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Bold Responses to Inhibition in Cannabis Using Adolescents and Emerging Adults

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BOLD RESPONSES TO INHIBITION IN CANNABIS USING ADOLESCENTS AND EMERGING ADULTS

by

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ABSTRACT

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Cannabis use has been associated with increased blood oxygen level dependent (BOLD) responses absent of behavioral deficits during a response inhibition task compared to controls. We investigated whether gender and cannabis use result in differences in BOLD responses and behavioral performance during a Go-NoGo task. Participants included eighty-three 16-26 year olds (MJ=36, Controls=46). An emotion based Go-NoGo task required participants to inhibit their response during a "neutral" face. A whole-brain analysis looked at differences between cannabis group, gender, and their interaction. Significant increased 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. There were no significant differences on task performance or group by gender interactions. Supporting previous research, cannabis users showed increased BOLD responses in core areas associated with response inhibition during a Go-NoGo task further elucidating the relationships between cannabis and brain-behavior.

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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) reported using cannabis in the past 12 months (Johnston et al., 2018; Schulenberg et al., 2017). 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 function (Crane, Schuster, Fusar-Poli, & Gonzalez, 2013; Lubman, Cheetham, & Yücel, 2015; A. D. Schweinsburg, Brown, & Tapert, 2008).

Cannabis contains the compound Δ^9-tetrahydrocannabional (THC), which is responsible for its psychoactive effects (Hall & Solowij, 1998). THC bonds with cannabinoid receptors that are located within both the central and peripheral nervous system (Mackie, 2005). The cannabinoid receptor 1 (CB1) is the most abundant cannabinoid receptor found in the brain (Chevaleyre, Takahashi, & Castillo, 2006) and stimulation of CB1 is responsible for the psychoactive effects of THC (Mackie, 2005; Wilson & Nicoll, 2002). High density of CB1 receptors have been found in the amygdala (Katona et al., 2001), basal ganglia (Herkenham et al., 1991), hippocampus (Herkenham et al., 1991; Jansen, Haycock, Ward, & Seybold, 1992), and prefrontal and parietal cortices (Auclair, Otani, Soubrie, & Crepel, 2000). In these regions, THC binds with CB1 receptors primarily on presynaptic gamma-aminobutyric acid (GABA) neurons to inhibit and excite neurotransmitter activity such as glutamate, dopamine, acetylcholine, and serotonin (Katona et al., 1999; Lopez-Moreno, Gonzalez-Cuevas, Moreno, & Navarro, 2008). Disruption of the natural endocannabinoid system during development by repeated exogenous cannabis may result in neurocognitive deficits, especially in CB1-rich areas underlying executive functioning (Casey, Getz, & Galvan, 2008; Casey & Jones, 2010; Lisdahl, Gilbart, Wright, & Shollenbarger, 2013; Lopez-Moreno et al., 2008).

Executive functioning is a core cognitive function responsible for engaging in purposeful, independent, self-directed behaviors (Lezak, 2012). Facets of executive functioning include planning and decision-making, selective attention, volition, task-switching, and behavioral inhibition (Hofmann, Schmeichel, & Baddeley, 2012; Lezak, 2012). Prior work has reported that chronic cannabis use has been linked with executive functioning deficits (Gonzalez et al., 2012; Grant, Chamberlain, Schreiber, & Odlaug, 2012; Hanson et al., 2010; Harvey, Sellman, Porter, & Frampton, 2007; Lisdahl & Price, 2012; Mathias et al., 2011; Medina et al., 2007; Schuster, Crane, Mermelstein, & Gonzalez, 2012). Specifically, studies have shown that cannabis use is associated with decreased complex attention (Hanson et al., 2010; Lisdahl & Price, 2012; Mathias et al., 2011; Medina et al., 2007; Tapert, Baratta, Abrantes, & Brown, 2002), verbal working memory deficits, (Becker, Collins, & Luciana, 2014; Dougherty et al., 2013; Hanson et al., 2010; Medina et al., 2007; Solowij et al., 2011), poorer decision making (Becker et al., 2014; Churchwell, Lopez-Larson, & Yurgelun-Todd, 2010; Gonzalez et al., 2012; Grant et al., 2012), and planning (Grant et al., 2012; Medina et al., 2007). With continued links between substance use and response inhibition (Fillmore & Rush, 2002; Monterosso, Aron, Cordova, Xu, & London, 2005; Nigg et al., 2006) and increased calls to examine inhibitory control as a future predictor of use (Ivanov, Schulz, London, & Newcorn, 2008) the role of cannabis on areas of the brain related to inhibition has garnered particular interest.

