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Cannabis-Using Youth Demonstrated Blunted Rostral Anterior Cingulate Cortex Activation, but Normal Functional Connectivity, During an Emotional Go/No-Go Task

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by

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ABSTRACT

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Cannabis use has been associated with deficits in self-regulation, including inhibitory control. Cannabis users have previously exhibited both structural and functional deficits in the rostral anterior cingulate cortex (rACC), a region involved in self-regulation of emotional response and inhibitory control. The present study aimed to examine whether abstinent cannabis users demonstrated abnormal functional activation and connectivity of the bilateral rACC during an emotional inhibitory processing task, and whether gender moderated these relationships. The study also aimed to examine whether bilateral rACC activation and connectivity in cannabis users was related to perceived stress. It was hypothesized that cannabis users would exhibit hypoactivation and hyperconnectivity of the rACC with the rest of the brain during emotional inhibitory processing. Further, it was predicted that female cannabis users would exhibit the most pronounced activation and connectivity abnormalities. It was also expected that abnormal functional activation and connectivity would be related to increased perceived stress. In the current study, cannabis users ages 16-25 underwent fMRI scanning while completing a Go/No-go task using fearful and calm emotional faces as non-targets. Participants were excluded for psychiatric disorders, major medical conditions, and excessive other drug use. Multiple linear regression and ANCOVA were used to

determine (1) if cannabis group status was related to rACC activation and functional connectivity after controlling for alcohol and nicotine use and (2) whether gender moderated these relationships. Functional connectivity analysis included linear modeling consistent with psychophysiological interaction (PPI) analysis. Subsequently, Pearson correlations were conducted to investigate whether significant activation and functional connectivity were associated with perceived stress. Results showed blunted bilateral rACC activation in cannabis users during fearful response inhibition. Male, relative to female, cannabis users had greater right rACC connectivity with the right cerebellum during calm response inhibition (marginal finding; cannabis x gender interaction did not reach significance). Further, across the entire sample, males, relative to females, had enhanced right rACC and precuneus/posterior cingulate connectivity during calm response inhibition, which was related to gender differences in perceived stress. These results suggest that chronic cannabis use may disrupt typical rACC development, conferring risk for later development of mood disorders.

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2-AG	2-Arachidonoylglycerol
3-D	3-Dimensional
3T	3-Tesla
ACC	Anterior Cingulate Cortex
ADHD	Attention-Deficit/Hyperactivity Disorder
AEA	N-arachidonoylethanolamine
AFNI	Analysis of Functional Neuroimages
ANOVA	Analysis of Variance
ANCOVA	Analysis of Covariance
BOLD	Blood Oxygen Level-Dependent
CB1	Cannabinoid receptor-1
CBD	Cannabidiol
CDDR	Customary Drinking and Drug Use Record
CNR1	Cannabinoid receptor-1 gene
dACC	Dorsal Anterior Cingulate Cortex
dlPFC	Dorsolateral Prefrontal Cortex
dmPFC	Dorsomedial Prefrontal Cortex
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition, Text Revision
eCB	Endocannabinoid
EPI	Echo-Planar
FAAH	Fatty Acid Amide Hydrolase

fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
GE	General Electric
HPA	Hypothalamic-Pituitary-Adrenal
HRF	Hemodynamic Response Function
IFG	Inferior Frontal Gyrus
lPFC	Lateral Prefrontal Cortex
MINI	Mini International Psychiatric Interview
mm	Millimeter
MNI	Montreal Neurological Institute template
mPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
ms	milliseconds
MSIT	Multi-Source Interference Task
OFC	Orbital Frontal Cortex
PAG	Periaqueductal Grey
PFC	Prefrontal Cortex
PPI	Psychophysiological Interaction
pre-SMA	Pre-supplementary Motor Area
PSS-14	Perceived Stress Scale-14
rACC	Rostral Anterior Cingulate Cortex
ROI	Region of Interest
rrACC	Right Rostral Anterior Cingulate Cortex

