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Functional Responding to Appetitive Faces Among Cannabis-Using Adolescents and Young Adults

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FUNCTIONAL RESPONDING TO APPETITIVE FACES AMONG CANNABIS-USING ADOLESCENTS AND YOUNG ADULTS

by

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ABSTRACT
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Cannabis use is associated with attenuated reward signaling, yet few studies have examined this relationship when viewing rewarding appetitive faces while undergoing functional neuroimaging. Furthermore, few neuroimaging analyses have examined the moderating role of gender on task-based fMRI outcomes. This study explored functional BOLD response elicited by appetitive faces while engaged in an affective go/no-go task, and specifically investigated the differences between cannabis-using and control groups, whether gender moderate findings, and brain-behavior associations. Participants (ages 16-26 years) were scanned after at least 3-weeks of monitored abstinence (cannabis-using group = 35; control group = 33). The findings demonstrated aberrant activation in the left inferior parietal region among cannabis-using participants and a cannabis-by-gender moderation in the right parahippocampal gyrus. In addition, marginal brain-behavior associations were observed between depressive symptoms and novel reward-seeking with the left inferior parietal region. Results may be due to the abstinence window our sample maintained, attentional allocation, or a premorbid risk factor for cannabis use maintenance. Future studies are needed to longitudinally determine the trajectory of affective development and how it relates to cannabis use in adolescence and young adulthood.

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Introduction

Cannabis is one of the most commonly used substances in the United States—second to alcohol (Schulenberg et al., 2019)—with approximately 25.2% of adolescents (grades 8, 10, 12) and 39.1% of young adults (aged 19 to 28) reporting use within the past year (Johnston et al., 2020; Schulenberg et al., 2019). As prevalence rates are known to vary by state policies (Carliner, Brown, Sarvet, & Hasin, 2017), the scientific community is increasingly interested in understanding the impact of repeated and regular cannabis use on adolescent and young adult neurodevelopment.

Cannabis and the Brain

Exogenous cannabinoids primarily consist of cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC), the latter is associated with recreational use and the subjective experience of feeling "high" (Hall & Solowij, 1998). Exogenous THC use can impact the brain by interacting with the endogenous cannabinoid system (Walter et al., 2013), which includes cannabinoid receptor 1 (CB1) (Herkenham et al., 1990) and is primarily distributed throughout the central nervous system (Eggan & Lewis, 2007). Receptors for this system are at density peak throughout adolescence, particularly in prefrontal and limbic regions (Ellgren et al., 2008; Heng, Beverley, Steiner, & Tseng, 2011; Terry et al., 2009) and is principally involved in neuromodulation (Mechoulam & Parker, 2013). Repeated and regular use of cannabis containing THC can affect CB1 binding (Villares, 2007) and in turn, results in functional and structural changes to the brain (Batalla et al., 2013). To that end, frequency of cannabis use has been related to significant reductions in the density of CB1 receptors throughout the cortex, with recovery reportedly occurring after one month of abstinence (Hirvonen et al., 2012). Moreover, chronic exposure to cannabis has been related to alterations in cognitive control, inhibitory control, and reward functioning (Batalla et al., 2013; Wrege et al., 2014; Yanes et al., 2018).

Albeit the link between cannabis use and reward processing in adolescents and young adult has yet to be fully characterized.

Reward Circuitry, Appetitive Face Processing, and Cannabis

Among typically developing adolescents and young adults, reward circuitry centers are broadly characterized by their strong signaling as they attune to evaluating and appraising rewarding stimuli (Galvan et al., 2006; Van Leijenhorst et al., 2009). Important regions for higher-order processes of inhibitory control (one's prepotent ability to withhold immediate responding)—including the prefrontal cortex—remain structurally and functionally underdeveloped relative to subcortical areas (Giedd et al., 1999; Luna et al., 2001). During this disproportionate development, it is suggested that reward signaling may be less downregulated by cortical control systems which results in increased impulsive or reward-driven outward behavior during adolescence (Van Leijenhorst et al., 2010). Somerville, Hare, and Casey (2011) proposed a novel way of examining this in adolescents and young adults with an emotional go/no-go rapid event-related paradigm examining appetitive (i.e., "happy") faces, which sought to tap into impulse control through examination of response patterns and functional elicitation related to rewarding cues. Teens (aged 13-17) displayed stronger activation in the ventral striatum—a subcortical region characterized by its role in the dopaminergic system related to reward processing—when responding to these cues compared to both children and adults (Somerville et al., 2011). Throughout adolescence, the ventral striatum—along with other reward-related regions—experiences an uptick in dopaminergic receptors (Tarazi & Baldessarini, 2000; Telzer, 2016) and are recruited differently depending on the context of reward processing. The striatum is associated with an increase in functional activation when responding to a reward (Bjork et al., 2004; Knutson, Adams, Fong, & Hommer, 2001); but this region also experiences

decreased activation when anticipating a reward (Bjork et al., 2004; Bjork, Smith, Chen, & Hommer, 2010; Geier, Terwilliger, Teslovich, Velanova, & Luna, 2010). The degree to which this region downregulates during reward anticipation is further associated with a greater propensity to risk-taking behaviors in adolescents in young adults (S. Schneider et al., 2012). With the onset of substance use generally occurring during adolescence (Johnston et al., 2020), elucidating differences in reward processing as it pertains to substance use risk and consequences has garnered greater attention in the field of addiction neuroscience (Luijten, Schellekens, Kuhn, Machielse, & Sescousse, 2017).

It has been demonstrated both across the animal and human literature that introduction of drugs of abuse alters and reprograms key reward appraisal regions by devaluing standard rewards; thus, requiring rewards of a larger value to recruit reward functioning to mirror similar levels of activation compared to their non-addicted counterparts (Hommer, Bjork, & Gilman, 2011; Koob & Volkow, 2010, 2016; Volkow, Koob, & McLellan, 2016). Specific to cannabis, THC has been shown to alter the reward regions (i.e., in the mesolimbic dopamine system, specifically the ventral tegmental area, ventral striatum, and amygdalar subregions) within preclinical models (Gardner, 2002; Wise, 1996), showcased through a decreased sensitivity to rewards and aberrant functioning of the reward systems (i.e., through overactivated dopamine signaling in the mesolimbic system after repeated THC administration) (Gardner & Vorel, 1998; Kenny, 2007; Tanda & Goldberg, 2003). Within humans, functional connectivity between these reward regions are disrupted in cannabis-using adolescents and young adults, with non-dependent users recruiting more activation from prefrontal regions and dependent users recruiting from subcortical regions (Filbey & Dunlop, 2014; Lichenstein, Musselman, Shaw, Sitnick, & Forbes, 2017), with broad functional connectivity differences that are partially

recovered after one month of abstinence in young adult cannabis-using males (Pujol et al., 2014). As aforementioned, functional responding in these reward regions can be assessed through (1) anticipation to a reward and (2) response to a reward—which has been typically examined using the Monetary Incentive Delay (MID) task (Bjork et al., 2004; Knutson et al., 2001). With a stronger investigative emphasis on reward anticipation, cannabis-using groups have demonstrated pronounced hypoactivation when anticipating a reward in striatal regions (Martz et al., 2016; Nestor, Hester, & Garavan, 2010; van Hell et al., 2010) [see, Luijten et al. (2017) for review], which was additionally correlated with lifetime cannabis use (Martz et al., 2016; Nestor et al., 2010). Regarding reward outcome—i.e., appraisal of rewards while participating in the MID task—cannabis-using groups show significant hyperactivation in striatal regions (Nestor et al., 2010; van Hell et al., 2010) [see, Luijten et al. (2017) for review]. This line of research indicates that cannabis use interplays with reward systems through exaggerated responding when engaged in reward processing, however, these findings are largely exclusive to the MID task and there is a paucity of research examining differences in functional reward responding to pleasurable cues (i.e., not through monetary appraisal)—such as through an emotional faces go/no-go task (Somerville et al., 2011).

