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Orbitofrontal cortex volume prospectively predicts cannabis and other substance use onset in adolescents

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Abstract

Background: Identifying neural characteristics that predict cannabis initiation is important for prevention efforts. The orbitofrontal cortex is critical for reward response and may be vulnerable to substance-induced alterations.

Aims: We measured orbitofrontal cortex thickness, surface area, and volume prior to the onset of use to predict cannabis involvement during an average nine-year follow-up.

Methods: Adolescents (n=118) aged 12–15 years completed baseline behavioral assessment and magnetic resonance imaging scans, then were followed up to 13 years with annual substance use interviews. Logistic regression examined baseline (pre-substance use) bilateral medial and lateral orbitofrontal cortex characteristics (volume, surface area, or cortex thickness) as predictors of regular cannabis use by follow-up. Post-hoc multinomial logistic regression assessed whether orbitofrontal cortex characteristics significantly predicted either alcohol use alone or cannabis+alcohol co-use. Brain-behavior relationships were assessed through follow-up correlations of baseline relationships between orbitofrontal cortex and executive functioning, reward responsiveness, and behavioral approach traits.

Results: Larger left lateral orbitofrontal cortex volume predicted classification as cannabis user by follow-up (p=0.025, odds ratio=1.808). Lateral orbitofrontal cortex volume also predicted cannabis+alcohol co-user status (p=0.008, odds ratio=2.588), but not alcohol only status. Larger lateral orbitofrontal cortex volume positively correlated with greater baseline reward responsiveness (p=0.030, r=0.348). There were no significant results by surface area or cortex thickness ($ps>0.05$).

Conclusions: Larger left lateral orbitofrontal cortex measured from ages 12–15 years and prior to initiation of substance use was related to greater reward responsiveness at baseline and predicted classification as a cannabis user and cannabis+alcohol co-user by final follow-up. Larger lateral orbitofrontal cortex volume may represent aberrant orbitofrontal cortex maturation and increasing vulnerability for later substance use.

Keywords

Cannabis, orbitofrontal cortex, cannabis use onset, alcohol, reward response

Introduction

By 12th grade (typically age 17–18 years), 45% of US students have tried cannabis, yet only 29% report that regular cannabis use is harmful (Miech et al., 2018). While longitudinal studies are limited, regular cannabis use is associated with neurocognitive performance decrements and alterations in brain morphometry and neural functioning (for review, see Gonzalez et al., 2017; Jacobus et al., 2015a; Meier et al., 2012), though genetics, socioeconomic status, and recency of use may play a significant role in behavioral outcomes (Meier et al., 2018; Scott et al., 2018). Adolescents may be more susceptible to neurotoxic influences (Schneider, 2008; Spear, 2000) as the brain, and the endocannabinoid system in particular (Mechoulam and Parker, 2013), undergoes vast change during this developmental period (Giedd and Rapoport, 2010; Gogtay et al., 2004; Shaw et al., 2008). Despite the high prevalence of cannabis use in youth and growing efforts to understand the effect of cannabis on neurodevelopment and cognition in adolescents and young adults, knowledge of neurobiological predictors of cannabis use onset remains scarce.

The orbitofrontal cortex (OFC) is postulated as vital to reward sensitivity and impulsivity (Costumero et al., 2013; Dom et al., 2005) and implicated at all stages of addiction (Volkow and Fowler, 2000). Sensitivity to reward, in turn, is strongly associated with substance use behaviors (Grant and Chamberlain, 2014). The OFC has multiple hypothesized roles in reward processing, including encoding rewards, reappraisal of stimuli, controlling inhibitory response, emotional appraisal, and decision making (Fettes et al., 2017; Walton et al., 2011). It is subdivided into medial and lateral sections that are anatomically and functionally

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distinct, as the lateral OFC contributes to choice value, prediction errors, extinction and devaluation, while the medial OFC is active in estimating relative subjective value and responding to reward (Fettes et al., 2017; Tekin and Cummings, 2002).