SMA	Supplementary Motor Area
SPGR	Spoiled Gradient-Recalled at Steady-State
SPSS	Statistical Package for the Social Sciences
STN	Subthalamic Nucleus
TE	Echo Time
THC	Δ-9-tetrahydrocannabinol
TI	Inversion Time
TLFB	Timeline Follow Back
TR	Repetition Time
vmPFC	Ventromedial Prefrontal Cortex
WRAT-4	Wide Range Achievement Test—Fourth Edition

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Examining the Functional Connectivity of Emotional Inhibitory Processing in Cannabis-Using Adolescents and Young Adults

Cannabis use is becoming more common, with 39% of young adults using during the past year, a 10% increase over the past decade (Johnston et al., 2016). This is concerning, as adolescents and young adults may be particularly vulnerable to the neurocognitive impact of cannabis use due neurodevelopment that continues into the late-20's (Casey, Jones, & Hare, 2008). The frontal executive system is one of the last areas to develop, taking longer to mature than limbic regions involved in emotion, such as the amygdala (Bava & Tapert, 2010). A dominant theory of adolescent substance use suggests that in emotionally laden situations, adolescents' limbic regions will exert stronger influence than the prefrontal cortex (PFC), leading to increased impulsivity, risk taking, and poorer ability to regulate emotions (Bava & Tapert, 2010; Casey, Jones, & Hare, 2008). Thus, adolescents and young adults may have an increased likelihood of participating in risky activities, such as substance use. In turn, the protracted neurodevelopment occurring during adolescence and young adulthood may leave them more susceptible to the neurocognitive effects of substance use (Bava & Tapert, 2010).

Endocannabinoid System & Cannabis

Δ-9-Tetrahydrocannabinol (THC), the primary psychoactive component of cannabis, binds receptors in the endogenous cannabinoid (eCB) system (Howlett, 1995). In the brain, THC binds the cannabinoid receptor-1 (CB1). The primary ligands in the eCB system, N-arachidonoylethanolamine (AEA or anandamide) and 2-arachidonoylglycerol (2-AG), also bind CB1 (Mechoulam & Parker, 2013). AEA is catabolized by the enzyme, fatty acid amide hydrolase (FAAH) (Ho & Hillard, 2005).

CB1 receptors are found throughout the brain, on pre-synaptic terminals of excitatory and inhibitory neurons and glial cells (Domenici et al., 2006; Pazos et al., 2005). CB1 receptor density is high in the PFC, cingulate cortex, hippocampus, amygdala, basal ganglia, and cerebellum (Herkenham et al., 1990; Glass et al., 1997; Mackie, 2005; Svizenska et al., 2008). The eCB system modulates a variety of functions (e.g., sleep, pain, inflammation, and energy intake), including stress and emotional regulation (Hillard, 2017). Balance of the eCB system in the medial PFC (mPFC) regulates limbic and hypothalamic-pituitary-adrenal (HPA) activation, which promotes healthy coping responses to stress (McLaughlin et al., 2014). Additionally, from a psychological perspective, the eCB system is involved in executive functioning, affective processing, and mood disorders (Gorzalka et al., 2008; Hillard, 2017). Variation in the *CNR1* gene, which codes for the CB1 receptor, has been associated with executive functioning (Stadelmann et al., 2011; Ruiz-Contreras et al., 2013; Ruiz-Contreras et al., 2014). Further, both *FAAH* (Hariri et al., 2008) and *CNR1* (Chakrabarti et al., 2006) genotypes influence brain activation in response to emotional faces. Chronic THC exposure leads to downregulation of CB1 receptor signaling in cortical regions (Hirvonen et al., 2012). Therefore, likely through CB1 downregulation, long-term cannabis use has the potential to disrupt eCB activity, impacting executive functioning, affective processing, and stress response.

