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BOLD Responses to Inhibition in Cannabis Using Adolescents and Emerging Adults after Two Weeks of Monitored Cannabis Abstinence

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Abstract

Rationale.—Previous studies have suggested that chronic cannabis use has been associated with increased blood oxygen level dependent (BOLD) response during a response inhibition task; however, these studies primarily included males.

Objectives.—We investigated whether gender moderated the effects of cannabis use on BOLD response and behavioral performance during a Go-NoGo task in adolescents and young adults following two weeks of monitored abstinence.

Methods.—Participants included 77 16–26 year olds (MJ=36, Controls=41). An emotion based Go-NoGo task required participants to inhibit their response during a calm face. A whole-brain analysis looked at differences between cannabis group, gender, and their interaction.

Results.—Significant greater BOLD responses were observed in cannabis users compared to controls in the left frontal cortex, left cingulate cortex, and the left thalamus during correct response inhibitions; gender did not moderate these effects.

Conclusion.—Supporting previous research, cannabis users showed greater BOLD responses in core areas associated with response inhibition during a Go-NoGo task, even after a minimum of two weeks of abstinence.

Introduction

Cannabis use remains one of the most commonly used drugs by adolescents and emerging adults with 37.1% of high school seniors and approximately 35.3% of young adults (aged 19–28) reporting use in the past 12 months (Johnston et al., 2019; Schulenberg et al., 2019). Due to the ongoing brain development during this time (Giedd et al., 1999), research suggests that adolescent cannabis use has significant negative impact on brain structure and

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function (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; Lubman, Cheetham, & Yücel, 2015; A. D. Schweinsburg, Brown, & Tapert, 2008), particularly in frontal regions associated with executive functioning, although there has been controversy as to whether these deficits remain following at least 72 hours of abstinence (Scott et al., 2018).

Inhibition is a key component to executive control and attention that is best defined as the ability to suppress responses to a stimulus (Aron, 2007). In particular, response inhibition has garnered significant interest within the field of research (Aron, 2007; Chambers, Garavan, & Bellgrove, 2009; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). Response inhibition is one's ability to suppress automatic/prepared/cued responses to a task, which is often measured through tasks such as Go/NoGo or Stop tasks (Nigg, 2000). Regular cannabis use has been associated with inhibitory deficits on tasks such as the Stroop (Battisti et al., 2010; Fontes et al., 2011; Gruber & Yurgelun-Todd, 2005), Go/NoGo related tasks (Bolla, Brown, Eldreth, Tate, & Cadet, 2002), and decision making tasks (Solowij et al., 2012). These inhibitory deficits have been shown to moderate the relationship between cannabis use and negative behavioral outcomes, such as risky sexual behavior (Schuster, Crane, Mermelstein, & Gonzalez, 2012). While these deficits have been shown within attention based tasks (Battisti et al., 2010; Bolla et al., 2002; Fontes et al., 2011; Gruber & Yurgelun-Todd, 2005; Solowij et al., 2012) and self-report measures (Gruber, Silveri, Dahlgren, & Yurgelun-Todd, 2011), some studies suggest that there are no observable differences with response inhibition in young adult cannabis users (Gonzalez et al., 2012; Grant, Chamberlain, Schreiber, & Odlaug, 2012). However, it is possible that there are still differences in the inhibitory network, even in the absence of downstream behavioral deficits.