In cross-sectional studies of adolescents and emerging adults, cannabis use has been linked to smaller OFC volume (Battistella et al., 2014; Churchwell et al., 2010; Price et al., 2015), though not consistently (Chye et al., 2017; Lorenzetti et al., 2015). Teenage cannabis users have similarly shown thinner cortices in frontal regions (Lopez-Larson et al., 2011). Other studies have found thicker OFC in cannabis users, though some of these findings have not survived correction for multiple comparisons (Levar et al., 2018; Mashhoon et al., 2015). Continued use of cannabis over time has also been linked to increased cortical thickness in frontal regions (Epstein and Kumra, 2015; Jacobus et al., 2015b). Functionally, adolescents with history of cannabis use disorder (CUD) show different OFC resting state connectivity patterns (Camchong et al., 2017), including hypoactivation to rewarded outcomes after making risky decisions and hyperactivation to no-reward-outcomes compared to non-users (De Bellis et al., 2013). OFC activation patterns during a psychotherapy intervention have also been shown to predict substance-related behavioral change (Feldstein Ewing et al., 2017).

Early features of the OFC, then, may be potential biomarkers of risk for cannabis use onset, as has been argued by others (Whelan et al., 2012). Indeed, smaller OFC volumes in pre-teens predicted cannabis initiation four years later (Cheetham et al., 2012), and volumetric differences in OFC and other frontal regions predicted later problematic drinking and substance use disorder (SUD) (Cheetham et al., 2014, 2017).

Three primary cortical components are often considered as measures of neuroanatomy: cortical thickness, surface area, and volume. Each component demonstrates a different developmental trajectory (Ostby et al., 2009; Wierenga et al., 2014). Cortical thickness follows a linear curve, surface area is cubic, and volume (the product of thickness and area) is quadratic (Wierenga et al., 2014). Cortical thickness and surface area differ in neuroarchitecture (Wierenga et al., 2014), as it has been suggested that surface area is determined by the number of cortical columns while the number of cells within a column determines cortical thickness (Rakic, 1995). As each component may uniquely stand as a biomarker, each measurement is individually considered in this investigation.

Understanding neurobiological factors that predict cannabis use onset in adolescents may focus the development of prevention and intervention efforts (Volkow et al., 2015, 2016). To this end, we aim to investigate whether OFC estimates of thickness, surface area, and volume prior to substance use initiation (ages 12–15 years) predict cannabis use over a nine-year follow-up period. Based on previous findings (Cheetham et al., 2012, 2017), we hypothesize that smaller surface area, smaller volume, and thinner OFC at baseline will predict increased probability of classification as a regular (weekly) cannabis user at a follow-up appointment (ages 14–26 years). In addition, we expected smaller surface area, smaller volume, and thinner OFC would predict broader substance use, including heavy alcohol use, as has been found previously (Cheetham et al., 2017).

Methods

Participants. One hundred and eighteen participants were selected from a larger prospective study of adolescent substance use (n=295). All participants were between the ages of 12–15 years at baseline, recruited from local San Diego area schools and were followed for up to 13 years. At baseline, participants underwent structural and functional brain magnetic resonance imaging (MRI) scanning, neuropsychological assessment, and detailed assessment of substance use, mental health, and other life events, with annual follow-up consisting of detailed substance use assessment. Here, we focus on follow-up substance use information collected nine years post-baseline assessment (on average) as the outcome of interest. Structural imaging data collected at baseline (cortical thickness, area, and volume) from medial and lateral OFC were examined as predictors of substance use outcomes. All participants underwent written informed consent (or assent if under age 18 years and consent from their guardians) in accordance with the University of California, San Diego Human Research Protections Program.