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). The concept of inhibition is complex and can be broken down into 4 subsets or processes, interference control, cognitive inhibition, behavioral inhibition, and oculomotor control (Nigg, 2000). While these differing inhibitory processes have distinct implications, the subtype that has garnered significant interest is the role

of behavioral inhibition, also thought of as response inhibition (Aron, 2007; Chambers, Garavan, & Bellgrove, 2009; Ridderinkhof, van den Wildenberg, Segalowitz, & Carter, 2004). Behavioral inhibition is one's ability to suppress automatic/prepared/cued responses to a task, which is often measured through tasks such Go-NoGo or Stop tasks (Nigg, 2000). With continuing advances in imaging data, the relationship between response inhibition performance on these tasks and the brain has garnered increasingly more research interest.

While it has long been known that the process of inhibition has been linked to the prefrontal cortex (Holmes, 1938), extensive research has been done to uncover the specific regions associated with response inhibition. In particular, regions of the prefrontal cortex including the inferior frontal gyrus (IFG) [both right (Aron, Fletcher, Bullmore, Sahakian, & Robbins, 2003; Aron, Robbins, & Poldrack, 2004, 2014; Hampshire, Chamberlain, Monti, Duncan, & Owen, 2010) and left (Swick, Ashley, & Turken, 2008)], dorsomedial prefrontal cortex (Garavan, Ross, Murphy, Roche, & Stein, 2002), and the anterior cingulate cortex (Carter & van Veen, 2007). Regions outside of the prefrontal cortex have also been implicated in response inhibition, in particular the basal ganglia (Chambers et al., 2009; Rieger, Gauggel, & Burmeister, 2003), which is associated with motor suppression. Due to the varying regions that play a role in inhibition, problems within this cognitive domain may be linked to damage or dysfunction within several of the aforementioned regions. Further, as adolescents emerge into young adulthood, these regions in particular experience neuromatruation (Casey et al., 2008; T. L. Jernigan, Trauner, Hesselink, & Tallal, 1991). The regular exposure of exogenous cannabis during this developmental period may significantly disrupt the functioning of these neuronal networks (Casey & Jones, 2010; Ehrenreich et al., 1999; A. D. Schweinsburg et al., 2008).

As mentioned above, 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 et al., 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 no observable differences with response inhibition in young adult cannabis users (Gonzalez et al., 2012; Grant et al., 2012). It is possible that there are still subtle differences in the inhibitory network, even in the absence of downstream behavioral deficits. Further, cannabis users have shown increased activity in attention based networks (Abdullaev, Posner, Nunnally, & Dishion, 2010) and cerebral blood flow in brain regions pertinent to inhibition (Vaidya et al., 2012) during tasks requiring executive function. These findings suggest that cannabis users require increased effort or compensatory resources in order to inhibit responses.

Only a handful of imagining studies have directly examined BOLD responses 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 largely found that while there are no significant behavioral differences in task performance, adolescent and young adult cannabis users display significantly more BOLD activation 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; J. L. Smith et al., 2014; Tapert et al., 2007), inferior frontal gyri (Behan et al., 2014; J. L. Smith 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). Through ovarian hormones, 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).

Most human studies to date have not reported gender differences in the effects of cannabis on verbal learning (Crane, Schuster, & Gonzalez, 2013; Solowij et al., 2011), memory (Pope, Jacobs, Mialet, Yurgelun-Todd, & Gruber, 1997; Solowij et al., 2011), and inhibitory control (Crane, Schuster, & Gonzalez, 2013). However, two studies have found that male cannabis users demonstrated impaired psychomotor speed (Lisdahl & Price, 2012) and poorer decision making (Crane, Schuster, Fusar-Poli, et al., 2013) compared to male controls while females did not show this effect. In contrast, studies have found that heavier using females cannabis users demonstrated poorer visuospatial (Pope et al., 1997) and verbal memory compared to male cannabis users (Crane, Schuster, & Gonzalez, 2013). Further, female adolescent cannabis users have shown marginally increased prefrontal cortex volumes and larger right amygdala volumes compared to female controls (McQueeny et al., 2011; Medina et al., 2009). While these findings have not been replicated within functional studies, these altered brain volumes suggest that female cannabis users may be at greater risk from cannabis exposure compared to male users. However, these gender findings are still in the preliminary stages and animal models examining gender and cannabis remain relatively mixed (Crane, Schuster, Fusar-Poli, et al., 2013),. Most notably, gender differences in the impact of cannabis use on inhibition are particular scarce. While studies have largely not found any gender differences in response inhibition between cannabis users and their non-using counterparts, these studies also did not observe deficits with inhibition in cannabis users at all and did not examine fMRI BOLD response (Crane, Schuster, & Gonzalez, 2013; Lisdahl & Price, 2012).