Within investigations of cannabis use and emotional faces paradigms, responding to emotionally-valenced faces has chiefly comprised of negative stimuli processing, with cannabis users showing amygdala reactivity and aberrant brain activation particularly in frontal and cingulate regions (Gruber, Rogowska, & Yurgelun-Todd, 2009; Ma et al., 2020; Spechler et al., 2015). Comparatively, only a few small-sample studies have examined functional neuroimaging differences between cannabis users and non-users when viewing positively-valenced emotional stimuli. Gruber et al. (2009) examined functional brain response to appetitive face viewing in a

sample of cannabis-using adults, where a whole-brain analysis found greater activation in non-using adults in the left temporal lobe and left sublobar region compared to cannabis-using adults; whereas, an ROI analysis demonstrated decreased amygdala and increased cingulate activity in cannabis-using participants when compared to non-using adults which was correlated with urinary cannabinoid toxicology levels and weekly cannabis use. Conversely, cannabis-using adults displayed no differences in brain activation when viewing positively-valenced situations compared to non-using adults (Wesley, Lile, Hanlon, & Porrino, 2016); and, no associations were observed between functional brain activation to appetitive faces and cannabis use disorder scores in adolescents, albeit, this treatment-seeking sample comprised of increased psychopathological comorbidity prevalence (Leiker et al., 2019). Thus, the small number of studies have shown mixed results in differing brain activation between cannabis-using and non-using adults with one adolescent study (Leiker et al., 2019) showing no link between affective processing and cannabis dependence scores. To that end, no studies to date have examined differences in appetitive face responding between cannabis-using and non-using adolescents and young adults that comprise a community sample with no comorbid psychopathology.

Necessity of Gender as a Moderator

An important moderating factor possibly clarifying the relationship between appetitive face responding and cannabis use is gender. Sex differences exist in functional activation elicited by emotional faces (Burghy et al., 2012; Lee et al., 2013), with effects seen in amygdalar responding where males showed greater responding (Victor, Drevets, Misaki, Bodurka, & Savitz, 2017) and females showing greater amygdala response to appetitive faces than sad faces (Killgore & Yurgelun-Todd, 2001). Preclinical models have demonstrated sexual dimorphic CB1 diffusivity in the endocannabinoid system, with greater desensitization of these receptors shown

in adolescent female rodents after THC administration compared to males (Burston, Wiley, Craig, Selley, & Sim-Selley, 2010; Rodriguez de Fonseca, Ramos, Bonnin, & Fernandez-Ruiz, 1993), and increased CB1 receptor density in males (Burston et al., 2010; Rubino et al., 2008). In addition, investigations into the moderating role of gender within humans showcase differences between CAN-using males and females and their non-using same-gender counterparts within use patterns, with cannabis-using males tending to use more frequently, severely, and higher potency products (Cuttler, Mischley, & Sexton, 2016; Khan et al., 2013). This literature helps to explain moderating effects of gender in structural brain outcomes (Lorenzetti, Chye, Silva, Solowij, & Roberts, 2019; McQueeny et al., 2011; Sullivan, Wallace, Wade, Swartz, & Lisdahl, 2020). For example, gender differences exist in limbic and prefrontal regions between cannabis-using and non-using adolescents and young adults (McQueeny et al., 2011; Medina et al., 2009). However, very few studies have examined moderating effects of gender on cannabis-related differences in functional activation (Batalla et al., 2013). One meta-analysis investigating functional activation across a wide variety of task fMRI paradigms found diffuse differences in increased temporal and superior and inferior frontal activation in cannabis-using adult samples with more females and greater middle frontal activation in those with less females, and in adolescents, greater activation in the caudate nucleus in cannabis-using samples with fewer adolescent females (Blest-Hopley, Giampietro, & Bhattacharyya, 2018); while our group found that gender did not moderate cannabis-related differences in inhibitory control functional processing in adolescents and young adults (Wallace, Maple, Barr, & Lisdahl, 2020). To date, studies examining appetitive facial responding differences among cannabis-using individuals have neglected to investigate the moderating effects of gender.

Brain-behavior Associations

Further, in cannabis research, investigations broadly examine cannabis-using participants against non-using controls in a dichotomous fashion. However, there is a push for examining intraindividual differences within cannabis use, as there are arguments for determining which measure best reflects use on a continuum and how best to characterize cannabis use severity. Cannabis exposure or frequency of use is characterized by past year uses, typically represented by summing the actual number of times used across the last year or determining total amount of grams ingested. This characterization of use is typically used when determining how to measure cannabis use severity, as it has been previously linked with neuropsychological detriments (Coulston, Perdices, & Tennant, 2007) and selective attentional difficulties (Solowij, Michie, & Fox, 1995). Yet, age at regular use onset represents a promising avenue for adolescence and young adult research as it approximates when use may have altered neurodevelopmental trajectories (Lisdahl, Wright, Medina-Kirchner, Maple, & Shollenbarger, 2014). Earlier age of onset has been linked with cognitive deficits (Pope et al., 2003), initiation of polysubstance and further development of problematic use (Agrawal et al., 2006), and associations with more severe psychopathology (De Hert et al., 2011; Veen et al., 2004). Lastly, severity of cannabis use can either be defined as cannabis use disorder or withdrawal symptomology. Endorsements of these provide a clinical profile on problematic and impairing cannabis use. While this has not been typically used to indicate cannabis use severity, asking chronic users to abstain with close and frequent monitoring of withdrawal symptoms may be indicative of more severe use (Budney & Hughes, 2006; Budney, Moore, Vandrey, & Hughes, 2003; Copersino et al., 2006). Continually, cannabinoid metabolites can take at the most 21-days to 28-days to fully excrete from the body (Ellis, Mann, Judson, Schramm, & Tashchian, 1985; Goodwin et al., 2008);

therefore, requiring participants to abstain for approximately 25-days will ensure that assessments reflect chronic cannabis-related differences, as otherwise results are indeterminable by potential acute effects (Crean, Crane, & Mason, 2011), which has yet to be accounted for in previous examinations of reward responding in cannabis-using adolescents and young adults. On the other hand, there is an additional push to examine brain-behavioral relationships and potential moderators of cannabis on reward-related neuroimaging findings, such as interactions with depressive symptoms and behavioral reward processing measures. Cannabis-using adolescents and young adults report higher rates of depressive symptoms (Bonnet & Preuss, 2017; Wright, Scerpella, & Lisdahl, 2016), and frequency of symptoms are related to white matter integrity and functional connectivity (Medina et al., 2009; Shollenbarger, Price, Wieser, & Lisdahl, 2015; Shollenbarger et al., 2019); yet no study has evaluated brain-behavioral relationships in an emotional faces go/no-go task with depressive symptoms in cannabis-using groups. Further, behavioral reward processing measures have yet to be relate to functional neuroimaging outcomes despite differences observed between cannabis-using and non-using adolescents and young adults (Wright et al., 2016) and more broadly in substance-using college students (Franken & Muris, 2006). Thus, correlating severity of use variables, depressive symptoms, and reward processing indices with significant clusters of blood-oxygen-level-dependent (BOLD) activation may yield valuable information on appropriate variable selection when considering the associations with aberrations in reward processing.

The Present Study

The aims of the thesis are to: (1) Examine differences in whole-brain BOLD activation elicited by appetitive (i.e., happy go) faces during an emotional go/no-go paradigm (Somerville et al., 2011; Wallace, Maple, et al., 2020) between cannabis-using and non-using adolescents and

young adults from a non-treatment seeking sample with no psychopathological comorbidities, who underwent 3-weeks of monitored abstinence. It is hypothesized that despite similar behavioral performance, the ventral striatum and amygdala regions will show decreased BOLD activation in cannabis-using adolescents and young adults compared to controls. (2) For Aim 2, we will investigate the interaction between gender and cannabis group status on BOLD activation elicited by appetitive stimuli in the same sample. We hypothesize that in ventral striatum and amygdala regions, cannabis-using male participants will show decreased BOLD activation elicited by appetitive stimuli (i.e., happy faces) compared to non-using male counterparts, and cannabis-using female participants will show increased BOLD responding to appetitive stimuli (i.e., happy faces) compared to non-using female counterparts. (3) Lastly, for an exploratory aim, we will explore links between cannabis use severity (i.e., total past year use, age of regular use onset, and total cannabis abuse/dependence symptoms, length of abstinence), mood symptoms (depressive symptoms), and reward processing on functional activation in regions that differed according to cannabis group status or cannabis group-by-gender interaction in Aims 1 & 2. It is hypothesized that density of past year use will have a significant correlation with functional activation in significant clusters. In addition, depressive symptoms and novelty-seeking will be significantly correlated with beta-values in significant clusters in Aims 1 & 2.