Only a handful of imaging studies have directly examined Blood Oxygenated Level Dependent (BOLD) responses in cannabis users engaging in an inhibitory functional magnetic resonance imaging (fMRI) task (Behan et al., 2014; Gruber & Yurgelun-Todd, 2005; A. M. Smith et al., 2011; Tapert et al., 2007). These studies have found significantly more BOLD activation with similar task performance in brain regions related to response inhibition compared to controls (J. L. Smith, Mattick, Jamadar, & Iredale, 2014; Tapert et al., 2007). Across multiple studies, cannabis users were shown to have greater BOLD responses within brain regions of interest (ROI's) that are linked with inhibitory processes as well as recruited additional neighboring brain regions to complete the inhibitory task. Specifically, cannabis users demonstrated aberrant activation in the anterior cingulate cortex (Gruber, Dahlgren, Sagar, Gonenc, & Killgore, 2012; Hester, Nestor, & Garavan, 2009), right insula (Hester et al., 2009; A. M. Smith et al., 2011; Tapert et al., 2007), dorsolateral prefrontal cortex (Gruber & Yurgelun-Todd, 2005; A. M. Smith et al., 2011; Tapert et al., 2007), superior frontal gyri (Behan et al., 2014; Tapert et al., 2007), inferior frontal gyri (Behan et al., 2014), and inferior parietal lobules (Behan et al., 2014; A. M. Smith et al., 2011; Tapert et al., 2007) during inhibitory tasks. However, these studies notably had relatively small samples (N=18–35) and were predominately male; thus, additional research is needed to understand neuronal response to inhibitory control tasks in cannabis users.

Of further interest is whether gender moderates these effects. As mentioned above, most neuroimaging studies looking at cannabis use with response inhibition are predominately male. In animal models, THC exposure has been shown to down-regulate CB1 receptors

more in female brains compared to their male counterparts (Burston, Wiley, Craig, Selley, & Sim-Selley, 2010). Female rats have also been shown to have significantly decreased density of CB1 receptors in the prefrontal cortex and amygdala compared to males as well as a more hyperactive profile and lower prepulse inhibition (Paola Castelli et al., 2014). These findings suggest that female populations may be more susceptible to neurocognitive deficits from cannabis that were highlighted above. However, while these findings within animal models are important, gender effects of cannabis and cognition in human populations have been limited (Craft, Marusich, & Wiley, 2013; Fattore & Fratta, 2010). Two studies did not report gender differences in behavioral inhibitory control (Crane, Schuster, & Gonzalez, 2013; Lisdahl & Price, 2012); however, these studies did not examine fMRI BOLD response.

The purpose of the current study is to investigate the relationship between cannabis use and brain functioning during an inhibitory task and how these effects may differ between males and females following a minimum of two weeks of monitored abstinence. We hypothesize that despite having similar behavioral performance on an fMRI task, cannabis users will demonstrate significantly greater BOLD responses compared to controls during correct inhibitions on the Go-NoGo task in the right dorsolateral prefrontal cortex, bilateral medial frontal, bilateral inferior and superior parietal lobules, middle, inferior, superior frontal gyri, and in neighboring brain regions as well as aberrant BOLD responses in the anterior cingulate cortex. Finally, we wish to examine how cannabis use may alter functional activity between male and female users.

Method

Participants

The proposed study utilized data from 77 participants collected from a larger parent study investigating frontolimbic functioning and affective processing in cannabis using youth (R01 DA030354; PI: Lisdahl). Participants were recruited through flyers and advertisements in the local community. Participants were included if they were 16–26 years-old, right handed, were willing to abstain from substance use over a 2-week period and fit into either a cannabis user or non-user (see below) and balanced for gender (53% male). Participants who achieved at least two weeks of abstinence prior to scanning were included in the current analysis. Exclusion criteria included having an independent DSM-IV Axis I (attention, mood, anxiety or psychotic) disorder in the past year, major medical or neurological disorders, traumatic brain injury or head trauma (loss of consciousness >2 minutes), history of learning disability or intellectual disability, prenatal medical issues or premature birth (gestation <35 weeks), reported prenatal alcohol/illicit drug exposure, or excessive other drug use (>20 times of lifetime use for each drug category). *Cannabis Users (n=36)*: In order to capture current cannabis users, cannabis users had to have endorsed using cannabis greater than 40 times in the past year (nearly weekly; cannabis use measured by number of reported cannabis joints on the Timeline Followback). Cannabis users include 23 males and 13 females. *Controls (n=41)* were defined as having used cannabis no more than 5 times in the past year and no more than 50 cannabis uses in their lifetime. Control participants included 18 males and 23 females.

