small=.02-.14, medium=.15-.34, and large=>.35 (Cohen, 1988).

For the brain-behavior analysis, a series of correlations were run to examine the bivariate relationships between ROIs that significantly differed by group and complex attention, working memory, and cognitive inhibition. Next, Fisher Z tests were calculated to examine whether brain-behavior relationships were significantly different according to group.

Results

Participants were 59 right-handed emerging adults, 27 MJ users (12 female) and 32 controls (18 female; see Table 1). There were no group differences according to age [$F(1,58)=.28$, $p=.60$], gender composition [30 females, 29 males; $\chi^2(1)=.82$, $p=.37$], ethnicity [64.41% Caucasian, $\chi^2(4)=2.55$, $p=.64$], WRAT-4 Reading standard score [$F(1, 58)=2.65$, $p=.11$], education [$F(1, 58)=1.08$, $p=.30$], or BMI [$F(1, 58)=0.01$, $p=.93$]. There were no significant differences between groups for cognitive inhibition [$F(1, 58)=1.03$, $p=.31$], WAIS-III Letter Number Sequencing [$F(1, 58)=1.85$, $p=.18$], or PASAT Total Correct [$F(1, 58)=0.35$, $p=.54$].

All participants reported abstinence from all drugs and alcohol for at least six days. Urine toxicology results were negative for all illicit substances with the exception of THC, and measured blood alcohol content (BAC) levels were 0.00. 14 MJ users yielded positive urine toxicology results for THC during the second session. Groups did not differ in past year stimulant [$F(1,58)=2.35$, $p=.13$], ecstasy [$F(1,58)=2.47$, $p=.12$], inhalant [$F(1, 58)=1.19$, $p=.28$], sedative [$F(1, 58)=1.28$, $p=.26$], or opioid use [$F(1, 58)=1.90$, $p=.17$]. There were significant differences between groups for cotinine (a nicotine metabolite) level [$F(1, 58)=28.50$, $p=.000$] and past year nicotine [$F(1, 58)=9.12$, $p=.004$], alcohol [$F(1, 58)=7.26$, $p=.009$], MJ [$F(1, 58)=29.01$, $p=.000$], and hallucinogen [$F(1, 58)=5.36$, $p=.02$] use (see

Table 2). Overall, MJ users used more substances, especially nicotine, alcohol, MJ, and hallucinogens, within the past year versus controls, and these variables were included in all regressions as covariates.

There were significant differences between groups for lifetime nicotine [$F(1, 58)=8.73, p=.005$], alcohol [$F(1, 58)=11.97, p=.001$], MJ [$F(1, 58)=9.08, p=.004$], stimulant [$F(1, 58)=3.86, p=.05$], ecstasy [$F(1, 58)=6.51, p=.013$], and hallucinogen [$F(1, 58)=4.21, p=.05$] use, but not for inhalant [$F(1, 58)=2.13, p=.15$] or sedative [$F(1, 58)=1.98, p=.16$] use. In addition, there was a marginally significant difference between groups for lifetime opioid use [$F(1, 58)=3.40, p=.07$] (see Table 2). There was also a trend towards significance for age of first MJ use [$F(1, 58)=3.29, p=.078$]. MJ users not only tended to try more substances and accumulate higher frequencies over their lifetimes, but they also appeared to initiate MJ use slightly earlier than controls.

MJ Group Status & ROI Volume

After controlling for the aforementioned covariates, MJ users demonstrated significantly smaller medial orbitofrontal cortex (mOFC) [$\beta=-.36, p=.004, f^2=.18, FDR p=.024$] and inferior parietal volumes [$\beta=-.24, p=.04, f^2=.09, FDR p=.12$] (see Figures 1 and 2 and Table 3). Following FDR correction (Benjamini and Hochberg, 1995 method), only the mOFC finding was still significant. There were no significant group-by-gender interactions.

Dose-Dependent Relationships between Past year MJ use & Significant ROI Volume

As previously stated, the dose-dependent analysis was run in a subset of participants who reported at least 1 past year MJ use ($n=31$, mean=262 joints). Past year MJ use did not independently or in interaction with gender predict mOFC volume [$\beta=-.34, p=.135, f^2=.12$]. See Figure 3.