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. We hypothesize that despite having similar behavioral performance on an fMRI

task, cannabis users will demonstrate significantly increased 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 hypothesize that there will be altered functional activity between male and female users, with female users experiencing increased compensatory BOLD activation and increased help from neighboring brain regions of key inhibitory ROIs during successful inhibitions on the Go-NoGo task compared to male users and controls.

Method

Participants

The proposed study utilized data from 82 participants collected from a larger parent study investigating frontolimbic functioning in cannabis using youth (R01 DA030354; PI: Lisdahl). Participants were recruited through flyers and advertisements in the local community and college campuses. Participants were included if they were 16-26 years-old, right handed, spoke English, were willing to abstain from substance use over a 3-week period, and fit into either a cannabis user or non-user (see below). 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, inability to complete exercise physiology testing, 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). *Controls*

(n=46) were defined as having abstained from using cannabis more than 5 times in the past year. A total of 44 males and 38 females were included in the study. After grouping participants into cannabis users and controls, cannabis users included 21 males and 25 females (Males=46%) and controls include 23 males and 13 females (Males=64%).

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 (aged 18 or older). All minors below 18 years of age provided written assent after parent consent was acquired. Participants who were deemed ineligible were informed and compensated, but not told the specific reasons for failed inclusion.

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 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 and parents of 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).

Customary Drinking and Drug Use Record. To determine lifetime patterns of drug and alcohol use, youth participants were given the Customary Drinking and Drug Use Record (CDDR) (Brown et al., 1998) at baseline. The CDDR measured the frequency of alcohol, nicotine, cannabis, and other drug use, substance use disorder symptoms, and the age of onset for first time substance use as well as regular weekly use.

Timeline Followback. Timeline Follow-Back 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 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 [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 and number of amphetamine pills), hallucinogens (number of hits or uses of ketamine/salvia/shrooms/other hallucinogens), opioids (number of hits of heroin/opium), and inhalants (number of hits)].

Drug Toxicology/Abstinence Testing. To insure 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. Participants were also required to wear PharmChek Drugs of Abuse Patches throughout the duration of the study. Sweat drug patches were made of a semi-permeable polyurethane membrane that allowed for the natural secretion of water/sweat, but collects heavier molecules such as illicit drugs. In this way, drug use that quickly leaves the system, such as amphetamines, would be detected during the week period between testing sessions. Sweat patches were tested for amphetamine, methamphetamine, opiates, cocaine metabolites, PCP, and THC.

CPT. The Conners Continuous Performance Task (CPT) is a 14 minute long task that required individuals to respond to stimuli on a computer screen (Conners et al., 2000). Participants were asked to respond to all letters except for the letter "X" which they should try to stop themselves from pressing the response button. During this task, average reaction time across all "go" trials were recorded. Previous research has shown that cannabis users have significantly differed from controls on reaction time during this task (Wallace, Wade, Hatcher, & Lisdahl, 2018).

fMRI Affective No-Go Task. Participants were exposed to 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). 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 trail, 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 is 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. Further, for each trial, participants were instructed to respond as fast as possible and not wait for the target/nontarget stimuli, but also try to make as few errors as possible.

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. High-resolution anatomical images were acquired using a T1-weighted spoiled gradient-recalled at steady-state (SPGR) pulse sequence (TR = 8.2 ms, TE = 3.4 s, TI = 450 and flip angle of 12°). The in-plane resolution of the anatomical images was 256x256 with a square field of view (FOV) of 240 mm. One hundred fifty slices were acquired at 1 mm thickness.