Baseline exclusion criteria and groups at follow-up. Exclusion criteria for all participants at baseline included: more than two drinks of alcohol per week in their lifetime; any history of illicit drug use; history of SUD; diagnosis of a primary Diagnostic and Statistical Manual of Mental Disorders-4th Edition (DSM-IV; American Psychiatric Association, 1994) Axis-I psychiatric disorder other than conduct disorder; left-handedness; learning disability; history of head trauma or serious neurological disorder; serious physical health problems; use of psychotropic medications that alter brain function and/or blood flow; family history of bipolar I disorder or schizophrenia within a first-degree relative; antisocial personality disorder in either parent; color blindness; prenatal medical issues or exposure to substance use; claustrophobia; metal implants; or pregnancy.

All follow-up substance use data was examined and participants were categorized to clearly differentiate regular cannabis initiators from those with minimal to no use of cannabis, which resulted in two sub-samples: (a) cannabis users (CUs, n=50), defined as endorsing one year of regular cannabis use ($\geqslant$50 past-year cannabis use episodes); and (b) those with minimal to no cannabis use (minimal cannabis users (MCUs), n=68), defined as having no more than five past-year cannabis use episodes at any follow-up interview, never having engaged in regular weekly cannabis use, and having fewer than 50 lifetime cannabis use episodes. Neither group could have more than 50 lifetime other drug use episodes. Alcohol use was not considered in cannabis group categorization.

Measures

Substance use. The Customary Drinking and Drug Use Record (CDDR) was used to assess lifetime alcohol, cannabis, cigarette, and other drug use (Brown et al., 1998) defined as cumulative use (e.g. alcohol, cannabis) and episodes (i.e. number of days) reported at study entry. For other substance use, participants were individually asked about each of the following: amphetamines, barbiturates, hallucinogens, inhalants, benzodiazepines, opiates, ecstasy, ketamine, phencyclidine, gamma-hydroxybutyrate, or "any other drug" which was then recoded into the appropriate category. Substance use patterns were recorded at baseline and each annual follow-up. Consistent with prior work (Guttmannova et al., 2017; Jacobus et al., 2016; Pfefferbaum et al., 2016; Silins et al., 2015), subjects were classified as CU or MCU, based on past-year and lifetime cannabis consumption.

Demographics, emotional and executive functioning. To identify and exclude those individuals with Axis-I disorders other than conduct disorder, the Diagnostic Interview Schedule for Children (DISC) Predictive Scales (DPS; Lucas et al., 2001; Shaffer et al., 1996) was administered to each youth and parent at screening. During baseline study participation, parental income was reported during a clinical interview prior to the baseline imaging session. Parents also completed the Family History Assessment Module (Rice et al., 1995), which assessed family history of psychiatric and SUDs. Participants completed the Behavioral Inhibition System and Behavioral Approach System (BIS/BAS; (Carver and White, 1994)). BIS/BAS measures approach and avoidance behaviors of moving towards/away from appetitive or unpleasant stimuli, respectively, through five subscales: total approach, total avoidance, reward responsiveness, drive, and fun seeking. In addition, participants completed subtests from the Delis-Kaplan Executive Function System (D-KEFS; (Delis et al., 2001)), including Color-Word Interference, Trails, and Tower Task, as measures of executive functioning. The Wide Range Achievement Test (WRAT-3) Word Reading subtest was included as an estimate of premorbid intellectual functioning (Wilkinson, 1993).

MRI acquisition and processing. Prior publications detail MRI acquisition and processing (Jacobus et al., 2014); a brief description also follows. All processing was completed within our laboratory. A 3.0 Tesla CXK4 short-bore Excite-2 magnetic resonance system (General Electric, Milwaukee, Wisconsin, USA) with an eight-channel phase array head coil was used to acquire each scan at the University of California San Diego Center. A high-resolution T1-weighted anatomical spoiled gradient recall (SPGR) scan was acquired (TE/TR=min full, field of view=24 cm, resolution=1 mm^3, 170 continuous slices).