Brain-Behavior Relationships

In the *MJ users*, smaller mOFC volumes were significantly associated with poorer PASAT scores ($r=.44, p=.02$). Similarly, smaller inferior parietal volumes were significantly associated with poorer PASAT ($r=.39, p=.05$). In the *controls*, smaller inferior parietal volumes were significantly correlated with poorer PASAT ($r=.60, p<.001$).

Although the individual group correlations were not significant, there was a significant difference between the brain-behavior correlations for mOFC and LNS by group ($z=1.87, p<.05$). For MJ users, smaller volumes were associated with poorer working memory as measured by LNS, whereas the controls demonstrated the opposite relationship. There were no other significant differences in brain-behavior correlations between MJ users and controls.

Correlations in bold signify significantly different brain-behavior relationships by group.

Conclusions

This study examined PFC and parietal volumes and cognitive ability associated with MJ use in a sample of healthy emerging adults without independent Axis-I diagnoses. On average,

MJ users in the present study smoked just over one joint per day, ranging from twice monthly to greater than four joints daily, and were abstinent for approximately 13 days. MJ user group status significantly predicted smaller medial orbitofrontal (mOFC) and inferior parietal cortex volumes, although the latter did not survive FDR correction, after controlling for intracranial volume (ICV), gender, premorbid IQ and comorbid nicotine, alcohol and hallucinogen use. Effect size was medium for the association between MJ group status and smaller mOFC volume; the effect size for the parietal cortex was small. Increased past year MJ use did not significantly predict smaller mOFC volumes; the effect size was small. Examination of brain-behavior correlations revealed that in the MJ users, smaller mOFC and inferior parietal cortices were associated with poorer complex attention.

Results finding abnormal structure in the mOFC in MJ users are consistent with previous findings suggesting disruption of neurodevelopmental processes associated with chronic MJ use in adolescents and emerging adults. In particular, these findings represented replication of findings among adolescents from Churchwell et al. (2010) and Medina et al. (2009). Participants in this study were approximately 3 years older than those in Medina's (2009) study (mean ages = 21 years and 18 years, respectively). There was no evidence of an interaction between MJ use and gender in this sample. It would be expected that females would have undergone neural pruning processes earlier than males, as girls exhibit smaller gray matter volumes compared to same-aged boys in normal adolescent development (Giedd et al., 1996). The pattern of smaller mOFC volumes for emerging adults may demonstrate continued disruption of developmental processes associated with approximately 4 years of exposure to MJ. For this older cohort, considerable gray matter pruning in addition to white matter proliferation would be expected with increased age; thus, the smaller volumes noted may reflect a sensitive developmental time point during which gray matter pruning has occurred without progression of white matter proliferation, perhaps due to inadequate feedback from regions densely populated with cannabinoid receptors and heavily impacted by MJ exposure, such as PFC regions (Belue et al., 1995; Howlett et al., 2002; Viveros et al., 2005; Burston et al., 2010). Of note, while past year MJ use did not significantly dose-dependently predict mOFC volume, there was a trend in the hypothesized direction with a small effect size (.12, $p=.135$), such that increased past year use was associated with smaller volumes in the sample (see Figure 3). At this effect size, there was only 45% power; a sample size of 68 would be necessary to confirm the dose-dependent relationships.

Subtle neuropsychological deficits among MJ users are consistent with a separate report from a larger dataset, which examined relationships between past year MJ use and attention/executive function in emerging adults (Lisdahl & Price, 2012). Among MJ users, smaller mOFC and inferior parietal volumes were associated with poorer complex attention, as measured by the PASAT total score. Further, MJ users significantly differed from controls in the relationship between mOFC and working memory (LNS); MJ users demonstrated a significant negative relationship (poorer working memory, smaller mOFC) while the controls demonstrated the opposite pattern. It is important to note that in this study, raw scores were converted to z-scores for all measures (Delis et al., 2003), and mean z-scores were found to be within normal limits not suggestive of clinically significant findings (i.e., within 1 standard deviation). The orbitofrontal cortex has been associated with cognitive functions including reward and value-based decision-making, (Glascher et al., 2012) and is