MRI Pre-Processing Plan

Data were processed and analyzed using Analysis of Functional NeuroImages (AFNI (Cox, 1996)) and Matlab (Matheworks, 2012). Imaging data were processed through a standard preprocessing pipeline within AFNI. To account for high and low frequency artifactual signals caused by hardware instabilities, head motion, and physiological changes, the time series per each voxel were “despiked” and these isolated spikes were replaced to fit the modeled data for the voxel utilizing 3dDespike. Further, the first 3 TRs (time it took to conduct one full scan) were removed to eliminate initial scanner “noise.” Voxel time series were corrected so that all acquired data is aligned to the same temporal spot of origin utilizing AFNI’s 3dTshift. To further

reduce the influence of head motion within the BOLD signal, volume registration were 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) by making use of AFNI's 3dVolreg. Using 3dmerge, data were spatial smoothed using a Gaussian function using the default 4mm full width at half maximum (FWHM) to blur data to half of other surrounding voxels. Each voxel was scaled by default to a mean of 100 to allow for interpretation of echo-planar imaging (EPI) values as a percentage of the mean. Data was deconvolved using AFNI's 3dDeconvolve (Ward, 2000). Data was convolved after a gamma variate function. Further, 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 neutral Go-NoGo stimuli across cannabis users and controls. In this way, we only examined correct inhibitory responses to the neutral NoGo stimuli. Bold signal responses during these correctly inhibited neutral NoGo were used to compare across cannabis users and controls.

Statistical Analyses

Preliminary Analysis. Analyses were conducted utilizing AFNI with follow-up analyses occurring in SPSS. All statistical decisions were made at a p value less than .05. Demographic information was examined using chi-square and ANOVA testing. Successful NoGo performance between both groups were observed to determine if cannabis users and controls have similar rates of accuracy during the task. Group comparisons on these commission errors were evaluated using an ANCOVA with past year alcohol use as a covariate.

Primary Analysis. BOLD responses were compared across subject's time series at points when subject's correctly inhibited their response during a neutral NoGo stimuli. In order to

optimize the number of neutral NoGo data points per a subject, trials that included both happy Go and fearful Go were concatenated together. However, as a follow-up analysis, correct neutral NoGo responses were compared between both the happy Go and fearful Go trials. To examine group differences, a voxel by voxel ANCOVA was conducted using AFNI's 3dMVM at a voxel-wise p-value of p=.01. Monte carlo simulation for cluster-thresholding was completed using 3dFWHM and 3dClustSim (Forman et al., 1995) to control for multiple comparisons at a p-value of .05. In order to investigate whether gender moderates the effect between cannabis use and BOLD responses, AFNI's 3dMVM incorporated models including gender and cannabis use. In this way, F-statistical maps were computed to determine significant interactions between gender and cannabis use after controlling for past year alcohol use as a covariates. Similar to the primary analyses, cluster-thresholding was conducted using 3dClustSim (Forman et al., 1995).

Follow-Up Analyses. In order to examine brain-behavior relationships, significantly different ROI clusters between cannabis users and non-users were extracted into SPSS (beta weights) and correlated with CPT-II scores.

Results

Demographics

Controls and cannabis users did not significantly differ in age (t(80)=-.842, p=0.40), years of education (t(80)=.98, p=0.31), race (χ^2=3.83, p=0.70), ethnicity (χ^2=3.62, p=0.16), or gender (χ^2=2.70, p=0.10). Demographic information is displayed in Table 1.

Table 1.

Demographics

	Age (M,SD)	Race (% Caucasian)	Ethnicity (% Not Hispanic)	Gender (% Male)	Years of Education (M,SD)
MJ Users	21.6 (2.2)	58.3%	77.8%	63.9%	14.0 (1.5)

Controls	21.1 (2.5)	65.2%	89.1%	45.7%	14.4 (2.1)

Notes. *MJ denotes the cannabis user group

Substance Use

Controls had on average .54 cannabis uses in the past year (SD=1.17, Min=0.00, Max=4.75), used alcohol on average 132.97 times in the past year (SD=189.23, Min=0.00, Max=698.50), and used an average of 25.82 cigarettes in the past year (SD=171.71, Min=0.00, Max=1165.00). Cannabis users had 425.51 cannabis uses on average in the past year (SD=441.75, Min=44.70, Max=2306.00), alcohol 331.52 on average in the past year (SD=299.52, Min=0.00, Max=1120.50), and 184.59 cigarettes in the past year (SD=460.91, Min=0.00, Max=1867.00). Cannabis users last reported cannabis use on average was 31.08 days (SD=22.90, Min=17.00, Max=150) before the MRI scan (including the 3 weeks of monitored abstinence). As expected, cannabis users and controls differed significantly on past year cannabis use ($t(35)=5.78$, $p<.001$) and past year alcohol use ($t(56)=3.47$, $p=.001$). Past year nicotine use was not significantly different between cannabis users and controls ($t(43)=1.96$, $p=.06$). Due to the significant differences in alcohol use, past year alcohol use will be incorporated into the statistical analyses.