Neuroimaging data processing used FreeSurfer software (version 5.1, surfer.nmr.mgh.harvard.edu) to compute cortical surface reconstruction, volume, and thickness estimates (Dale et al., 1999). Standard preprocessing steps were conducted, including motion correction and averaging of T1-weighted images, removal of non-brain tissue and transformation to standardized space, segmentation of subcortical white and deep gray matter structures, intensity normalization, and tessellation of the gray/white matter boundary. A surface deformation algorithm places smooth borders differences in tissues classes, as indicated by the greatest shift in intensity and as it is guided by local MRI intensity gradients (Dale et al., 1999). Thus, submillimeter group differences are quantified (Fischl and Dale, 2000).

Distance from the gray/white matter boundary to the gray matter/cerebral spinal fluid boundary at each cortical surface vertex was used to calculate cortical thickness (Fischl and Dale, 2000). This process of cortical thickness measurement has been deemed valid and verified using histological analysis and manual measurements (Kuperberg et al., 2003). The entire cortex was also parcellated by gyral and sulcal regions to calculate surface area.

While blind to participant characteristics, one rater (JJ) followed reconstruction edit procedures to correct errors made during cortical reconstruction, including verifying the automated skull stripping and conducting a coronal plane slice-by-slice inspection of gray/white matter and gray matter/cerebral spinal fluid surfaces. Tissue misclassifications, such as residual dura matter classified as cortex, were modified as needed for correction.

Data analysis

Primary analyses. Analyses of variance (ANOVAs) were run between groups to evaluate differences on demographic and substance use variables. CUs and MCUs differed by age at baseline, which was included as covariates in regression analyses. In the primary analysis, logistic regression predicted cannabis group classification at follow-up by bilateral medial and lateral OFC volume, surface area, and cortical thickness, controlling for age at baseline, time to follow-up, intracranial volume (ICV), and family history of substance/alcohol use disorder (AUD). Twelve logistic regressions analyses in total were conducted to assess each hemisphere (right and left), subregion (medial and lateral region), and structural characteristics (volume, surface area, and cortical thickness).

Selection of covariates. To account for other factors that may be significantly related to OFC metrics and/or substance use onset, four covariates were selected. Family history of SUD was included as it has previously been associated with altered neuromaturation, even in substance-naïve adolescents (Cservenka, 2016) and increased risk of substance initiation (Gray and Squeglia, 2018). As adolescence marks a unique period of neurodevelopment (Giedd et al., 2015; Gogtay et al., 2004) and participants were between the ages of 12–15 years at baseline with varying lengths of follow-up, both age at baseline and time to follow-up were also included as covariates. ICV was included as a proxy for headsize, as this may influence volumetric differences in some individuals (Barnes et al., 2010).

Post-hoc cannabis analyses. To assess the potential for significant OFC metrics as a predictor not just of use but of level of use, correlational analyses were used to determine whether significant OFC metrics (i.e. baseline left lateral OFC volume) correlated with number of either past-year or lifetime cannabis use episodes.

Post-hoc alcohol analyses. Multinomial regression analyses examined the influence of significant baseline OFC regional predictors on alcohol use status in these groups by follow-up. For these analyses, three-groups (n=96) were subsequently defined for the alcohol status outcome variable and included: (a) a control group (n=23) that consisted of individuals who had used cannabis less than five times in the past year, had not binged nor had used alcohol more than 12 times in the past year, (b) an alcohol only group (n=25), where individuals had engaged in at least one binge episode and drank alcohol at least every other week and who had not used cannabis more than five times in the past year, and (c) a cannabis and alcohol group, consisting of individuals who, in the past year, had used cannabis at least 50 times, had engaged in binge drinking at least once, and drank alcohol at least every other week on average (n=48). Participants who did not fall into one of the three groups (n=22) were not included in the alcohol post-hoc analyses. For example, those individuals reporting some infrequent alcohol use were not able to be classified as a control or regular alcohol user based on our criteria above and therefore were not included in these analyses.