Methods

Participants

Participants included in the present project are taken from a larger parent study (R01-DA030354; PI: Lisdahl) examining health and neurocognitive factors among adolescent and young adult cannabis users and non-users (Wallace, Maple, et al., 2020). The parent sample was recruited through community online advertisements and flyers distributed to the local community

and college campuses. Inclusion criteria for the parent study consisted of right handedness, English speaking, and willingness to abstain from all substance use (except for nicotine) over a 3-week period prior to neuropsychological testing and neuroimaging. Exclusionary criteria included having an independent DSM-IV-TR Axis I disorder (mood, anxiety, attention, or psychotic), major medical or neurological disorder (including metabolic disorders), current use of psychoactive medication, loss of consciousness for more than two minutes, history of intellectual or learning disability, prenatal medical issues or premature birth (i.e. gestation less than 35 weeks), reported significant prenatal substance exposure [i.e., alcohol exposure (≥4 drinks in a day or ≥6 drinks in a week), nicotine exposure (average >5 cigarettes per day for >1 month), or any other illicit substance exposure], magnetic resonance imaging (MRI) contraindications (e.g., metal in body, pregnancy, or claustrophobia), elevated Physical Activity Readiness Questionnaire (Thomas, Reading, & Shephard, 1992)—indicating difficulty completing aerobic fitness testing (that was included in the parents study), or any other excessive illicit drug use (>20 lifetime use for each drug category, including cannabis use for non-using control participants).

In the present analysis, cannabis users are categorized as current users who used cannabis at least 40 times in the last year (i.e., near weekly) and at least 100 lifetime uses. Non-using controls in the present analysis did not use cannabis within the past year and used less than 20 times in their lifetime. In addition, participants must have usable task fMRI data to be included in the present analysis (n=3 removed for missingness). Thus, 68 participants will be included in the present study. This sample is between the ages of 16 and 26 years (M=21.3, SD=2.4), were equally balanced for gender (50.0% female), were largely non-Hispanic (80.9% non-Hispanic),

and racial identities consisted of predominantly: White (64.7%), Asian American (11.8%), Multi-racial (11.8%), and Black (5.9%). (See Table 1)

Procedures

Data in the thesis will be used from a larger parent study examining the neurocognitive effects of cannabis use in adolescents and young adults (R01-DA030354; PI: Lisdahl), all aspects of the protocol were approved by the University of Wisconsin-Milwaukee IRB. Youth and parents interested provided verbal assent (minors)/consent (youth aged 18+ and parents) and were first screened by phone for basic demographic, medical and substance use information to determine initial eligibility. If they remained eligible, written informed consent/assent was provided by mail by both parents and youth. Both were then screened by phone or in person utilizing a semi-structured interview for independent lifetime and past-year DSM-IV-TR Axis I disorder—other than substance use disorder, lifetime substance use patterns, and exercise readiness. If eligible, youth were scheduled for study sessions; prior to participating, parents provided consent for minors (17 years old and younger) while youth aged 18 or older provided written consent.

The study included five in-person study sessions over the course of three weeks. The first three sessions occurred one week apart and consisted of brief neuropsychological battery [described further in Wallace, Wade, and Lisdahl (2020)], behavioral measures, urinary and sweat drug toxicology testing. Sessions four and five occurred at least one week after session three and consisted of conducting aerobic fitness measures, full neuropsychology battery, drug toxicology, psychological questionnaires, and brain MRI that occurred within 24 to 48 hours of each other.

Throughout the study period, participants were asked to remain abstinent from cannabis, alcohol, and other substances (other than tobacco), which was confirmed through breath, urine, and sweat toxicology screening at each visit. If positive for illicit drug use, showed an increase in THCOOH levels, or had a breath alcohol concentration greater than 0.000 at the start of any subsequent session after baseline, participants were asked to conduct the session after a week of abstinence. Participants were not allowed to complete sessions four and five (i.e. MRI scan) if positive for any illicit drug use, a rise in THCOOH levels, or had a breath alcohol concentration greater than 0.000. Participants who used tobacco were asked to abstain from use for at least an hour prior to MRI scan to prevent nicotine withdrawal interference with functional task data.

Measures

MINI Psychiatric Interview—Participants and parents of participants over the age of 18 were interviewed with the Mini International Psychiatric Interview (MINI) (Sheehan et al., 1998) and participants and parents of participants under 18 were interviewed with the MINI-Kid (Sheehan et al., 2010) to rule out for potential Axis-I Disorders.

Customary Drinking and Drug Use Record—To determine lifetime patterns of drug and alcohol use, participants were given the Customary Drinking and Drug Use Record (CDDR) (Brown et al., 1998) at baseline to measure maximum frequency of alcohol, nicotine, cannabis, and other drug use, SUD abuse and dependence symptoms, and the age of onset for first and regular (defined as weekly for one year) use.

Timeline Followback—A modified version of the Timeline Follow-Back (TLFB) interviews were conducted by trained RAs to measure substance use patterns on a weekly basis for the past year while providing memory cues such as holidays and personal events (Lisdahl & Price, 2012; Sobell & Sobell, 1992). Substances were measured by standard units [alcohol

(standard drinks), nicotine (number of cigarettes and hits of chew/snuff/pipe/cigar/hookah), cannabis (smoked/vaped flower, concentrates, edibles were measured and dosing was converted to joints based grams), ecstasy (number of tablets), sedatives (number of pills or hits of GHB), stimulants (cocaine and methamphetamine use converted to milligrams and number of amphetamine pills), hallucinogens (number of hits or occasions of ketamine/salvia/shrooms/other hallucinogens), opioids (number of hits of heroin/opium), and inhalants (number of hits)].

Drug Toxicology/Abstinence Testing—As participants were expected to remain abstinent from all alcohol and drugs (other than tobacco) throughout the course of the study, abstinence was evaluated at each session through urine toxicology. The ACCUTEST SplitCup 10 Panel drug test measures amphetamines, barbiturates, benzodiazepines, cocaine, ecstasy, methadone, methamphetamines, opiates, PCP, and THC. Urine samples were also tested using NicAlert to test cotinine level, a metabolite of nicotine. Participants also wore PharmChek Drugs of Abuse Patches, which continuously monitor sweat toxicology for the presence of cocaine, benzoylecgonine, heroin, 6MAM, morphine, codeine, amphetamines, methamphetamine, delta-9-tetrahydrocannabinol (THC), and phencyclidine. Participants also underwent breathalyzer screens to test for alcohol use at the start of each session.

Descriptive Behavioral Measures—Wide Range Achievement Test-Fourth Edition. The Wide Range Achievement Test-Fourth Edition (WRAT-4) word reading subtest was used to estimate quality of education and estimate intelligence through letter identification and word recognition (Manly, Jacobs, Touradji, Small, & Stern, 2002; Wilkinson & Robertson, 2004). Cannabis Withdrawal Symptom Criteria. The Cannabis Withdrawal Symptom Criteria (CWSC) was administered across all sessions. The CWSC presents participants with a list of 17 common symptoms associated with cannabis withdrawal and asks them to rate them based on a 0-10 scale,

asking to what extent symptoms were experienced within the past 24-hours (Allsop, Norberg, Copeland, Fu, & Budney, 2011). Beck's Depression Inventory-II. The Beck's Depression Inventory-II (BDI) was administered at session one and four of the study protocol. The BDI provides participants with 21 grouped statements, and respondents pick one statement that best describes their mood or feelings during the past two weeks. Summed score was calculated (Beck, Steer, & Brown, 1996). Behavioral Inhibition System/Behavioral Activation System Scale. The Behavioral Inhibition System/Behavioral Activation System Scale consists of a 24-item questionnaire asked on a 4-point Likert scale (1=Very true for me; 4=Very false for me) (Carver & White, 1994), Resulting in four subscales which consist of: Behavioral Inhibition System (BIS), Behavioral Activation System (BAS) drive, BAS reward, and BAS fun-seeking.