also significant in addiction literature. ERP and fMRI studies have demonstrated increased activity in the ventromedial PFC/medial orbitofrontal cortex related to marijuana-cue reactivity and craving (Asmaro et al., 2013; Goldman et al., 2013). Further, the orbitofrontal cortex is located in close proximity to subcortical networks involved in reward and emotion and is involved in the dopaminergic mesolimbic pathway, a key circuit in addiction (Koob and Volkow, 2010). One quarter of the participants in this sample met criteria for a cannabis use disorder, and examination of neurocognitive differences according to severity of addiction may further explain dose-dependent findings. Certainly, smaller mOFC volumes would be expected to confer less efficiency in top-down executive control for complex attention, suggesting that subcortical regions involved in the reward circuit may instead demonstrate relatively greater functional contribution.

The primary findings lend further evidence of subtle inferior parietal abnormalities in adolescent and emerging adult MJ users, which is consistent with previous reports of inferior parietal abnormalities including increased cortical thickness (Lopez-Larson et al., 2011) and poorer white matter integrity (i.e., lower FA; Bava et al., 2009). In addition, inefficient activation patterns in this region have been identified among young users, during inhibitory processing (Tapert et al., 2007), spatial working memory (Schweinsburg et al., 2008b), and verbal working memory tasks (while also undergoing nicotine withdrawal; Jacobsen et al., 2007). However, this finding did not survive correction for multiple comparisons and the effect size was small. These results need replication in larger samples.

Longitudinal studies have found that early MJ use initiation (prior to age 18) is related to poorer cognition, including attention, executive ability, verbal IQ, and one standard deviation reduction on full-scale IQ, even following prolonged abstinence (Tamm et al., 2013; Pope et al., 2003; Fontes et al., 2011; Meier et al., 2012). Other groups have also found that early initiation is associated with greater abnormalities. For example, Gruber and colleagues (2011; 2012; 2014) have demonstrated that age of onset as well as frequency were related to poorer cognition, decreased FA, and increased impulsivity; further, among users with early onset, significant correlations between FA and impulsivity were noted. Both decreased superior PFC cortical thickness (Lopez-Larson et al., 2011) as well as total mOFC volume (Churchwell et al., 2010) have been associated with earlier onset of use. Thus, further examination of age of onset of regular use in addition to frequency of recent use is suggested by recent literature, as it may identify individuals at risk for negative neurocognitive consequences.

Limitations of the current study exist. Most MJ users engaged in relatively low to moderate use compared to samples of heavier users from other studies. In addition, several of the heavier MJ users tended to report: a) greater lifetime exposure to different substances (i.e., more likely to initiate use in multiple drug classes); b) regular use of alcohol and nicotine along with MJ use; and c) infrequent but recent use of other illicit drugs. These characteristics occurred despite significant effort to recruit appropriate groups for comparison, but speaks to the culture of MJ use among emerging adults in this region (e.g., chronic, recent comorbid nicotine, alcohol, and MJ use with increased recreational use of hallucinogens) as well as nationally (Ramo et al., 2013). While it is possible such group composition differences related to comorbid drug use may have contributed to the present

findings, only past year alcohol, hallucinogen and nicotine use were significantly different between groups. Indeed, alcohol and nicotine use have also been associated with alterations in brain structure and function (Squeglia et al., 2014; Fried et al., 2006; Jacobsen et al., 2005; Musso et al., 2006). As such, they were controlled for in regression analyses, and results demonstrated *independent* prediction according to group status. Future studies should seek to address the comorbidity of other drug use, particularly nicotine, through appropriate recruitment and study design in order to compare patterns as well as frequency of other substance and MJ use associated with neurocognition. Additionally, as both hemispheres were combined in order to improve detection, hemispheric differences were not assessed. Finally, because this project examined anatomical structure in a sample of emerging adults, results may not generalize to individuals outside of this cohort and should be interpreted in the context of neurodevelopment.