Procedures

All procedures were IRB-approved through the University of Wisconsin – Milwaukee and the Medical College of Wisconsin. Potential participants who expressed interest in the parent study were screened through an initial semi-structured interview for independent past-year Axis I disorders other than substance use disorder (SUD) over the phone. If determined eligible, study staff obtained written consent from participants.

Participants who were eligible for the study came in for five study sessions over the course of three weeks. Data from the baseline session (day 1) and fourth session (day 20 of 21) are assessed here. Participants completed a series of demographic questions (including participant's gender), psychological questionnaires, drug use interview, neuropsychological battery, and an MRI scan over the course of three weeks. During that period, participants were required to remain abstinent from alcohol, cannabis, and other drug use, which was confirmed through urine and sweat toxicology screening.

Measures

MINI Psychiatric Interview.—To rule out for potential Axis-I Disorders to prevent comorbid psychiatric history from confounding results, participants over 18 were given the Mini International Psychiatric Interview (MINI) (Sheehan et al., 1998) and participants and parents of participants under 18 were given the MINI-Kid (Sheehan et al., 2010) to get both self and parent report of participant's DSM-IV criteria.

Timeline Followback.—Timeline Followback interviews were conducted with all participants to measure substance use patterns over the past year (Sobell & Sobell, 1992). Utilizing memory cues of common holidays and personal events, participants were asked to describe the frequency and quantity of their drug use over the past year by a month-to-month basis. Memory cues were adapted to be appropriate to both adolescents and emerging adults and included things such as developmental milestones, school grades, and relationship changes. Substances were measured by standard units [e.g., for alcohol (standard drinks), nicotine (number of cigarettes and hits of chew/snuff/pipe/cigar/hookah), cannabis (all methods converted to joints or mg in concentrates), ecstasy (number of tablets), sedatives (number of pills or hits of downers and GHB), stimulants (cocaine and methamphetamine use converted to mg), hallucinogens (number of hits or uses of ketamine/salvia/psilocybin/other hallucinogens), opioids (number of hits of heroin/opium), and inhalants (number of hits)].

Drug Toxicology/Abstinence Testing.—To ensure abstinence during the course of the study, participants were required to complete immediate urine drug toxicology screenings. Screenings were conducted using ACCUTEST SplitCup to test for the presence of the following substances: amphetamines (1000 ng/ml), barbiturates (300 ng/ml), benzodiazepines (300 ng/ml), cocaine (300 ng/ml), ecstasy (MDMA; 500 ng/ml), methadone (300 ng/ml), methamphetamine (1000 ng/ml), opiates (2000 ng/ml), PCP (25 ng/ml), and THC (marijuana; 50 ng/ml). Further, NicAlert was also used to measure cotinine levels within participants' urine samples, as participants were only required to be abstinent from smoking an hour before testing and the MRI scan. Participants were also required to wear

PharmChek Drugs of Abuse Patches throughout the duration of the study. Sweat patches were tested for amphetamine, methamphetamine, opiates, cocaine metabolites, PCP, and THC (Gentili, Mortali, Mastrobattista, Berretta, & Zaami, 2016; Saito et al., 2004). Participant who had recently engaged in cannabis use before the study had their sweat patches monitored for increases in THC levels. In this way, cannabis users could test positive for THC, but were allowed to continue in the study as long as they demonstrated downward trends in THC level for the duration of the study. Decision-making on substance use abstinence is described in more detail in Wallace, Wade, & Lisdahl, 2020.