MRI 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. Echoplanar images (EPI) were collected while performing the Affective Go/No-go task [designed using E-Prime software (W. Schneider, Eschman, & Zuccolotto, 2002), see below] using a T2*-weighted gradient-echo EPI pulse sequence (TR/TE=2500ms/30ms, FOV=200cm, matrix 64x64 pixels, slice-thickness=3.2mm, flip angle=90 degrees, 44 contiguous sag slices).

fMRI Affective Go/No-go Task—Participants completed a Go/No-go task featuring faces expressing feelings of happy, fearful, or calmly valenced emotions which was originally designed by the research group at Sackler Institute for Developmental Psychobiology (Hare et

al., 2008; Somerville et al., 2011). For this paradigm, two facial expressions were used within a trial. Using a rapid event-related design, participants were instructed what specific stimuli (i.e. expression) they should respond through pressing the target box (Go) and what specific stimuli they should withhold from responding and not pressing the target box (No-go). For each trial, faces would appear for 500 milliseconds followed by jittered interstimulus interval from 2 to 14.5 seconds in duration. Participants were exposed to 48 total stimuli which were presented in a pseudorandomized order (35 "Go" stimuli and 13 "No-go" stimuli) in each trial. Participants completed a total of six trials which permitted every combination of happy, fearful, and calm valenced expressions to serve as either Go or No-go stimuli for each participant. In this way, participants responded to approximately 70 correct happy Go stimuli that will be contrasted against approximately 70 correct calm Go activation. Directions for the task included instructing participants to respond as fast as possible and to not wait for the stimuli to disappear, while also making as few errors as possible.

MRI Pre-processing Plan

Data will be processed analyzed using Analysis of Functional NeuroImages [AFNI; Cox (1996)] and Matlab (MathWorks, 2012). Imaging data will be processed through standard preprocessing pipelines within AFNI (i.e. 'afni_proc.py'). The first three repetition times (TRs) will be removed to eliminate initial scanner noise. To account for low and high frequency artefactual signals caused by head motion, physiological changes, and hardware instabilities, the time series per each voxel will be "despiked" and these isolated spikes will be replaced to fit the modeled data for the voxel using '3dDespike'. Voxel time series will be corrected to align all acquired data to the same temporal spot of origin through utilization of '3dTshift'. To further limit head motion within BOLD signaling, volumes will be 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) through '3dVolreg'. Motion censoring was employed when 10% or more of head motion was observed as based on previous literature of similar samples (Tapert et al., 2007). Data will then be spatially smoothed using a Gaussian function with the default 4mm full width at half maximum (FWHM) to blur data to half of other surrounding voxels with '3dmerge'. Each voxel will be scaled by default to a mean of 100 to allow for interpretative purposes of echo-planar imaging (EPI) values as a percentage of the mean. Functional responding to correct happy Go trials will be examined (including trials presented during fearful or calm No-Go blocks) against functional responding to correct calm Go trials (including trials presented during the fearful or happy No-Go blocks). These trials will first be deconvolved with a gamma-variate hemodynamic response function (HRF) for each individual participant with AFNI's 3dDeconvolve (Ward, 2000), while accounting for six motion parameters (i.e., roll, pitch, yaw, dp, dl, and ds) by regressing them out. Data points of incorrect responses on the Go trial will be removed from the data to compare correct happy Go stimuli across cannabis users and non-users contrasted against correct calm Go activation. In this way, we are only examining functional activation at correct responding to the happy Go stimuli and not incorrect responding.

Statistical Analysis

Power Analysis—An a priori analysis was conducted using G*Power 3 (Faul, Erdfelder, Lang, & Buchner, 2007) to determine whether we were statistically powered to examine the current proposal. Based on the presented aims, a fixed linear multiple regression model will be run with medium effect size of $f^2 = 0.15$, an error probability of $\alpha = 0.05$, and power ($1-\beta$) equal to 0.80. This results in a sample size of 55 to be adequately powered to examine our two-group,

or first primary, analysis (with a total number of predictors at 4, i.e., including nuisance variables). Secondly, a sample size of 68 is needed to adequately examine our interaction with gender, or secondary primary, analysis (with a total number of predictors at 5). Our sample size of 68 positions us at the required number of participants needed to examine these analyses.

Preliminary Analysis—Differences in demographic variables will be examined using ANOVAs and Chi-square tests in *R* (R Develoment Core Team, 2010). Behavioral task performance [i.e., % commission errors, % omission errors, response time (RT)] will be examined to determine potential group differences in responding through utilization of an ANOVA. Decisions for statistical significance will be determined at $p = .05$ for all preliminary analyses.

Primary Analysis—To satisfy the Aim 1, a whole-brain analysis examining BOLD responses to correct happy Go stimuli (against correct calm Go stimuli) was conducted at the group-level through a voxel-by-voxel ANCOVA with '3dMVM', while controlling for gender, past year alcohol use, and cotinine level on the day of fMRI scanning. To satisfy the Aim 2, a cannabis group-by-gender interaction will be incorporated into the model and rerun. A family-wise error (FWE) threshold of $p_{FWE}<0.05$ [individual voxel threshold at $p<0.005$ at the individual voxel level, which prior cannabis-related research has used to detect subtle effects (i.e., small to medium effect sizes) (Heitzeg, Cope, Martz, Hardee, & Zucker, 2015)] was applied to all models using a cluster-threshold method of correcting for multiple comparisons using Monte Carlo simulations within 3dClustSim ("AFNI program: 3dClustSim," 2019). This methodology for cluster thresholding has been shown to effectively control false-positive rates (Cox, Chen, Glen, Reynolds, & Taylor, 2017; Slotnick, 2017).

Exploratory Analysis—In order to examine influential properties of differing cannabis-related variables, beta-values from significant BOLD regions from Aims 1 & 2 will be extracted and correlated with cannabis use severity (total past year cannabis use, age of first regular onset, and total cannabis abuse/dependence symptoms) and length of abstinence in days from MRI scan, within cannabis-users alone. In addition, beta-values from significant BOLD regions in Aims 1 & 2 will be extracted and correlated with descriptive behavioral measures (CWSC, BDI, BIS, BAS drive, BAS reward, and BAS fun-seeking) within the whole sample. Corrections for multiple comparisons using false discovery rate (*FDR*) were computed for the series of brain-behavior correlations (Benjamini & Hochberg, 1995), both raw p-values and FDR-corrected p-values are reported below.

Results

Demographic Data

There were no significant differences between cannabis-using and control groups in regard to age (p=.53), gender distribution (p=.052), ethnicity (p=.31), race (p=.48), educational attainment (p=.33), WRAT-4 Word Reading (p=.62), BAS drive (p=.56), BAS reward (p=.79), and CWSC sum (p=.09). As expected, there were significant differences in lifetime (p<.001) and past year cannabis use (p<.001), past year tobacco use (p=.02), cotinine levels at MRI (p=.049), and alcohol consumed within the past year (p<.001); thus, alcohol and cotinine levels were included as covariates in all fMRI analyses. In addition, cannabis-using group and control groups differed in BDI (p<.001), BIS (p=.02), and BAS fun-seeking (p=.04). (See Table 1).

Behavioral Data

Cannabis-using participants did not significantly differ on the number of commission errors, omission errors, and Go RTs when compared to control participants (all p's>.05) (See

Table 2). These findings were also non-significant after controlling for past year alcohol use and cotinine level (all *p*'s>.05). When examining gender, males and females also did not differ in their number of commission errors, omission errors, and Go RTs (all *p*'s>.05).

fMRI BOLD Response

Cannabis Effects. Cannabis-using participants showed a significant cluster of increased BOLD responses in a cluster extending the left inferior parietal lobe (see Table 3, Figure 1, Figure 3). Cannabis-using participants did not display any significant clusters of decreased BOLD activation compared to controls.