Results

Demographics

Mean age at baseline assessment was 13.48±0.71 years and mean age at last follow-up assessment was 22.22±2.03 years, with an

average of 8.74±1.93 total years in the study (see Table 1). CUs (n=50) included those who initiated regular (⩾50 past year episodes, averaging at least weekly use for a year) cannabis use by final follow-up. MCUs (n=68) were cannabis-naïve at baseline and had used cannabis less than five times in the last year at their final follow-up and used cannabis less than 50 times in their lifetime. CUs differed significantly from MCUs in lifetime alcohol use (F(1,116)=23.55, p<0.001), lifetime cannabis use (F(1,116)=84.69, p<0.001), past year cannabis use (F(1,116)=200.54, p<0.001), and lifetime other drug use (F(1,116)=41.50, p<0.001) by follow-up. They also differed by baseline age (F(1,116)=8.73, p=0.004). Baseline OFC surface area, volume, and cortical thickness did not significantly differ between CUs and MCUs.

Primary aims. Baseline left lateral OFC volume (Wald's χ^2=5.012, p=0.025; odds ratio (OR)=1.808, confidence interval (CI): 1.077–3.036; see Figure 1) predicted cannabis group classification, such that individuals with larger volume at baseline were more likely to have initiated regular cannabis use by follow up, controlling for age at baseline, time to follow-up, ICV, and family history of SUD/AUD. In addition, being older at baseline predicted cannabis group status (Wald's χ^2=8.635, p=0.003; OR=2.510, CI: 1.359–4.636). Neither surface area nor cortical thickness significantly predicted cannabis use status by follow-up.

Post-hoc analyses. Correlational analyses assessed whether either lifetime or past year cannabis use was associated with baseline left lateral OFC volume. Neither relationship was significant (lifetime: p=0.44, r=0.07; past year: p=0.11, r=0.15).

A multinomial logistic regression was performed to assess the relationship between baseline left lateral OFC volume and membership in an alcohol use group as defined above (i.e. controls, alcohol only, and alcohol+cannabis). Larger baseline left lateral OFC volume predicted alcohol+cannabis group status relative to controls (Wald's χ^2=7.102, p=0.008; OR=2.588, CI: 1.286–5.207), with no significant results between controls and alcohol only (Wald's χ^2=2.4111, p=0.120; OR=1.796, CI: 0.858–3.760) or alcohol only and alcohol+cannabis (Wald's χ^2=1.120, p=0.290; OR=0.694, CI: 0.353–1.365). Older age at baseline (Wald's χ^2=5.869, p=0.015; OR=2.987, CI: 1.232–7.238) also predicted alcohol+cannabis status relative to controls. Results remain the same whether or not other substance use is included as a covariate.

Exploratory analysis. Bivariate correlations were conducted between left lateral OFC volume estimates and measures of cognitive and behavioral control (i.e. D-KEFS subtests and BIS/BAS) in the CU group. Full results are presented in Table 2. Baseline left lateral OFC positively correlated with baseline BIS/BAS Reward Responsiveness in the CUs (r=0.348, p=0.030) in that greater volume was associated with greater reward responsiveness. No significant relationships were found between left lateral OFC volume and other BIS/BAS or executive functioning measures at baseline (ps>0.05).

Discussion

This study investigated structural characteristics of orbitofrontal regions from adolescents aged 12–15 years prior to substance-use initiation (i.e. cannabis and alcohol) as a predictor of regular cannabis use onset monitored over a period of nine years, on average. Novel findings indicate that a larger left lateral OFC volume predicted cannabis use group status (individuals who used cannabis at least weekly) in later adolescence/young adulthood, in contrast to prior studies of smaller OFC volume predicting cannabis use (Cheetham et al., 2012, 2017). Further, larger left lateral OFC volume uniquely predicted classification as a heavier substance user (i.e. cannabis and alcohol co-use), and was not related to classification as an alcohol user only. Baseline left lateral OFC volume also positively correlated with baseline reward responsiveness. However, neither SA nor CT predicated cannabis use group status. The ORs presented here suggest small to medium effect sizes; together these results suggest lateral OFC volume may be one biomarker of vulnerability to regular use of cannabis and alcohol, or heavier substance use patterns in general.