Behavioral Measures

Cannabis users did not significantly differ on the number of incorrect responses to fMRI Neutral NoGo stimuli (M=1.58, SD=1.75) compared to controls (M=2.44, SD=2.41, $t(80)=-1.78$, $p=.08$). These findings were also non-significant after controlling for alcohol (cannabis users: estimated mean=1.78, SE=0.37; controls: estimated mean=2.28, SE=0.32) ($F(1)=.824$, $p=0.37$). There were no significant differences between males and females on incorrect NoGo responses ($t(80)=0.133$, $p=0.89$). Cannabis users did not significantly differ on Go stimulus reaction time (M=541.12, SD=90.82) compared to controls (M=518.20, SD=79.07, $t(80)=1.22$, $p=.23$) nor did

cannabis users differ on omission errors (M=1.08, SD=1.59) compared to controls (M=2.02, SD=3.96, t(80)=-1.34, p=.18).

fMRI Responses

Cannabis Effects. Whole brain analyses showed that during correct inhibitory responses to neutral NoGo trials, cannabis users showed significant clusters of increased BOLD responses in the left Cingulate Gyrus, the left Superior Frontal Gyrus, the left Thalamus, the left Medial Frontal Gyrus, and right Cerebellum compared to their control counterparts (see Table 2, Figure 1). Cannabis users did not display any significant clusters of decreased BOLD activation compared to controls.

Table 2.

Regions of Increased BOLD Responses in Cannabis Users

Cluster #	Voxels	MNI coordinates[a]			Annotations	Effect Size Cohen's d
		Peak x	Peak y	Peak z		
1	167	+4.5	-19.5	+37.5	Left Cingulate Gyrus	0.69908
2	102	+22.5	-49.5	+22.5	Left Superior Frontal Gyrus	0.71082
3	101	+4.5	+13.5	+7.5	Left Thalamus	0.68041
4	74	+7.5	-58.5	-1.5	Left Medial Frontal Gyrus	0.70428
5	73	-31.5	+67.5	-25.5	Right Declive (Cerebellum VI)	0.70518

Notes. [a]MNI coordinates refer to peak signal intensity group difference within the cluster

Figure 1.

BOLD Responses in Cannabis Users vs. Controls

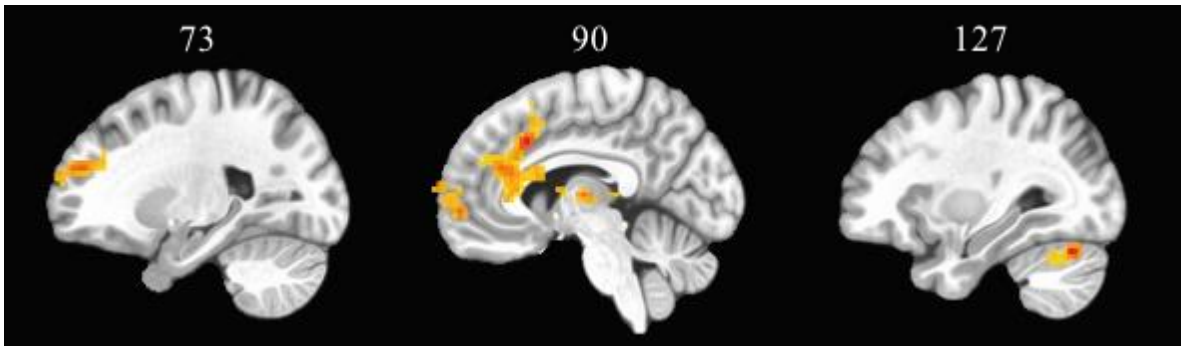

Figure 1. Displays regions of increased significant BOLD responses in cannabis users compared to controls during correct inhibitions during "neutral" NoGo trials. Increased BOLD responses in the left Superior Frontal Gyrus, left Cingulate Gyrus, left Thalamus, left Medial Frontal Gyrus, and right cerebellum are displayed in the sagittal view with numbers above each slice indicating the position of the slice in X coordinates in MNI space.