Cannabis*Gender Effects. *Gender.* Male participants showed significant clusters of decreased BOLD responses in right supramarginal, left cingulate, left precentral, right middle frontal, left cerebellum, left middle cingulate, right cuneus, and left middle temporal regions relative to female participants (see Table 3). *Cannabis*Gender.* A significant interaction was observed in the right parahippocampal gyrus (see Table 3, Figure 2), such that cannabis-using males showed increased BOLD response and cannabis-using females showed decreased BOLD response, relative to their same-gender control counterparts (see Figure 3).

Substance Use Covariates. Past year alcohol use predicted increased BOLD activation within the right precuneus and cotinine levels predicted decreased BOLD activation in the right primary visual cortex (See Table 3).

Brain-Behavior Relationships

Substance Use Variables. Beta-values from clusters displaying significantly different BOLD responses in cannabis group main effect and cannabis-by-gender interaction was not related to length of abstinence, age of first regular onset, past year cannabis use, and total cannabis abuse/dependence symptoms (all *p*'s>.05) (see Table 4).

Post-hoc Descriptive Behavioral Measures. Beta-values from clusters displaying significantly different BOLD responses in cannabis group main effect and cannabis-by-gender interaction was not related to BIS, BAS drive, and BAS reward. A significant positive correlation was observed between BDI scores and beta-values from the left inferior parietal cluster (i.e., cannabis group effect finding) but the correlation was only marginal following FDR-corrections, r=0.26, p=.03, p_{FDR}=.09. No significant correlations were observed between BDI scores and the cannabis-by-gender cluster. A significant positive correlation was observed between BAS fun-seeking and beta-values from the left inferior parietal cluster (i.e., cannabis group main effect finding) but the correlation was only marginal following FDR-corrections, r=0.31, p=.01, p_{FDR}=.07. No significant correlations were observed between BAS fun-seeking scores and the cannabis-by-gender cluster (see Table 4, Figure 4).

Discussion

Cannabis use is one of the more commonly used substances in the United States (Johnston et al., 2020; Schulenberg et al., 2019), thus, understanding the impact of cannabis use on neurodevelopment amongst adolescents and young adults is of increasing importance. Prior research has shown associations between cannabis use and reward circuitry (Filbey & Dunlop, 2014; Lichenstein et al., 2017; Luijten et al., 2017; Martz et al., 2016; Nestor et al., 2010); yet minimal studies have investigated response to appetitive faces within cannabis-using adolescents and young adults. In the present study, we found that cannabis-using participants demonstrated increased BOLD responding elicited by happy faces in the left inferior parietal lobe despite similar behavioral performance. As previously reported, significant gender differences were observed with male participants showing decreased BOLD responses relative to female participants in several regions; notably, a significant cannabis-by-gender interaction was

observed in the right parahippocampal gyrus with cannabis-using males displaying increased activation and cannabis-using females exhibiting decreased activation relative to their same-gender control counterparts. In the whole-sample, increased depressive symptoms and fun-seeking scores were marginally correlated with increased BOLD response in the left inferior parietal lobe while responding to happy faces.

Evaluation of Cannabis Effects

Cannabis-using adolescents and young adults had increased activation in the left inferior parietal region relative to control participants while responding to appetitive faces. In other studies of fMRI tasks of cannabis-using individuals, the inferior parietal region has exhibited increased BOLD responding in go conditions of a go/no-go task in adolescents (Tapert et al., 2007), decreased BOLD responding in positive word conditions in young adults (Heitzeg et al., 2015), and aberrant fronto-parietal and inferior parietal-cerebellar connectivity in a go/no-go task (Behan et al., 2014; Harding et al., 2012). Principally, the inferior parietal region is part of the attention system involved in automatic allocation of attention to task-relevant information (Ciaramelli, Grady, & Moscovitch, 2008), is associated with cognitive control (Liu, Hairston, Schrier, & Fan, 2011), and consists of overlapped processes representing task-reward associations (i.e., associating behaviors with outcomes) (Wisniewski, Reverberi, Momennejad, Kahnt, & Haynes, 2015). In addition, the inferior parietal cortex has a high density of CB1 receptors (Terry et al., 2009) and has observed structural abnormalities in this region among cannabis-using adolescents and young adults (Price et al., 2015). Thus, as a compensatory mechanism, cannabis-using participants may be more heavily recruiting the inferior parietal region to assist in the integration of the attentional components of the paradigm (e.g., facial affect, task instructions, and switching between go/no-go trials) to perform the task at the same

level as their non-using counterparts. Similarly, the notion of numerous functional regions exhibiting aberrant activation in cannabis-using individuals relative to controls across fMRI tasks has been implicated in the literature previously, particularly in tasks requiring increased attention, inhibition, and/or set shifting (Abdullaev, Posner, Nunnally, & Dishion, 2010; Batalla et al., 2013; Blest-Hopley et al., 2018), further positing the mechanism of compensation—through the downregulation of CB1 receptors (Tapert et al., 2007)—to exhibit similar behavioral performance relative to non-using peers.

Interestingly, increased activation in the inferior parietal region was marginally linked with both increased depressive symptoms (i.e., BDI) and increased motivation to seek out novel rewards (i.e., BAS fun-seeking), suggesting this pattern of activation may be subtly linked with overall mood and reward engagement. Research has previously indicated that cannabis-using adolescents and young adults experienced increased reporting of depression (Bonnet & Preuss, 2017; Wright et al., 2016) and decreased BAS fun-seeking scores (Wright et al., 2016), although other findings have reported increased BAS fun-seeking reporting across all substance use in this age range (Franken & Muris, 2006). Further, we have previously reported links between reduced white matter volume, lower fronto-limbic and fronto-parietal white matter integrity, and increased frontolimbic functional connectivity with increased depressive symptoms in adolescent and young adult cannabis users, even in the absence of independent Axis I mood disorders (Medina et al., 2009; Shollenbarger et al., 2015; Shollenbarger et al., 2019). Taken together, these subtle mood symptoms and increased motivation to seek out novel rewards may be behavioral markers for increased risk for neuronal dysfunction in adolescent and young adult cannabis users, although these findings did not survive multiple comparison correction and need to be confirmed in a larger sample. Future longitudinal studies with larger samples are needed to

further characterize the relationships between mood and reward-seeking behavior and neuronal markers to rewarding emotional stimuli as adolescent and young adult cannabis users develop.

Notably, we did not observe decreased ventral striatum or amygdala BOLD activation in response to appetitive stimuli as we hypothesized in Aim 1. This may be due to the longer-than-average abstinence period our study maintained compared to other similar studies (Batalla et al., 2013; Lisdahl, Gilbart, Wright, & Shollenbarger, 2013). Prior findings have indicated ventral striatal and amygdala BOLD activity elicited by reward processing paradigms, yet, little to no abstinence period was maintained in these studies (Luijten et al., 2017). Thus, it is possible that activation patterns observed previously is linked with acute use or withdrawal and otherwise healthy adolescents and young adults can recover in their appetitive face response differences within three-weeks of abstinence. Consistent with this, a previous study demonstrated no connectivity differences with reward regions in cannabis-using versus non-cannabis-using participants after one month of abstinence (Pujol et al., 2014). It is also plausible that subtle effects may not be observed in whole-brain fMRI analyses—as demonstrated in a residential sample of cannabis-using adolescents responding to emotional faces using cannabis dependency scores as the predictor (Leiker et al., 2019)—and that more specific analyses examining ROIs would yield more pronounced group differences. Nonetheless, future directions include investigating appetitive face responding prospectively and longitudinally and specific investigations of ROIs are needed, as elucidating appetitive face responding has useful clinical implications for determining how reward related stimuli in our day-to-day may be appraised and responded to differently in cannabis-using adolescents and young adults. Still, cannabis-using participants demonstrated increased BOLD activation in left inferior parietal region possibly

indicating increased effortful recruitment of this region which is necessary to link behaviors with outcomes.