The lateral OFC contains axonal projections to the striatum, as well as connections with sensory networks (Fettes et al., 2017). Functionally, the lateral OFC plays a greater role in cognitive control regions and reversal learning, while the medial OFC is central in evaluating and assigning hedonic value, key for reward encoding (Fettes et al., 2017). It is possible that lateral OFC characteristics measured prior to substance use initiation may predict reward-based learning for substance use behaviors.

Our results are consistent with findings linking neurostructural characteristics of the OFC to substance use behaviors in adolescents and young adults (Cheetham et al., 2012, 2014, 2017), albeit directionally different. These results are also unique in that volume, SA, and CT were simultaneously assessed, rather than only examining volume, as other studies have done (Cheetham et al., 2012, 2014, 2017). For example, a similar study found that a smaller lateral OFC volume predicted cannabis use onset in adolescents over a four-year follow-up (Cheetham et al., 2012), with onset defined as any cannabis use by follow-up. A more recent study by the same research team also found that smaller OFC volume predicted lifetime history of SUD diagnosis by age 18 years, including CUD (Cheetham et al., 2017). In both of these studies, only 22–23% of the sample had transitioned to substance use/disorder and the baseline time-point was restricted to only 12-year-olds. In contrast, 42% of our sample transitioned to cannabis use and only 6% of users had a diagnosis of CUD (3% of total sample). Our inclusion of a broader baseline age range prior to substance use initiation (up to age 15 years) may provide new insight into how alterations in the pattern of cortical development beyond age 12 years may relate to neural vulnerability and behavioral outcomes. For example, decreases in estimates of cortical volume are typically expected during neuromaturation (Giedd and Rapoport, 2010). Given that prefrontal volume peaks around age 10.5–11 years for girls and 11.5–12 years for boys and then declines (Lenroot et al., 2007; Pfefferbaum et al., 2016; Vijayakumar et al., 2016), our findings suggest that youth who go on to regularly use cannabis may have a different neuromaturational trajectory in volumetric growth or may begin neuronal pruning processes later than optimal, putting them at greater risk of less efficient neural processing in reward networks and thus substance use initiation.

Further, consistent with proposed theories of OFC function (Costumero et al., 2013; Dom et al., 2005; Fettes et al., 2017), our results suggest a significant correlation between larger left lateral OFC volume and reward responsiveness at baseline. The combined

Table 1. Demographics and substance use characteristics.