Cannabis*Gender Effects. ***Gender.*** Female participants showed significant clusters of increased BOLD response in the bilateral Posterior Cingulate, left Medial Frontal Gyrus, right Cerebellum, left Superior Occipital Gyrus, the right Cingulate Gyrus, and the left Thalamus 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 predict increased BOLD activation within the left Inferior Parietal Lobule.

Happy vs Fearful Go Trials. Follow up whole brain analyses of correct neutral NoGo and happy Go trials showed significant clusters in the left Anterior Cingulate Cortex, the left Middle Frontal Gyrus, and the left Parahippocampal Gyrus (see Figure 2). There were no significant clusters that survived correction in the trial with fearful go stimulus.

Figure 2.

BOLD Responses in Cannabis Users vs Controls in Happy Go Trials

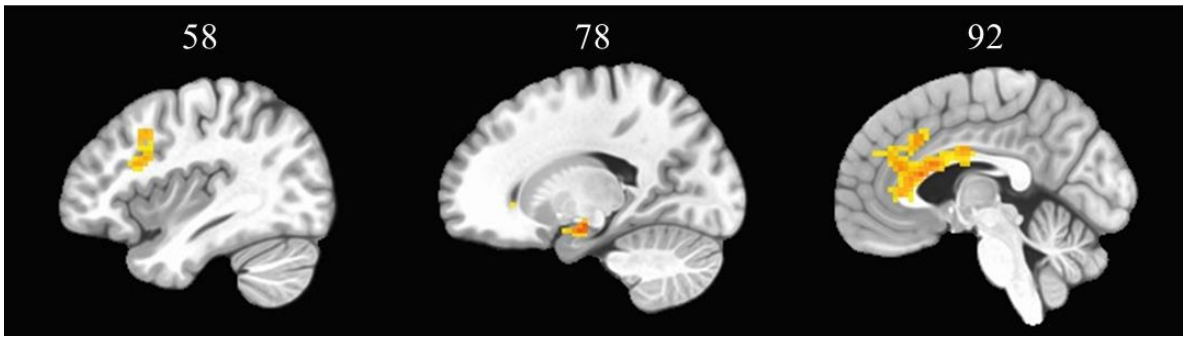

Figure 2. Displays regions of increased significant BOLD responses in cannabis users compared to controls during correct inhibitions during "neutral" NoGo trials on trials where the Go stimulus was a "happy" face. Increased BOLD response in the left Frontal Middle Gyrus, left Parahippocampal Gyrus, and the left Cingulate Gyrus are displayed in the sagittal view with numbers above each slice indicating the position of the slice in X coordinates in MNI space.

Brain-Behavior Relationships

Beta values from regions displaying increased BOLD responses in cannabis users were not significantly correlated with the Connor CPT, but did show slight positive correlations (see Table 3) with increased reaction time and increased beta values in the left cingulate gyrus

(r(80)=0.10, p=0.37), left superior frontal gyrus (r(80)=0.11, p=0.33), and the left medial frontal gyrus (r(80)=0.18, p=0.10).

Table 3.

Pearson Correlations of Beta Coefficients of Significant ROI's

	Left Cingulate Gyrus Coefficients	Left Superior Frontal Gyrus Coefficients	Left Thalamus Coefficients	Left Medial Frontal Gyrus Coefficients	Right Cerebellum Coefficients	CPT Average Hit Response Time
Left Cingulate Gyrus Coefficients	1	.661**	.639**	.521**	.649**	0.100
Left Superior Frontal Gyrus Coefficients	.661**	1	.536**	.412**	.548**	0.109
Left Thalamus Coefficients	.639**	.536**	1	.379**	.685**	-0.070
Left Medial Frontal Gyrus Coefficients	.521**	.412**	.379**	1	.429**	0.184
Right Cerebellum Coefficients	.649**	.548**	.685**	.429**	1	-0.042
CPT Average Hit Response Time	0.100	0.109	-0.070	0.184	-0.042	1

Notes. **. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed).