Evaluation of Gender as a Moderator

Investigating cannabis-by-gender interactions, we observed a significant BOLD cluster in the right parahippocampal gyrus, with cannabis-using males exhibiting increased BOLD response and cannabis-using females exhibiting decreased BOLD response, relative to their same-gender control counterparts when responding to appetitive face stimuli. This finding demonstrates that gender has a subtle moderating role in the relationship between cannabis use and reward-related affective processing, which has been demonstrated as an important factor when examining affective processing among non-substance using individuals (Burghy et al., 2012; Killgore & Yurgelun-Todd, 2001; Lee et al., 2013), but has yet to be utilized as a moderating factor more broadly in cannabis-related fMRI investigations. The parahippocampal gyrus has been shown to be aberrant in more frequent cannabis-using individuals with increased BOLD activation during an encoding task (Becker, Wagner, Gouzoulis-Mayfrank, Spuentrup, & Daumann, 2010), increased BOLD activity coupled with worse memory performance among cannabis-using individuals (Nestor, Roberts, Garavan, & Hester, 2008), and decreased structural volume in this region (Battistella et al., 2014; Matochik, Eldreth, Cadet, & Bolla, 2005). In addition, the parahippocampal gyrus exhibits sex differences in affective processing tasks, with males showing more right lateralization in this region (S. Schneider et al., 2011), females showing greater activation in negative face conditions (Hofer et al., 2006) and activation in the right parahippocampal gyrus elicited by positive face conditions across sexes (Hofer et al., 2006) and more pronounced activity in young adult participants (relative to older adults) (Iidaka et al., 2002). Taken together, cannabis-using adolescent males are showing more sensitive effects in

this region relative to other groups due to the starker difference (*M*=0.01, *SD*=0.15) compared to male controls (*M*=-0.15, *SD*=0.15; see Figure 3). Thus, the interaction between cannabis and gender in this region, and the lack of an interaction in other hypothesized regions (i.e., ventral striatum and amygdala), could be due to numerous factors. Sex-specific pruning patterns may be impacted by introducing cannabis into staggered developmental trajectories (Medina et al., 2009; Rubino & Parolaro, 2015), which differ in timing across the sexes (Giedd et al., 1999; Lenroot et al., 2007). As aforementioned, males exhibit increased CB1 receptor density relative to females (Burston et al., 2010; Rubino et al., 2008), yet females show greater desensitization of these receptors after THC administration in pre-clinical models (Burston et al., 2010; Rodriguez de Fonseca et al., 1993). Moreover, females in our sample used less frequently, which is in line with previous literature indicating that cannabis-using males tend to use more frequently, severely, and with higher potency products (Cuttler et al., 2016; Khan et al., 2013), but female cannabis-using participants were abstinent for fewer days relative to males. Future research should consider the moderating role of gender when investigating the relationship between appetitive face processing and cannabis use.

Cannabis Severity Null Findings

There were no significant correlations observed between beta-values and length of abstinence, age of first regular use onset, past year cannabis use, and total cannabis abuse/dependence symptoms. Research has previously linked these variables with fMRI activation particularly when engaged in reward-related paradigms (Martz et al., 2016; Nestor et al., 2010) and other outcomes related to cannabis use (Coulston et al., 2007; De Hert et al., 2011; Pope et al., 2003; Solowij et al., 1995; Veen et al., 2004). Yet, most of these studies have linked indices of cannabis severity with shorter to no windows of abstinence and thus, these variables

may have had stronger correlations at the outset of the study period but are no longer correlated after 3-weeks of abstinence in adolescents and young adults. In this way, it is plausible these cannabis use severity variables may be related to specific ROIs (i.e., ventral striatum and amygdala), which were not significantly different between groups when conducting a whole-brain analysis. It is also likely that due to the functional regions of the clusters identified in the whole-brain analysis, neurocognitive measures of attention or executive functioning for the inferior parietal cluster or verbal memory for the parahippocampal cluster may yield stronger brain-behavior correlations, or that premorbid differences relative to these neurocognitive measures may represent a risk for cannabis use (Jackson et al., 2016; Meier et al., 2012; Tervo-Clemmens et al., 2018).

Limitations and Future Directions

It is worth noting limitations of the present thesis. Notably, causality cannot be determined from the present sample due to cannabis use initiation occurring prior to the study protocols, studies such as the Adolescent Brain Cognitive Development (ABCD) (Casey et al., 2018; Lisdahl et al., 2018) study can assess functional activation elicited by affective processing tasks in substance-naïve youth and determine how this process either represents a risk factor for cannabis use or is affected by use. Second, we did only exclusively ask for participant's reported gender and not sex assigned at birth, which limits our ability to elucidate sex-specific mechanisms in this relationship. Third, based on the parent study protocols, the sample was balanced for aerobic fitness and excluded individuals who could not undergo acute aerobic fitness measurements; this decreases generalizability to adolescent and young adult populations who may primarily be sedentary. Fourth, although we did find a significant cannabis-by-gender interaction, the smallest cell in the present study was control male participants (n=12), which

limits our power; we expect that a larger sample size could reveal more robust interactions. Fifth, a more lenient decision on individual voxel thresholding (set at $p<.005$) was made to detect more subtle effects (e.g., small to medium effect sizes), yet, research has shown that thresholding at $p<.001$ decreases the likelihood of false positives and bolsters fMRI finding interpretation (Woo, Krishnan, & Wager, 2014). Thus, findings will need to be replicated in a larger sample in order to detect small effect sizes. Finally, cannabis metabolites (i.e. THCCOOH) cycle out within a three-to-four week period (Goodwin et al., 2008); thus, future studies are needed to determine whether differences exist at the acute stage (i.e., no abstinence period) and if subtle abnormalities would recover with longer periods of sustained abstinence.

Conclusions

The current thesis found that after 3-weeks of monitored abstinence, cannabis-using adolescents and young adults displayed increased BOLD activation in left inferior parietal region relative to control participants when responding to appetitive faces. Post-hoc brain-behavior correlations indicate this region was positively correlated with depressive symptoms and motivations for novel rewards; yet these relationships were only marginally linked after correction for multiple comparisons. This region's relative over-activation may indicate compensation amongst cannabis-using individuals who are recruiting other functional regions to assist in responding to the go/no-go task. In addition, we observed a significant cannabis-by-gender interaction in BOLD activation in a cluster positioned within the right parahippocampal region. Cannabis-using females showed decreased BOLD activity and cannabis-using males showed increased BOLD activity, relative to their same-gender control group counterparts; this region did not have any significant brain-behavior correlations. These findings, coupled with the existing literature, suggest that BOLD activity elicited by responding to appetitive faces—even

after 3-weeks of monitored abstinence—is aberrant between cannabis-using and control adolescents and young adults and that gender has a moderating effect on this relationship, particularly in subcortical regions. Future prospective, longitudinal studies, such as the ABCD Study (Lisdahl et al., 2018) are needed to further elucidate the causal relationship between escalating cannabis use and functional activation elicited by appetitive face responding in male and female adolescent and young adult cannabis users.