Cannabis Use & Inhibitory Control

Inhibitory control, or response inhibition, is conceptualized as withholding a prepotent or prepared response (Aron et al., 2004; Aron et al., 2014; Nigg, 2000; Nigg, 2017). The inhibitory control network consists of primarily fronto-striatal regions

including the anterior cingulate cortex (ACC), ventrolateral regions of the PFC, such as the inferior frontal gyrus (IFG) and anterior insula, as well as the pre-supplementary motor area (pre-SMA) in the dorsomedial PFC (dmPFC) (Aron et al., 2004; Levy & Wagner, 2011; Aron et al., 2014; Morein-Zamir & Robbins, 2015). Subcortical networks are also involved in response inhibition; the striatum interacts with the globus pallidus, while the subthalamic nucleus (STN) connects to the thalamocortical projections (Morein-Zamir & Robbins, 2015). With few exceptions (Takagi et al., 2011), chronic cannabis exposure has been associated with inhibitory control deficits. Cannabis users perform more poorly than non-users on behavioral or neuropsychological inhibitory control tasks, including the Stroop, Multi-Source Interference Task (MSIT), Continuous Performance Test, Two Choice Impulsivity Test, and gambling tasks (Griffith-Lendering et al., 2012; Lisdahl & Price, 2012; Cousijn et al., 2013; Dougherty et al., 2013; Martinez-Loredo et al., 2015; Scott et al., 2017).

Functional magnetic resonance imaging (fMRI) studies have revealed greater activation across inhibitory control regions, in cannabis users versus non-users (Tapert et al., 2007; Roberts & Garavan, 2010). In a sample of adolescents who completed a Go/No-go task, cannabis users demonstrated hyperactivity of right dorsolateral prefrontal, bilateral medial frontal, bilateral inferior and superior parietal, and right occipital areas, suggesting increased brain processing effort was necessary to achieve inhibition (Tapert et al., 2007). Other research suggests that activation distribution may depend on whether response inhibition is accurately achieved. Roberts and Garavan (2010) conducted separate analyses for correct and incorrect inhibition trials of a Go/No-go task, which yielded no performance differences between recreational drug

(ecstasy and cannabis) users and non-users. When inhibition was successful, drug users had hyperactivity in regions of the cognitive control network including the right middle and inferior frontal gyrus and the right inferior parietal lobule, indicating—similar to Tapert and colleagues' (2007) findings—that increased activation was required to achieve inhibition (Roberts & Garavan, 2010). During unsuccessful inhibition trials, drug users had greater activation relative to controls in areas of the default mode network, involved in self-referential thought, including the left medial frontal gyrus, right middle and temporal gyri, and left posterior cingulate (Roberts & Garavan, 2010). Therefore, cannabis users may not be engaging cognitive control regions effectively when making errors.

Chronic cannabis use has also been associated with greater functional connectivity during inhibitory control tasks. For example, upon successful response inhibition during a stop signal task, cannabis-dependent individuals had greater connectivity between the right frontal control network and substantia nigra/STN network relative to nondependent users (Filbey & Yezhuvath, 2013). Further, during a MSIT, heavy, long-term cannabis users had greater connectivity between the PFC and occipitoparietal cortex as task demands increased; however, no performance differences were found between cannabis users and controls (Harding et al., 2012). Within this study, greater connectivity was associated with lower age of onset and longer lifetime exposure to cannabis (Harding et al., 2012). This pattern is also evident in cannabis users with a developmental history of attention and impulsivity problems. During resting state, cannabis users have increased functional connectivity in the middle frontal gyrus, precentral gyrus, superior frontal gyrus, posterior cingulate cortex,

and cerebellum, which is related to higher motor impulsivity on the Barrett Impulsiveness scale (Cheng et al., 2014). Therefore, cannabis use has been associated with increased connectivity across the cognitive control network, including prefrontal regions, in association with response inhibition and impulsivity.

The ACC has been implicated as a key area mediating the impact of cannabis use on inhibitory control. In a Go/No-go paradigm, cannabis users showed reduced awareness of commission errors compared with controls, which was related to decreased activity in the ACC and right insula (Hester et al., 2009). During Stroop tasks, cannabis users have exhibited ACC hypoactivity, as well as aberrant lateral PFC activation patterns, without demonstrating performance deficits (Eldreth et al., 2004; Gruber & Yurgelun-Todd, 2005). Further, Gruber and colleagues (2012) found that chronic, heavy cannabis users exhibited a more dispersed pattern of ACC activity relative to controls during a behavioral inhibition task. In this same study, early-onset compared with late-onset cannabis users demonstrated a more focal pattern of activation, but made more commission errors (Gruber et al., 2012). Cannabis use is also associated with deficient learning from errors, combined with lower activation of the ACC during processing of error-related feedback (Carey et al., 2015). Thus, cannabis users demonstrate aberrant ACC activation and increased functional connectivity during inhibitory control.