fMRI Affective No-Go Task.—Participants completed a Go-NoGo task featuring faces expressing feelings of happy, fearful, or calm that had been originally designed by the research group at Sackler Institute for Developmental Psychobiology (Hare et al., 2008; Somerville, Hare, & Casey, 2011). Calm faces are similar to neutral faces, but often interpreted as less negative in youth (Tottenham et al., 2009). For this NoGo task, two facial expressions were used within a trial. Using a rapid event-related design, participants were told what particular stimuli/expression they should respond to by hitting a target box (Go), and what stimuli/expression they should stop themselves from responding and hitting the target box (NoGo). For each trial, faces would appear for 500 milliseconds followed by a jittered intertrial interval ranging from 2 to 14.5 seconds in duration. In each run, the participants were exposed to 48 trials that were presented in a pseudorandomized order (35 “go” trials and 13 “nogo” trials). Participants completed six trials, which allowed every combination of happy, fearful, and calm expressions to appear as a Go and NoGo trial for each participant. By utilizing a task that incorporates facial expressions as stimuli for participants to respond to, this task may capture a more ecologically valid approach to response inhibition.

MRI Data Acquisition—MRI scans were acquired on a 3T Signa LX MRI scanner (GE Healthcare, Waukesha, WI) using a 32-channel quadrature transmit/receive head coil. Echoplanar images (EPI) were collected while performing the NoGo task using a T2*-weighted gradient-echo EPI pulse sequence (TR/TE=2500ms/30ms, FOV=200 cm, matrix 64 × 64 pixels, slice-thickness=3.2 mm, flip angle=90 degrees, 44 contiguous sag slices). The go/no-go task was designed using E-Prime software (Psychology Software Tools Inc., Pittsburgh, PA).

MRI Pre-Processing—Data were processed and analyzed using Analysis of Functional NeuroImages (AFNI (Cox, 1996)) and Matlab (Mathworks, 2012). Imaging data were processed through a standard preprocessing pipeline within AFNI. Time series per each voxel were “despiked” and these isolated spikes were replaced to fit the modeled data for the voxel utilizing 3dDespike; the first 3 TRs were removed; voxel time series were corrected so that all acquired data is aligned to the same temporal spot of origin utilizing AFNI’s 3dTshift; volume registration was registered based on the volume run with the least amount of motion artefacts within the dataset and then warped into standard Montreal Neurological Institute (MNI) coordinate space (Mazziotta et al., 2001) using AFNI’s 3dVolreg; using 3dmerge, data were spatially smoothed using a Gaussian function using the default 4mm full width at half maximum (FWHM) to blur data; each voxel was scaled by default to a mean of

100; data was deconvolved using AFNI's 3dDeconvolve (Ward, 2000) using a gamma variate function. Six motion parameters were regressed out (roll, pitch, yaw, ds, dl, and dp) to account for motion artifacts. Data points of incorrect responses on the Go-NoGo trial were removed from data in order to compare correct calm Go-NoGo stimuli across cannabis users and controls. In this way, we only examined correct inhibitory responses to the calm NoGo stimuli. Fearful and happy NoGo stimuli were not incorporated into the analyses so as not to confound BOLD responses with potential responses to emotional-based stimuli. BOLD signal responses during these correctly inhibited calm NoGo were used to compare across cannabis users and controls.

Statistical Analyses

Behavior Analyses.—Demographic, substance use, and NoGo behavioral performance information was examined using chi-square and ANOVA testing. All statistical decisions were made at a p value less than .05.

Primary Analysis.—BOLD responses were compared across subject's time series during trials where participants correctly inhibited their response during a calm NoGo stimuli. In order to optimize the number of calm NoGo data points per a subject, trials that included both happy Go and fearful Go were concatenated together. To examine group differences, a voxel by voxel ANCOVA was conducted using AFNI's 3dMVM. Monte carlo simulation for cluster-thresholding was completed using 3dFWHM and 3dClustSim (Cox, Chen, Glen, Reynolds, & Taylor, 2017; Forman et al., 1995) to control for multiple comparisons (voxel-wise $p=.001$; $p=.05$). In order to investigate whether gender moderates the effect between cannabis use and BOLD responses, AFNI's 3dMVM incorporated models including gender, cannabis use group, and gender-by-cannabis use group interactions with past year alcohol and past year nicotine use as the covariate within all analyses.