	CU (*n*=50) M (SD) *range*	MCU (*n*=68) M (SD) *range*
Age, baseline[a]	13.70 (0.69) 12.39–15.07	13.32 (0.68) 12.13–14.71
Age, follow-up	22.11 (2.01) 16.11–26.84	22.30 (2.06) 14.40–26.52
Est. IQ (WRAT-3), baseline	111.54 (10.26) 80–132	112.50 (10.02) 83–132
% Female	66%	50%
% Hispanic	24%	24%
% Caucasian	64%	69%
Total length of follow-up interval in years	8.41 (2.00) 2.99–12.02	8.98 (1.86) 1.98–13.14
Number of follow-up visits	9.02 (2.05) 4–13	9.65 (1.73) 4–13
BDI, baseline	1.26 (2.28) 0–9	1.28 (2.47) 0–15
Family history of SUD/AUD	0.23 (.28) 0–1	0.17 (.29) 0–1
Cannabis use episodes, baseline	–	–
Lifetime cannabis use episodes, follow-up[a]	624.18 (555.44) 50–2518	5.24 (8.78) 0–39
Past year cannabis use episodes, follow-up[a]	197.20 (114.66) 50–381	0.59 (1.11) 0–4
% CUD diagnosis, follow-up	6%	–
Age of onset of regular cannabis use	18.78 (1.90) 15–23	–
Length of regular cannabis use, years	3.33 (2.09) 0.04–8.64	–
Alcohol use days, baseline	0.08 (.40) 0–2	0.02 (0.12) 0–1
Lifetime alcohol use days, follow-up[a]	437.88 (354.80) 40–1427	170.43 (243.92) 0–1113
Past year alcohol use days, follow-up[a]	118.80 (100.95) 7–443	57.04 (71.29) 0–337
Past year binge episodes, follow-up[a]	27.70 (48.37) 0–206	6.00 (11.92) 0–72
Lifetime other drug use, follow-up[a]	13.50 (15.79) 0–49	0.87 (3.09) 0–19
Left lateral OFC volume	9498.18 (1089.36) 7317–11361	9136.40 (1128.65) 6946–11423
Right lateral OFC volume	9640.84 (1230.05) 6287–11400	9378.12 (1187.16) 6785–12458
Left medial OFC volume	6384 (1139.00) 4608–8754	6407.78 (958.78) 4587–8790
Right medial OFC volume	6370.28 (861.95) 4635–8493	6338.26 (683.23) 5179–8239
Left lateral OFC cortical thickness	2.80 (0.18) 2.39–3.15	2.77 (0.18) 2.32–3.10
Right lateral OFC cortical thickness	2.83 (0.22) 2.19–3.33	2.81 (0.16) 2.42–3.18
Left medial OFC cortical thickness	2.73 (0.19) 2.22–3.06	2.74 (0.17) 2.38–3.27
Right medial OFC cortical thickness	2.72 (0.21) 2.18–3.08	2.73 (0.17) 2.34–3.18

(Continued)

Table 1. (Continued)

	CU (*n*=50) M (SD) *range*	MCU (*n*=68) M (SD) *range*
Left lateral OFC surface area	2867.94 (325.99) 2169–3382	2777.13 (316.04) 2099–3478
Right lateral OFC surface area	2938.92 (329.38) 2263–3383	2870.28 (330.56) 2193–3682
Left medial OFC surface area	1966.020 (344.28) 1506–2661	1961.50 (286.80) 1329–2716
Right medial OFC surface area	1945.36 (275.00) 1418–2618	1945.35 (248.55) 1529–2658

AUD: alcohol use disorder; BDI: Beck Depression Inventory; CU: cannabis user; CUD: cannabis use disorder; IQ: intelligence quotient; MCU: minimal cannabis user; OFC: orbitofrontal cortex; SUD: substance use disorder; WRAT-3: Wide Range Achievement Test.
Regular cannabis use is defined as weekly cannabis use.
[a]$p<0.05$.

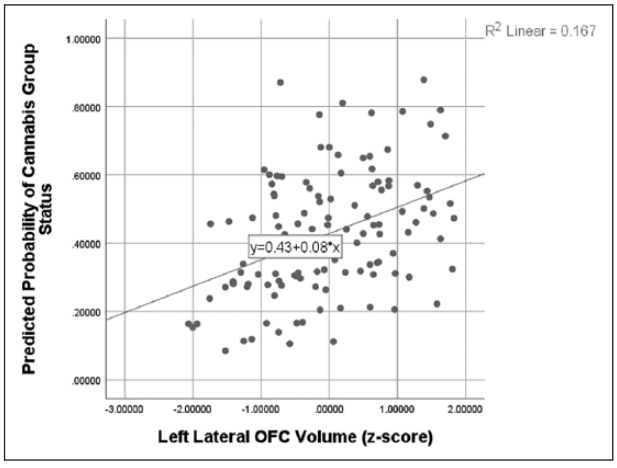

Figure 1. Scatterplot of relationship between baseline left lateral orbitofrontal cortex (OFC) volume and predicted odds (as determined through logistic regression) of initiating regular cannabis use by average nine-year follow-up.