Cannabis Use & Affective Processing

Affective processing paradigms seek to measure response to emotionally salient material. A distributed cortical-subcortical network comprised of primarily frontolimbic regions mediates affective processing (Davidson, 2003; Kober et al., 2008; Pessoa,

2017). Emotionally salient stimuli are processed by the amygdala, ventral striatum, periaqueductal grey (PAG), anterior insula, and dorsal ACC (dACC), while prefrontal areas regulate response to emotional stimuli (Davidson, 2003; Etkin et al., 2015).

Most studies investigating affect in cannabis users have examined basic emotion processing, such as the passive viewing of emotional stimuli, without an inhibitory component. Facial emotion processing is commonly studied, given its importance in navigating human social networks (Phillips et al., 2003). Acutely smoked cannabis which contains higher levels of THC compared to cannabidiol (CBD; a cannabinoid present in cannabis), causes poorer emotion identification (Clopton et al., 1979). Acute THC exposure is related to facial emotion identification deficits (Ballard et al., 2012; Bossong et al., 2013; Hindocha et al., 2015), though CBD improves emotion recognition abilities (Hindocha et al., 2015). In response to emotional faces, acute THC and CBD affect limbic, temporal, frontal, ACC, parietal, occipital, posterior cingulate, and cerebellar regions (Phan et al., 2008; Fusar-Poli et al., 2009b; Bhattacharyya et al., 2010; Bossong et al., 2013). During explicit emotion regulation (cognitive reappraisal of negatively-valenced emotional scenes), acute THC administration increases amygdala activation and attenuates dorsolateral PFC (dlPFC) and amygdala functional coupling, without reducing negative affect (Gorka et al., 2016). Acutely, CBD administration reduces ACC activation and attenuates ACC and amygdala connectivity to fearful faces (Fusar-Poli et al., 2009a; Fusar-Poli et al., 2010). In contrast, under acute THC influence during an emotion discrimination task, increased connectivity between the rostral ACC (rACC)/mPFC and the amygdala has been observed (Gorka et al., 2014). THC has also been shown to attenuate ACC activation during hyperalgesia (Lee et al.,

2013a).

Chronic cannabis users, relative to non-users, are less accurate in identifying and discriminating between facial emotions (Platt et al., 2010; Hindocha et al., 2014; Bayrakci et al., 2015; Huijbregts et al., 2014). Reduced amygdala activation is observed when cannabis users are presented with negative facial emotions and scenes (Gruber et al., 2009; Cornelius et al., 2010; Wesley et al., 2016). However, younger (14 years of age) cannabis users exhibit increased amygdala activation to negative stimuli (Spechler et al., 2015). Further, frontal regions such as the medial PFC (mPFC) and IFG are hypoactive in cannabis users during conscious emotional evaluation of scenes (Wesley et al., 2016). Cannabis users also have attenuated ACC activation to masked emotional faces (Gruber et al., 2009) and in response to emotional scenes (Wesley et al., 2016). Further, bilateral rACC resting state hyperconnectivity in cannabis users is associated with increased depressive symptoms, suggesting greater connectivity of the rACC in association with emotionality (Shollenbarger et al., under review). Taken together, the evidence indicates that while viewing emotional stimuli, chronic cannabis users have abnormalities in frontolimbic regions, including activation and connectivity of the ACC.