Post-Hoc Analyses.—Age of first cannabis use has previously been indicated as an important factor in cannabis users and response inhibition (Gruber, Dahlgren, Sagar, Gonenc, & Killgore, 2012). Further, the length of abstinence in relation to increased BOLD responses has also been marked as a variable of interest (Tapert et al., 2007). In order to examine this relationship, post-hoc correlations were utilized to examine beta values from significant clusters and age of first cannabis use, age of first regular cannabis use (i.e., using cannabis once a week), and length of cannabis abstinence in cannabis users.

Results

Demographics

Controls and cannabis users did not significantly differ in age ($t(75)=-.77$, $p=0.44$), years of education ($t(71)=1.04$, $p=0.30$), race ($\chi^2=4.34$, $p=0.63$), ethnicity ($\chi^2=4.21$, $p=0.12$), or gender ($\chi^2=3.08$, $p=0.11$). Demographic information is displayed in Table 1.

Substance Use—Cannabis users last reported cannabis use on average was 31.08 days ($SD=22.90$, $Min=17.00$, $Max=150$) before the MRI scan. As expected, cannabis users and controls differed significantly on past year cannabis use ($t(35)=-5.77$, $p<.001$), past year

alcohol use ($t(56)=-3.67$, $p=.001$), past year nicotine use ($t(35)=-2.40$, $p=.02$), and age of first cannabis use ($t(51)=3.98$, $p<.001$; see Table 1 for substance use information). Cotinine levels between cannabis users and controls were significantly different on the day of the MRI scan ($t(43)=-2.22$, $p=.03$); however, percent of positive urine THC tests ($\chi^2=2.34$, $p=0.22$) did not significantly differ between groups. Due to the significant differences in past year alcohol use and past year cigarette use (and cotinine levels), past year alcohol use and nicotine use were controlled for and incorporated into the statistical analyses.

Behavioral Measures

Cannabis users did not significantly differ on the number of incorrect responses to fMRI calm NoGo stimuli compared to controls ($t(75)=-1.87$, $p=.07$ (see table 2)). Cannabis users also did not significantly differ on Go stimulus reaction time ($t(75)=-.93$, $p=.36$) nor omission errors ($t(75)=.90$, $p=.37$). There were no significant differences between males and females on incorrect NoGo responses ($t(75)=.83$, $p=.93$), Go stimulus reaction time ($t(75)=.01$, $p=0.99$), or omission errors ($t(75)=-0.85$, $p=0.93$). The interaction between cannabis use group and gender was also not significant in follow-up regressions for incorrect NoGo responses ($t(76)=1.16$, $p=0.25$), Go stimulus reaction time ($t(76)=-1.75$, $p=0.08$), or omission errors ($t(76)=-0.74$, $p=0.47$).

fMRI Responses

Cannabis Effects.—Whole brain analyses showed that during correct inhibitory responses to calm NoGo trials, cannabis users showed significant clusters of greater BOLD responses in the left cingulate gyrus, the left medial frontal gyrus, and the left superior frontal gyrus compared to their control counterparts (see Table 3, Figure 1). Cannabis users did not display any significant clusters of decreased BOLD activation compared to controls.

Cannabis x Gender Effects.

Gender. Female participants showed significant clusters of greater BOLD response in the right cerebellum during correct NoGo activation. **Cannabis*Gender.** There were no significant clusters that survived correction for the interaction between cannabis use and gender. **Covariates.** Past year alcohol use did not predict any significant clusters; however, past year nicotine use predicted greater BOLD activation within the right cerebellum, right parahippocampal gyrus, right superior temporal gyrus, and the left middle frontal gyrus.

Post-Hoc Analyses.

Post-hoc correlations did not demonstrate significant associations between the left cingulate gyrus (age of first use $r=-0.03$; age of first regular use $r=-0.03$; length of abstinence $r=0.20$), the left medial frontal gyrus (age of first use $r=-0.05$; age of first regular use $r=0.00$; length of abstinence $r=-0.09$), and the left superior frontal gyrus (age of first use $r=-0.15$; age of first regular use $r=-0.13$; length of abstinence $r=0.04$) with age of first cannabis use, age of first regular use, and length of abstinence.