Table 1. Demographic, Substance Use, and Behavioral Characteristics

	Whole-sample	Cannabis-using Group			Control Group		
		All	Male	Female	All	Male	Female
N	68	35	22	13	33	12	21
M (SD) or %							
Age	21.3 (2.4)	21.5 (2.1)	21.5 (2.2)	21.4 (2.0)	21.1 (2.6)	21.4 (3.1)	20.9 (2.4)
Race (% Caucasian)	64.7%	60.0%	68.2%	46.2%	69.7%	58.3%	76.2%
Ethnicity (% Non-Hisp)	80.9%	77.1%	77.3%	76.9%	84.9%	91.7%	81.0%
Educational Attainment	14.2 (1.9)	14.0 (1.5)	14.0 (1.7)	14.1 (1.3)	14.5 (2.2)	14.8 (2.7)	14.3 (2.0)
WRAT-4 Word Reading	105.4 (12.0)	104.7 (13.0)	107.7 (13.4)	99.5 (10.9)	106.1 (11.0)	108.3 (11.5)	104.9 (10.9)
Past year Alcohol Use[a]*	209.8 (266.7)	325.0 (301.3)	356.5 (309.7)	271.6 (290.5)	87.7 (150.3)	127.1 (212.5)	65.1 (99.1)
Past year Tobacco Use[a]*	98.0 (345.8)	189.8 (466.6)	276.7 (573.2)	42.8 (68.1)	0.5 (2.2)	0.1 (0.3)	0.8 (2.7)
Cotinine Level[b]*	1.5 (1.5)	1.9 (1.9)	2.2 (2.2)	1.2 (0.8)	1.2 (0.7)	1.2 (0.7)	1.1 (0.7)
Past year Cannabis Use[a]*	-[d]	429.7 (447.5)	505.4 (523.1)	301.5 (245.4)	-[d]	-[d]	-[d]
Lifetime Cannabis Use [c]*	618.7 (1159.2)	1200.7 (1389.0)	1447.9 (1651.7)	782.5 (625.0)	1.4 (4.0)	0.2 (0.6)	2.2 (5.0)
Age at Regular Cannabis Use Onset	-[d]	17.5 (1.7)	17.8 (1.3)	17.4 (1.9)	-[d]	-[d]	-[d]
Cannabis Abstinence Length in days[e]	-[d]	31.3 (23.2)	34.8 (28.5)	25.5 (6.5)	-[d]	-[d]	-[d]
Total Cannabis Use Abuse/Dependence Symptoms[f]	-[d]	4.6 (1.8)	5.0 (1.6)	3.9 (1.9)	-[d]	-[d]	-[d]
Dx of Cannabis Abuse or Dependence[f]	-[d]	82.9%	81.8%	84.6%	-[d]	-[d]	-[d]
CWSC Sum – Session 4	16.1 (13.5)	18.9 (13.5)	19.8 (15.3)	17.2 (9.7)	13.2 (13.1)	11.8 (10.8)	14.0 (14.4)

BDI – Session 4*	3.8 (4.1)	5.5 (4.7)	5.4 (4.5)	5.7 (5.1)	2.1 (2.6)	2.0 (2.9)	2.1 (2.4)
BIS*	19.0 (3.3)	18.1 (2.5)	17.3 (2.4)	19.5 (2.0)	20.0 (3.8)	18.2 (3.9)	21.1 (3.3)
BAS Drive	10.9 (2.3)	11.0 (2.5)	10.9 (2.8)	11.2 (1.8)	10.7 (2.2)	11.3 (2.4)	10.3 (2.1)
BAS Reward	16.9 (2.8)	17.0 (3.1)	16.6 (3.7)	17.8 (1.8)	16.8 (2.5)	15.6 (3.0)	17.6 (1.8)
BAS Fun-Seeking*	11.7 (2.1)	12.2 (2.3)	12.1 (2.5)	12.2 (2.0)	11.1 (1.8)	10.8 (2.3)	11.3 (1.5)

Notes:

* $p < .05$

WRAT-4 – Wide Range Achievement Test-Fourth Edition

CWSC – Cannabis Withdrawal Symptom Criteria

BDI – Beck's Depression Inventory-II

BIS – Behavioral Inhibition System

BAS – Behavioral Activation System

[a] Measured in standard uses on TLFB (Sobell & Sobell, 1992)

[b] Measured at MRI Scan.

[c] Measured in standard uses on CDDR (Brown et al., 1998)

[d] Not applicable.

[e] Calculated from TLFB last CAN use date and date of fMRI.

[f] DSM-IV-TR

Table 2. Behavioral Task Data

	Cannabis-using Group	Control Group
Omission Errors to Happy Faces (%, ± S.D.)	0.8% ± 1.4	1.1% ± 1.8
Omission Errors to Calm Faces (%, ± S.D.)	1.3% ± 2.1	1.8% ± 3.7
RT to Correct Happy Faces (ms, ± S.D.)	547.2 ± 91.6	527.5 ± 76.5
RT to Correct Calm Faces (ms, ± S.D.)	574.0 ± 93.0	563.8 ± 103.2
Commission Errors to No-go Faces (%, ± S.D.)	7.1% ± 5.2	9.6% ± 6.7

Notes: RT – Response time

Table 3. Significant BOLD Clusters

Cluster #	Voxels	MNI coordinates			Annotations
		Peak x	Peak y	Peak z	
Cannabis Finding					
1	49	+25.5	+34.5	+34.5	Left Inferior Parietal
Gender Findings					
1	350	-52.5	+31.5	+25.5	Right Supramarginal
2	254	+16.5	-25.5	+13.5	Left Cingulate
3	135	+55.5	-1.5	+19.5	Left Precentral
4	100	-25.5	-31.5	+28.5	Right Middle Frontal
5	67	+16.5	+55.5	-28.5	Left Cerebellum
6	61	+19.5	+43.5	+37.5	Left Middle Cingulate
7	58	-16.5	+79.5	+34.5	Right Cuneus
8	53	+37.5	+52.5	+16.5	Left Middle Temporal
*Cannabis*Gender Finding*					
1	47	-25.5	+43.5	-4.5	Right Parahippocampal
Alcohol Use Finding					
1	76	-7.5	+73.5	+55.5	Right Precuneus
Cotinine Level Finding					
1	81	-7.5	+85.5	-19.5	Right Primary Visual

Table 4. Brain-behavior correlations between beta-values from significant BOLD clusters and cannabis severity indicators or behavioral measures

	Cannabis-using Group [a]		Cannabis-using Males [b]		Cannabis-using Females [b]	
	r	*p*	*r*	*p*	*r*	*p*
Length of Abstinence in Days	.13	.47	.25	.27	.02	.95
Age of First Regular Use Onset	-.03	.88	.42	.06	-.36	.23
Past-year Cannabis Use	-.17	.32	-.19	.39	.02	.96
Total Cannabis Abuse / Dependence Symptoms	-.11	.51	.01	.95	-.21	.49
	Whole-sample [a]		Whole-sample Males [b]		Whole-sample Females [b]	
	r	*p*	*r*	*p*	*r*	*p*
BDI – Session 4	**.26**	**.03**	.18	.31	-.16	.36
BIS	-.01	.93	-.02	.92	-.17	.33
BAS Drive	.16	.20	.15	.39	-.35	.06
BAS Reward	.16	.20	.14	.43	.06	.73
BAS Fun-Seeking	**.31**	**.01**	.28	.11	-.14	.46

Notes:
p represents raw p-values (i.e., not FDR-corrected p-value)
Bolded cells indicate significant correlation at uncorrected $p<.05$
CWSC – Cannabis Withdrawal Symptom Criteria
BDI – Beck's Depression Inventory-II
BIS – Behavioral Inhibition System
BAS – Behavioral Activation System
[a] Correlations were conducted with beta-values from significant BOLD cluster in the Left Inferior Parietal region from main cannabis group effect.
[b] Correlations were conducted with beta-values from significant BOLD cluster in the Right Parahippocampal region from cannabis-by-gender interaction.

Figure 1. BOLD Responses in Cannabis-using Group vs. Control Group

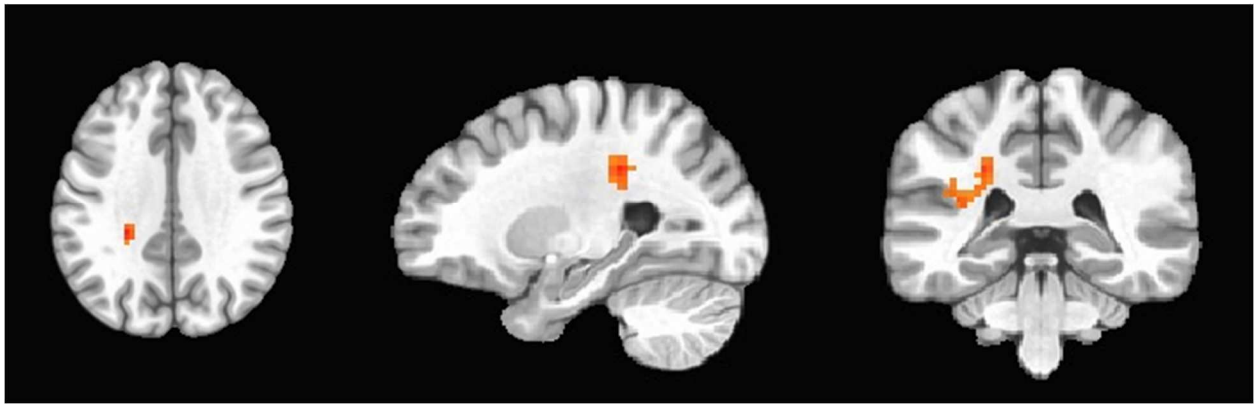


Figure 1. Displays region of increased significant BOLD responses in cannabis-using participants compared to control participants during correct responses to "happy" faces during Go trials (contrasted against correct responses to "calm" faces during Go trials). Increased BOLD responses in the Left Inferior Parietal (MNI, x = 25, y = 34, z = 34) region is displayed.