Cannabis Use, Affect, Inhibitory Control, and the rostral ACC (rACC)

Affective processing has been shown to modulate inhibitory control (Hare et al., 2005; Somerville et al., 2011; Tottenham et al., 2011; Dreyfuss et al., 2014). For example, emotional context can impact reaction time during Go/No-go paradigms (Hare et al., 2005). Additionally, both appetitive (happy faces) and negative (fearful faces) cues can lead to response disinhibition (Somerville et al., 2011; Dreyfuss et al., 2014). In fact, research suggests that inhibitory control is more significantly disrupted by

negative relative to positive cues in adolescents (Cohen-Gilbert & Thomas, 2013). During emotional Go/No-go in adolescents, successful inhibition of fearful non-targets is associated with increased recruitment of the left orbitofrontal cortex (OFC), mPFC, striatum, right IFG, and right ACC (Dreyfuss et al., 2014).

Prefrontal regions are critical to the interface of inhibitory control and emotion. The lateral PFC (lPFC) and dmPFC are involved in volitional control of emotions, while the ventromedial PFC (vmPFC) and rACC play an important role in the automatic control of emotions (Etkin et al., 2015). Automatic, or implicit, regulation of emotions occurs without conscious control or specific instruction (Etkin et al., 2015). The ACC is critical in automatic emotion regulation; aberrant ACC activity is observed in individuals with poor emotion regulation skills (e.g., Schmahl et al., 2002; Wingenfeld et al., 2009). The ACC has connections to both the amygdala and rest of the PFC and is also involved in cognitive control, attention modulation, motor control, motivation, error monitoring, visceral response (e.g., pain), emotional evaluation (Bush et al., 2000; Devinsky et al., 1995; Gasquuoine, 2013). The classical view of ACC function holds that two functionally distinct subdivisions of the ACC exist (Bush et al., 2000; Devinsky et al., 1995). This theory states that the rostral-ventral (subgenual and pregenual) ACC (rACC) mediates emotional and motivational functions, while the caudal-dorsal (anterior dorsal and posterior dorsal) ACC (dACC) plays a more significant role in cognitive functions such as attention modulation, response selection, complex motor control, novelty, error detection, motivation, and working memory (Bush et al., 2000). The rACC and dACC have different white matter connections that support these specializations. The rACC is structurally connected with emotion-processing regions, such as the

amygdala, PAG, nucleus accumbens, hypothalamus, anterior insula, hippocampus, and orbitofrontal cortex (Bush et al., 2000). The dACC is connected with lateral PFC, parietal cortex, premotor area, and Supplementary Motor Area (SMA) (Bush et al., 2000).

However, this early view of affective/cognitive divide within the ACC has recently been challenged (Shackman et al., 2011; Etkin et al., 2011). Etkin and colleagues (2011) argue that rostral and caudal regions of the ACC each serve unique roles in emotion processing. Their theory holds that the dACC is important in threat appraisal and expression, while the rACC plays a role in inhibiting conditioned fear (Etkin et al., 2011). Similarly, during emotional conflict (Stroop), which involves identifying facial emotion while a face is superimposed with a congruent or incongruent emotional word label (e.g., happy, sad), the dACC mediates emotional conflict evaluation/appraisal, while the rACC plays a role in regulating emotional conflict (Etkin et al., 2011; Etkin et al., 2015). Thus, current evidence suggests the rACC plays an important role in affective processing, inhibitory control, and emotional regulation.

Cannabis use is associated with structural abnormalities in the ACC, such as smaller volumes in individuals with (Szeszko et al., 2007; Rapp et al., 2013) and without (Maple et al., under review) psychotic disorders. Further, cannabis-dependent relationships with reduced cortical thickness have been observed in those with concurrent psychosis (Rais et al., 2010), alcohol use (Jacobus et al., 2014), and Attention-Deficit/Hyperactivity Disorder (ADHD) (Lisdahl et al., 2016). Thus, the literature indicates that cannabis use predicts reductions in ACC gray matter. Notably, these structural differences in the ACC may be accompanied by functional aberrations.

Within cannabis users, smaller left rACC volumes have been associated with deficits in ability to discriminate subtle differences in facial emotions (Maple et al., under review), aligning with previous reports that the ACC underlies emotional processing (Etkin et al., 2015).