Discussion

This study examined BOLD responses between cannabis users and controls during correct inhibitions of calm NoGo stimuli. Further, we aimed to determine if gender moderates the impact of cannabis use on brain activation. The data showed that despite similar behavioral task performance, adolescent and young adult cannabis users demonstrated greater BOLD activation within regions associated with response inhibition even after a minimum of two weeks of monitored abstinence. Gender did not moderate these effects.

Our findings support previous work examining functional and behavioral differences in response inhibition between cannabis using adolescents and emerging adults and their non-using counterparts. Cannabis users showed greater BOLD responses within the left superior frontal gyrus and the left medial gyrus replicating previous cannabis use and response inhibition work (Gruber & Yurgelun-Todd, 2005; Tapert et al., 2007). Similar to past research, cannabis users also demonstrated higher BOLD activation during response inhibition in the left anterior cingulate cortex (Hester et al., 2009). Together, these findings add to the previous literature which have produced relatively consistent findings indicating greater BOLD responses in prefrontal (Behan et al., 2014; Hester et al., 2009; A. M. Smith et al., 2011; Tapert et al., 2007) and ACC (Hester et al., 2009) regions in chronic cannabis users.

Other fMRI studies have also reported abnormalities in similar regions, including greater BOLD responses of the ACC during error monitoring (Hester et al., 2009) and visual working memory (Kanayama, Rogowska, Pope, Gruber, & Yurgelun-Todd, 2004) tasks. Altered activation in prefrontal regions have also been observed during working memory (Alecia D Schweinsburg et al., 2005) and reward anticipation (Van Hell et al., 2010) tasks, although the directionality of the BOLD responses (increased vs decreased) remain mixed. Still, these results support the notion that chronic cannabis use during adolescence and young adulthood affects brain regions dense in CB1 receptors such as the ACC (Herkenham et al., 1990). Animal models show that chronic cannabis use leads to a downregulation of CB1 receptors (González, Cebeira, & Fernández-Ruiz, 2005); therefore, impacting the natural functioning of the endogenous endocannabinoid system. With this downregulation in CB1 receptor functioning, differences in BOLD activation (as Tapert et al. (2007) suggests) may be compensatory in nature and indicate increased need for resources to perform similar inhibitory response as non-cannabis users in these CB1 rich brain regions. However, it is of note that recent PET studies in adults have demonstrated evidence for recovery in CB1 receptor density after a month or even a few days of abstinence from cannabis use (Hirvonen et al., 2012; D'Souza et al., 2016). While these findings have not been replicated in adolescents, this research casts doubt on the hypothesis that increased BOLD responses are a sign of downregulation. Instead, these consistent findings of increased BOLD responses in adolescent and young adult cannabis users may suggest a disruption rather than a downregulation of the endocannabinoid system during task engagement. Further exploration into circulating endocannabinoids and CB1 receptor density and functioning in the developing human brain may provide clarifying information on the mechanisms underlying potential differences observed in cannabis using youth.

We did not find a significant interaction between cannabis use and gender on the effect of BOLD responses during correct inhibitory responses. It may be that cannabis use does not disproportionately affect brain functioning or performance between genders in these regions as previous animal models suggest (Burston et al., 2010; Paola Castelli et al., 2014). Investigations into gender for this area remains relatively limited and findings are still mixed. While functional studies have not examined gender differences in cannabis users, structural studies indicate that brain based differences do occur in frontolimbic areas in adolescent users (Battistella et al., 2014; Gilman et al., 2014; McQueeney et al., 2011; Schacht, Hutchison, & Filbey, 2012). These brain structure findings between males and female cannabis users underline the diverging course in brain development, or possibly that the differences are very subtle and only detectible with larger sample sizes. In this way, our skew in number of male and female cannabis users (23 male and 13 female cannabis users) may have prevented us from detecting such subtle gender findings. Future work should continue to prioritize equal recruitment of male and female participants to help investigate the effects of gender on cannabis use and brain development.