Discussion

This study examined BOLD responses between cannabis users and controls during correct inhibitions of neutral 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 performance, adolescent and young adult cannabis users demonstrated increased and diffuse BOLD activation within regions associated with response inhibition even after three 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 increased BOLD responses within the left superior frontal gyrus and the left medial gyrus replicating previous findings (Gruber & Yurgelun-Todd, 2005; Tapert et al., 2007). Similar to past research, cannabis users also demonstrated greater BOLD activation during response inhibition in the left anterior cingulate cortex (Hester et al., 2009) and the thalamus (A. M. Smith et al., 2011). Further, as hypothesized, neighboring brain regions were incorporated showing increased BOLD responses with the significant cluster associated with the left cingulate cortex being particularly diffuse across the anterior cingulate cortex and pre-frontal regions of the brain. These findings add to the previous literature which have produced relatively consistent findings indicating increased BOLD responses in prefrontal (Behan et al., 2014; Hester et al., 2009; A. M. Smith et al., 2011; Tapert et al., 2007), ACC (Hester et al., 2009), and thalamus (A. M. Smith et al., 2011) regions. Gruber and colleagues (2005) did show mixed findings in the directionality of BOLD responses, which may be due to the use of differing task paradigms (i.e. Stroop versus Go-NoGo). Previous research suggests the use of the Stroop task may be measuring different mechanisms of inhibition, which differs from the more "pure" Go-NoGo inhibition task (Garavan et al., 2002; Nigg, 2000). Further, we previously reported, in an overlapping sample, that the cannabis users had impaired sustained attention on the CPT-3 task (Wallace et al., 2018) and this increased BOLD response was positively (although not significantly) correlated with poorer sustained attention. Taken together, this suggests that the increased BOLD response was not advantageous to the cannabis users.

Other fMRI studies have also reported abnormalities in similar regions, including increased 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 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 indicating increased need for resources to perform similar inhibitory response as non-cannabis users in these CB1 rich brain regions. While these differences in brain functioning may not contribute to observable behavioral differences at this point of development, continued chronic use could produce downstream behavioral differences in later years as brain development becomes less plastic. Further exploration into CB1 receptor functioning and endocannabinoid signaling in the developing human brain may help elucidate the mechanistic link between chronic cannabis use and long-term neurocognitive deficits.

This study examined inhibitory control within the context of an affective processing task. Therefore, in a follow-up analysis, we examined BOLD response to neutral NoGo stimuli during trials with happy Go stimuli and fearful Go stimuli. To examine the influence of this emotional environment, we compared BOLD responses during neutral NoGo inhibition within these two trials in cannabis users compared to controls. During the happy Go block, the areas of activation were similar to our main findings. However, there were no significant clusters that survived

corrections in the trials of the fearful Go stimuli. This suggests that the emotional environment did have an influence on the neuronal response to inhibition in the cannabis users compared to controls. However, the current power of this study does not support further investigation into the nature of these supplementary findings. Still, closer examination of how affective states influence brain responses during response inhibition must be conducted going forward to determine the true nature of this relationship.

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 the 21 days leading up to MRI scan, participants last cannabis use on average occurred 31.08 days prior to scanning. This period of abstinence provides evidence that these changes in brain functioning are due to chronic cannabis use rather than acute effects. 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). Therefore, this sample of cannabis users may have demonstrated some recovery of function and findings may not generalize to more recent users.

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 effects for this cognitive domain 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; McQueeny et al., 2011; Schacht, Hutchison, & Filbey, 2012). It is also possible that gender differences exist at earlier adolescent stages, but gender differences diminish by the early young adult years and the current sample average age was 20-21. Future studies are needed to examine how cannabis and gender interact to predict longitudinal neurodevelopment of neuronal areas underlying inhibitory control.

It is also important to note that increased 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 et al., 2008) with substance users across varying forms of use having been consistently shown to have inhibitory deficits across a myriad of studies (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 are needed to determine whether these observed differences are predictors of cannabis use onset and increased use and/or direct effects of chronic exposure.

Limitations should be noted. As noted above, the study's cross-sectional nature prevents us from determining causality of these increased BOLD responses in cannabis users compared to

controls. Prospective, longitudinal studies, such as the Adolescent Brain Cognitive Development (ABCD) Study (Terry L Jernigan, Brown, & Dowling, 2018), will help determine timing and causality of these findings. Further, the study population was primarily Caucasian, relatively average to high average education levels, and did not have comorbid medical or physical disorders. 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 increased BOLD responses during response inhibition. These findings suggest that regular cannabis during these neurodevelopmental years may impact neurodevelopment. 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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