Figure 2. BOLD Responses in Cannabis-by-Gender Interaction

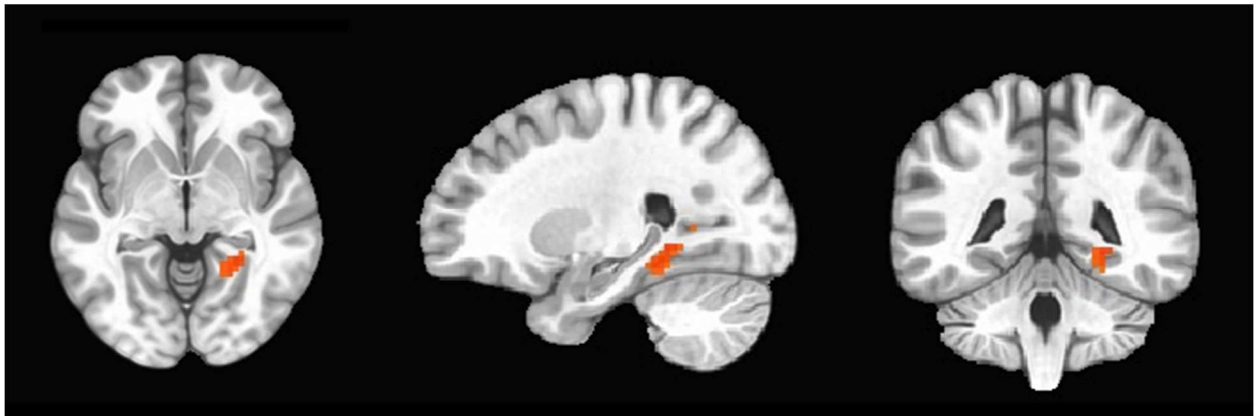


Figure 2. Displays region of significant BOLD cluster with cannabis-by-gender interaction during correct responses to "happy" faces during Go trials (contrasted against correct responses to "calm" faces during Go trials). Increased BOLD responses in the Right Parahippocampal (MNI, x = -25, y = 43, z = -4) region is displayed.

Figure 3. Beta-Values of Significant BOLD Clusters in Cannabis-using Group Main Effect and Cannabis-by-Gender Interaction

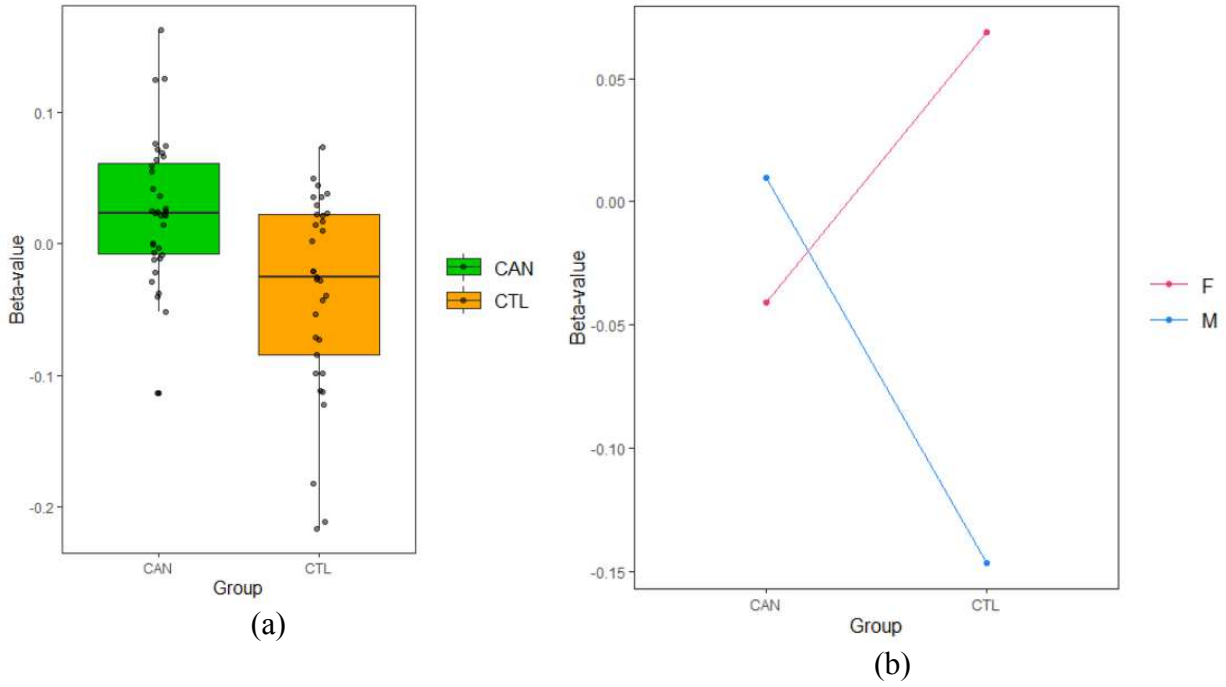
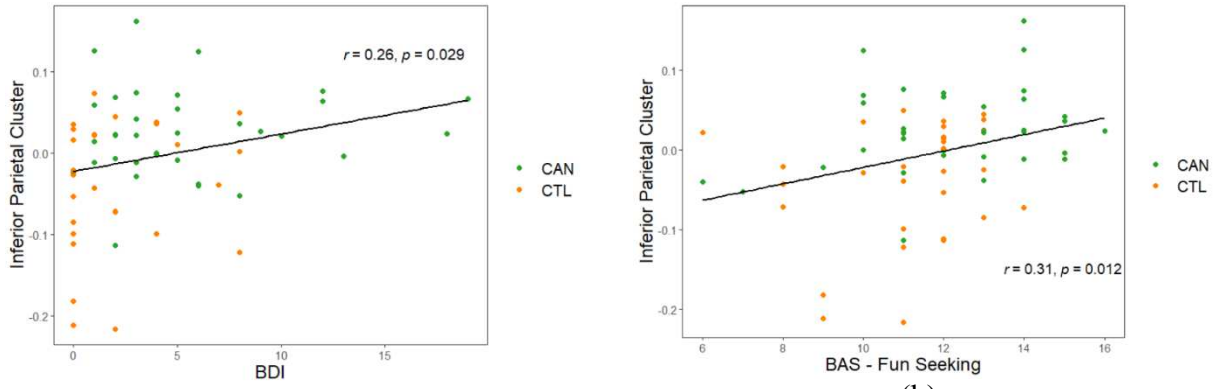


Figure 3. (a) Displays beta-values from Left Inferior Parietal cluster. Cannabis-users displayed increased BOLD activity during correct "happy" faces during Go trials, relative to controls. (b) Displays mean beta-values from Right Parahippocampal cluster. Cannabis-by-gender interaction demonstrated increased BOLD activity in cannabis-using males relative to control males and decreased BOLD activity in cannabis-using females relative to control females. CAN = Cannabis-using group; CTL = Control group; F = Female; M = Male.

Figure 4. Correlations Between Behavioral Measures and Beta-values from the Left Inferior Parietal Cluster



(a) (b)

Figure 4. (a) Displays correlation between BDI scores and beta-values from Left Inferior Parietal cluster in the whole-sample. (b) Displays correlation between BAS Fun-seeking scores and beta-values from Left Inferior Parietal cluster in the whole-sample. CAN = Cannabis-using group; CTL = Control group.

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