Past findings have wisely pointed out that increased BOLD responses in cannabis users may be attributed to recent use, in part due to cardiovascular effects of acute cannabis use (Tapert et al., 2007). However, these increases in blood flow have been shown to vanish by 28 days of last cannabis use (Sneider et al., 2008). Due to the requirement for cannabis users to remain abstinent for a minimum of 14 days leading up to MRI scan and participants last reported cannabis use on average occurred 31 days prior to scanning, these findings suggest that abnormal activation to inhibitory control task is observable beyond the acute withdrawal stage. Indeed, this length of abstinence is linked with resolution of withdrawal symptoms and past work has shown recovery of cognitive deficits in cannabis users following sustained abstinence (Hanson et al., 2010; Medina et al., 2007; Schuster et al., 2018). However, no studies to date have examined the impact of monitored, sustained abstinence that is longer than 30 days on BOLD response. Future studies may extend these findings to examine whether users demonstrate full recovery of function with longer periods of sustained abstinence.

It is also important to note that greater BOLD activity observed in cannabis users may be premorbid in nature; inherent brain differences in these regions may make individuals more susceptible to using cannabis in the adolescent and young adult years. Indeed, substance use has been heavily associated with impaired response inhibition (Ivanov, Schulz, London, & Newcorn, 2008) with substance users consistently demonstrating inhibitory deficits across a myriad of studies and forms of drug use (J. L. Smith et al., 2014). With evidence pointing to deficits in response suppression in children with high family risk for alcohol use disorder (Nigg et al., 2006), premorbid deficits of response inhibition may be a potential predictor of future substance use (Nigg et al., 2006; Squeglia, Jacobus, Nguyen-Louie, & Tapert, 2014). These findings are further replicated in fMRI studies. Most notably, longitudinal studies examining inhibitory control have shown that neural activity during inhibition response in adolescents can predict future substance use (Mahmood et al., 2013; Norman et al., 2011). Prospective, longitudinal studies that are carefully measuring substance exposure throughout adolescence, such as the Adolescent Brain Cognitive Development (ABCD) Study (Jernigan, Brown, & Dowling, 2018; Lisdahl et al., 2018), as well as fMRI studies examining

functional activity both immediately before and after abstinence will help determine timing and causality of these findings.

Other limitations should be noted. The study population was primarily Caucasian, relatively average to high average education levels, and did not have comorbid medical, physical, neurologic or psychiatric disorders. Further, participants with significant comorbid substance use or who were unwilling or unable to sustain abstinence were excluded. This narrows the generalizability of the study, and more representative samples of the general population (i.e. the ABCD study) should be utilized to examine these effects in subgroups.

These findings lend support to the growing literature suggesting that adolescent and young adult cannabis users demonstrate greater BOLD responses during response inhibition. These findings were consistent across gender and were evident following at least two weeks of monitored abstinence from cannabis. Further prospective, longitudinal research is needed to determine causality and whether sustained abstinence greater than one month is associated with complete recovery from cannabis effects.

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Figure 1.

Figure displays sagittal and axial views of regions of increased significant BOLD responses in cannabis users compared to controls during correct inhibitions during calm NoGo trials.

Table 1.