Lastly, it is possible that these structural abnormalities may be associated with premorbid factors that lead individuals to use MJ, or with lifetime exposure, rather than recent use. Indeed, several authors have discussed difficulty determining whether neurocognitive differences between MJ users and nonusers result from chronic use, or whether abnormalities may predict initiation of substance use (Lisdahl et al., 2013). Risk factors for substance use, such as family history of substance use disorders, have been related to structural and cognitive abnormalities (Hanson et al., 2010), including abnormalities in the OFC (Cheetham et al., 2012). While the current study was unable to support a dose-dependent relationship between past year MJ use and smaller mOFC volumes, there was a trend with small effect size in the hypothesized direction; additional prospective longitudinal studies with larger sample sizes would be necessary to determine whether causal relationships exist or if results are due primarily to premorbid differences.

In conclusion, these results demonstrate significantly smaller mOFC volumes in MJ users and a link between poorer complex attention and smaller mOFC volumes in otherwise healthy adolescents and emerging adults. Future directions should expand upon these findings towards examination of other tissue classes underlying volumetric abnormalities, including white matter structure and quality and indices of cortical architecture such as surface area, gyrification, and cortical thickness. Additionally, larger prospective longitudinal studies would provide clearer information regarding the timing of neurodevelopmental processes and impacts of initiation and frequency of MJ use. Considering legalization of medical and recreational MJ, increased potency of MJ (Sevigny et al., 2012), and diversion of medical MJ among youth (Salomonsen-Sautel et al., 2012), it is both timely and critical that researchers work towards an improved understanding of neurocognitive deficits associated with use as well as towards development of effective treatments aimed at delaying onset of MJ use among youth.

Acknowledgments

This research was supported by NIDA (R03DA027457-01, PI: Lisdahl; 2T32DA015036, PI: Scott E. Lukas), the Center for Environmental Genetics (CEG) pilot grant (#P30 ES06096, PI: Lisdahl), and URC Summer Graduate Student Research Fellowship Program (PI: Price, Mentor: Lisdahl).

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Figure 1.
Mean Medial Orbitofrontal Cortex Volume by Group According to Gender.

Figure 2.
Mean Inferior Parietal Cortex Volume by Group According to Gender.

Figure 3.
Scatterplot of Medial Orbitofrontal Cortex Volume by Past Year MJ Use According to Gender.

Table 1

Demographic and Neuropsychological Performance Information According to Group.

	MJ users (n = 27)	Controls (n = 32)
Age	21.41 (2.21) [18 – 25]	21.09 (2.32) [18 – 25]
Gender (% Female)	44.44%	56.3%
Ethnicity (% Caucasian)	62.97%	66.67%
WRAT-4 Reading Standard Score	106.81 (13.87) [85 – 134]	101.72 (10.14) [81 – 120]
Years of Education	13.48 (1.81) [9 – 17]	13.97 (1.79) [11 – 18]
Body Mass Index (BMI)	24.31 (4.30) [19.37 – 36.61]	24.43 (5.58) [18.90 – 40.23]
D-KEFS Color Word Interference Test (time in seconds)	44.33 (9.97) [27 – 70]	46.94 (9.69) [27 – 73]
LNS Total Score	12.63 (2.60) [8 – 16]	11.72 (2.53) [8 – 18]
PASAT Total Score	38.22 (8.91) [20 – 57]	36.45 (12.27) [15 – 59]

Notes:

**
 $p < .01$;*
 $p < .05$;▲ $p < .10$.

Table 2

Substance Use Information According to Group.