Table 2. Exploratory correlations between baseline left lateral orbitofrontal cortex (OFC) volume and cognitive and behavioral control factors in the cannabis users group.

	p	*r*
D-KEFS		
Towers – total achievement	0.57	0.08
Color-word interference – inhibition	0.51	0.10
Color-word interference – inhibition/switching	0.17	0.20
Trails – switching	0.26	0.16
BIS/BAS		
Drive	0.87	0.03
Fun seeking	0.60	0.09
Reward responsiveness	0.03	0.35
BAS total	0.20	0.21
BIS total	0.42	0.13

BIS/BAS: Behavioral Inhibition System and Behavioral Approach System; D-KEFS: Delis-Kaplan Executive Function System.
All D-KEFS scores represent scaled score value, while BIS/BAS scores represent total raw scores for each subcategory.

results may represent a vulnerability of the OFC to both sensitivity to reward and substance use onset which may combine to increase risk of SUD, consistent with theories of addiction (Jordan and Andersen, 2017; Koob and Volkow, 2010; Volkow and Fowler, 2000).

Here we did not find SA or CT of the OFC to be significant predictors of cannabis use onset, despite the fact that the product of these two characteristics (i.e. volume) predicted onset. Volume may be accounting for cellular (Rakic, 1995) and genetic (Panizzon et al., 2009) determinants that are not readily captured by SA or CT alone. Volume, then, may be a sensitive measure to underlying histological changes that nuanced factors of SA and CT do not reveal when assessed alone. Thus, as SA, CT, and volume may elucidate unique patterns that will not always be captured by just one factor (Infante et al., 2018; Raznahan et al., 2011; Winkler et al., 2010), consideration of all neuroanatomical structural characteristics is warranted.

As in prior studies (Cheetham et al., 2012, 2017), the present sample of CUs also had high levels of alcohol, cigarette, and other drug use. This raises the question of whether the findings better explain general vulnerability to substance use, alcohol use, or cannabis use alone. Given post-hoc analysis of left lateral OFC predicting alcohol and cannabis group status relative to controls, with no significant prediction of the alcohol only group, it appears that, at minimum, larger left lateral OFC predicts heavy substance use if not cannabis use in particular.

Our findings should be interpreted in light of several considerations. CUs had higher levels of both alcohol use and lifetime other-drug use by the time of follow-up, though both groups were naïve at baseline. Nevertheless, it cannot be ruled out that lateral OFC volume predicts overall substance use behaviors, rather than uniquely being related to cannabis use onset. Here we investigated aspects of neuroanatomical structure in one specific brain region, OFC, finding a modest effect; other regions and functional relationships are also likely important factors in substance use onset. Future research should include multi-modal imaging techniques. While all 12 primary analyses were planned *a priori*, it is important to note that multiple comparisons corrections were

not applied and therefore replication is needed. Neurodevelopment and substance use risk are both influenced by many environmental and genetic factors (Creze et al., 2014; Fjell et al., 2015; Giedd et al., 2015; Gray and Squeglia, 2018; Jordan and Andersen, 2017), and how these factors may directly or indirectly influence neuromaturation trajectories and behavioral outcomes associated with the OFC will be further investigated in future work (Jernigan et al., 2018). Finally, and consistent with other studies (Rosen et al., 2018), participants in this study were relatively high-functioning healthy individuals (e.g. non-treatment seeking).

Our study builds on the existing literature, suggesting larger lateral OFC volume prior to substance use initiation related to early reward responsiveness traits and future cannabis use onset. Specifically, larger left lateral OFC volume predicted onset of regular cannabis use and heavier substance use patterns in general (cannabis+alcohol) in adolescents followed over an average of nine years. Future studies are needed to provide additional information on biological and psychological risk factors that predispose adolescents to initiating cannabis use. Such information will inform novel prevention and intervention efforts that aim to prevent and/or reduce problematic substance use.

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