Demographics and Substance Use

	MJ Users	Male MJ	Female MJ	Controls	Male Controls	Female Controls
Age (M,SD)	21.6 (2.2)	21.7 (2.3)	21.4 (2.0)	21.1 (2.7)	20.9 (2.9)	21.3 (2.6)
Race (% Caucasian)	58.3%	65.2%	46.2%	68.23%	66.7%	69.6%
Ethnicity (% Not Hispanic)	77.8%	78.3%	76.9%	90.2%	100%	82.6%
Gender (% Male)	63.9%	-	-	43.9%	-	-
Years of Education (M,SD)	14.0 (1.5)	14.0 (1.7)	14.1 (1.3)	14.5 (2.2)	14.6 (2.7)	14.4 (1.9)
Past Year Cannabis Use (M,SD,Min/Max)	425.5 (441.8) 44.7/2306.0 *	495.6 (513.2) 54.6/2306.0	301.5 (245.4) 44.7/879.3	.4 (1.0) 0/4.75 *	.8 (1.4) 0/4.75	.1(0.5) 0/2.0
Lifetime Cannabis Use (M,SD,Min/Max)	1211.8 (1370.6) 101.0/6000.0 *	1454.5 (1614.0) 125.0/6000.0	782.5 (625.0) 101.0/2314.0	4.6 (10.0) 0/50.0 *	6.1 (13.1) 0/50.0	35 (6.9) 0/25.0
Past Year Alcohol Use (M,SD,Min/Max)	3315 (299.5) 0/1120.5 *	365.4 (305.6) 24.0/1120.5	271.6 (290.5) 0/883.0	120.5 (182.7) 0/698.5 *	189.9 (239.7) 0/698.5	66.2 (962) 0/450.0
Past Year Cigarette Use (M,SD,Min/Max)	184.6 (460.9) 0/1867.0 *	264.8 (562.9) 0/1867.0	42.8 (68.1) 0./232.3	0.5 (2.0) 0/12.0 *	.2 (.4) 0/1.0	.8 (2.6) 0/12.0
Age of First Cannabis Use (M,SD,Min/Max)	15.9 (2.2) 12/21 *	16.0 (2.2) 12/20	15.9 (2.3) 13/21	18.5 (2.1) 15/22 * ²	18.7 (2.4) 15/22	18.3 (2.0) 15/22
Age of First Regular (1x/week) Cannabis Use (M,SD,Min/Max)	17.5 (1.7) 14/21	17.4 (1.9) 14/21	17.2 (1.3) 16/21	18 (0) 18/18 ³	18 (0) 18/18	18 (0) 18/18
Length of Cannabis Abstinence	31.1 (22.9) 17.0/150.0 *	34.3 (28.0) 17.0/150.0	25.5 (6.5) 19.0/42.0	200.4 (101.5) 47.0/331.0 * ¹	191.0 (116.8) 47.0/331.0	228.5 (43.1) 198.0/259.0

Notes. MJ denotes the cannabis user group.

* Denotes that variable is significantly different between cannabis users and controls.

¹ Only 8 control participants had used cannabis in the past year (6 males, 2 females), so average length of last use is based off those subjects.

² Only 17 control participants (7 males, 10 females) had ever endorsed using cannabis.

³ Only 2 control participants (1 male, 1 female) had ever endorsed using cannabis for a period of once a week.

Table 2.

NoGo Task Behavioral Performance

	Reaction Time M (SD)	Omission Errors M (SD)	Commission Errors M (SD)
MJ Users	541.1 (90.8)	1.1 (1.6)	1.6 (1.8)
Controls	523.0 (80.3)	1.5 (2.4)	2.5 (2.5)
Females	531.3 (85.3)	1.3 (2.2)	2.1 (2.0)
Males	531.6 (86.4)	1.3 (2.0)	2.1 (2.4)
Female MJ Users	519.0 (57.2)	1.3 (2.0)	1.9 (1.5)
Male MJ Users	553.6 (104.3)	1.0 (1.4)	1.4 (1.9)
Female Controls	538.3 (98.2)	1.4 (2.3)	2.2 (2.3)
Male Controls	503.4 (44.5)	1.7 (2.6)	2.9 (2.8)

Notes. MJ denotes the cannabis user group. M and SD denotes Mean and Standard Deviations, respectively.

Table 3.

Regions of Increased BOLD Responses in Cannabis Users

Cluster #	Voxels	MNI coordinates ^a			Annotations
		Peak x	Peak y	Peak z	
1	58	+4.5	-58.5	-1.5	Left Medial Frontal Gyrus
2	35	+25.5	-49.5	+22.5	Left Superior Frontal Gyrus
3	17	+4.5	+19.5	+37.5	Left Cingulate Cortex

Notes.

^aMNI coordinates refer to peak signal intensity group difference within the cluster.