	MJ users (n = 27)	Controls (n = 32)
Past year nicotine use **	1546.30 (2229.04) [0 – 7350]	272.47 (789.61) [0 – 3052]
Cotinine levels **	4.04 (2.34) [0 – 6]	1.09 (1.87) [0 – 6]
Past year alcohol (# drinks) **	285.57 (319.79) [0 – 914]	96.67 (168.81) [0 – 878]
Past year marijuana (# joints) **	391.37 (418.47) [26 – 1558]	0.47 (1.27) [0 – 5]
Past year stimulants (# grams)	1.61 (5.66) [0 – 29]	0.13 (0.55) [0 – 3]
Past year ecstasy (# tablets)	0.07 (0.27) [0 – 1]	0.00 (0.00) [0]
Past year inhalants (# hits/pills)	0.04 (0.19) [0 – 1]	0.00 (0.00) [0]
Past year hallucinogens (# hits/pills) *	2.56 (6.25) [0 – 25]	0.00 (0.00) [0]
Past year sedatives (# hits/pills)	2.19 (10.96) [0 – 57]	0.00 (0.00) [0]
Past year opioids (# hits/pills)	2.78 (11.41) [0 – 59]	0.00 (0.00) [0]
Lifetime nicotine use **	8849.96 (15320.45) [0 – 64246]	755.91 (2266.11) [0 – 10697]
Lifetime alcohol (# drinks) **	1519.22 (1762.29) [37 – 6191]	373.21 (537.01) [0 – 2280]
Lifetime marijuana (# joints) **	1944.48 (3651.87) [57 – 15906]	1.91 (3.93) [0 – 15]
Lifetime stimulants (# grams) *	27.56 (78.30) [0 – 375]	0.41 (1.39) [0 – 6]
Lifetime ecstasy (# tablets) **	1.07 (2.39) [0 – 10]	0.00 (0.00) [0]
Lifetime inhalants (# hits/pills)	2.63 (10.22) [0 – 50]	0.00 (0.00) [0]
Lifetime hallucinogens (# hits/pills) *	11.04 (30.48) [0 – 155]	0.00 (0.00) [0]
Lifetime sedatives (# hits/pills)	3.70 (14.90) [0 – 77]	0.00 (0.00) [0]
Lifetime opioids (# hits/pills) ▲	5.04 (15.47) [0 – 79]	0.00 (0.00) [0]
Length of abstinence from MJ (days)	13.19 (7.42) [6 – 36]	102.00 (97.88) [18 – 292]; <i>n</i> =6
Age first used marijuana ▲	16.52 (1.97) [12 – 20]	17.82 (2.09) [15 – 22]; <i>n</i> =11

Notes:

**
p<.01;*
p<.05;▲ *p*<.10.

Table 3

Prefrontal and Parietal Volumes Expressed as a Percentage of ICV¹ by Group.

	MJ users (n = 27)		Controls (n = 32)		Regression values (<i>beta</i> ; <i>p</i>)	
	M (SD)	Range	M (SD)	Range	Group	Past Year MJ
Lateral Orbitofrontal	1.04 (0.28)	0.80 – 1.52	1.13 (0.22)	0.71 – 1.61	–0.18; 0.12	
Medial Orbitofrontal ^{**}	0.65 (0.13)	0.45 – 0.99	0.76 (0.16)	0.44 – 1.15	–0.36; 0.004 ^{**}	–0.27; 0.05 [*]
Rostral Middle Frontal	2.55 (0.49)	1.83 – 3.60	2.72 (0.42)	2.15 – 3.60	–0.14; 0.17	
Superior Frontal	3.52 (0.87)	2.21 – 6.22	3.49 (0.70)	2.34 – 4.89	–0.01; 0.92	
Total PFC Volume	7.77 (1.60)	5.42 – 12.15	8.10 (1.24)	6.15 – 10.25	–0.13; 0.17	
Inferior Parietal Cortex	2.13 (0.50)	1.41 – 3.29	2.25 (0.38)	1.60 – 3.08	–0.24; 0.04 [*]	

Notes:

¹Volumes reported in mm³ and totaled across hemispheres; Volume/ICV ratios multiplied by 100 (Churchwell et al., 2010).

^{**} *p*<.01;

^{*} *p*<.05.

Table 4

Bivariate Correlations and Fisher's z between ROI Volumes and Cognitive Variables by Group.

	MJ Users (n = 27)	Controls (n = 32)	Fisher's z
Medial Orbitofrontal Cortex			
D-KEFS Color Word Interference Test (time in seconds)	-.24	.06	-1.10
PASAT Total Score	.44*	.31 $\blacktriangle$	.55
WAIS-III Letter Number Sequencing	.35 $\blacktriangle$	-.15	1.87
Inferior Parietal Cortex			
D-KEFS Color Word Interference Test (time in seconds)	-.18	-.27	.34
PASAT Total Score	.39*	.60**	-1.02
WAIS-III Letter Number Sequencing	.30	.22	.31

Note: Correlations are Pearson Product Moment Correlations.

*
 $p < .05$;

**
 $p < .01$;

$\blacktriangle$ $p < .10$.