A very limited number of studies have examined functional connectivity of cannabis users during tasks that include aspects of both affective processing and inhibition. During explicit cognitive reappraisal of emotionally negative pictures (e.g., emotion regulation), heavy cannabis users, compared to controls, have increased activation in the bilateral precentral gyrus, SMA, and middle cingulate cortex, as well as reduced connectivity between the dlPFC and left amygdala (Zimmermann et al., 2017). In contrast, hyperconnectivity is evident when cannabis users are presented with rewarding stimuli that may lead to disinhibition or emotion dysregulation. In a task investigating response to cannabis cues, dependent cannabis users, relative to non-dependent cannabis-users, demonstrated greater functional connectivity between the amygdala seed and middle and inferior frontal gyri and superior temporal gyrus as well as between the ACC and superior and inferior parietal cortex, precuneus, and postcentral gyrus (Filbey & Dunlop, 2014). Therefore, while their designs differed (e.g., types of cues presented, explicit vs. implicit regulation), both these studies found aberrant connectivity of the frontolimbic network in cannabis users at the interface of inhibition and emotion.

Taken together, the current research indicates that within the ACC, cannabis users generally exhibit reduced grey matter volume and abnormal activation during cognitive control and emotion processing tasks. Additionally, cannabis and other

substances have often been associated with increased functional connectivity between the ACC and the rest of the brain, though the literature is not consistent. This possibly indicates that increased connectivity in cannabis users is necessary in order to achieve a behavioral response commensurate with controls.

Gender Differences

In healthy populations, females typically outperform males in response inhibition (Golden, 1974; Sarmany, 1977; Sjoberg & Cole, 2017). In addition to inhibitory processing differences, males and females also differ in basic emotional processing. In healthy populations, each gender demonstrates unique neural activation patterns while viewing emotional faces (Killgore & Yurgelun-Todd, 2001; Killgore et al., 2001; Killgore & Yurgelun-Todd, 2004; Whittle et al., 2011). Males exhibit increased frontal and parietal recruitment while females demonstrate greater temporal, ACC, and limbic activation to emotional faces (Hall et al., 2004; Kempton et al., 2009; Whittle et al., 2011). During emotional inhibitory processing, male, relative to female, adolescents exhibit increased disinhibition and medial frontal activation in response to fearful non-targets (Dreyfuss et al., 2014).

Evidence from animal studies indicates that eCB activity varies by sex in a regionally specific manner (Viveros et al., 2012). CB1 receptor density is modulated by estrogen activity (Rodriguez de Fonesca et al., 1994; Gonzalez et al., 2000; Viveros et al., 2012). Importantly, females may be more vulnerable to the effects of cannabis on affective circuitry. Female, relative to male, rats are more susceptible to the anxiety and depression producing properties of THC (Rubino et al., 2008). Females also exhibit greater CB1 desensitization to THC in frontolimbic regions (Rubino et al., 2008; Crane

et al., 2013). In humans, female cannabis users have volumetric differences in the PFC, amygdala, and ACC that are related to functional deficits (Medina et al., 2009; McQueeny et al., 2011; Maple et al., under review). In addition, female cannabis users, compared with males, demonstrate more pronounced differences in left rACC volumes, which are associated with poorer facial emotion processing (Maple et al., under review). Given the aforementioned gender differences, there may be neural differences in the left rACC during emotional response inhibition in cannabis using males versus females.

Cannabis, Stress, & Emotion Regulation

In individuals without substance use problems, there is a positive correlation between cortisol levels and the degree to which individuals perceive life events as stressful (Walvekar et al., 2015; Bedini et al., 2017). Both cortisol and increased perception of stress are associated with aberrant connectivity between the ACC and amygdala in response to threat (van Wingen et al., 2011; Hakamata et al., 2017). Substance misuse is associated with increased perception of life events as stressful (Tavolacci et al., 2013). Use of cannabis, more specifically, has been related to increased levels of perceived stress, and on the flip side, lower distress tolerance (Ketcherside & Filbey, 2015; Moitra et al., 2015; Hasan et al., 2015; Farris et al., 2016). Effective emotion regulation is a protective factor against the initiation of substance use (Quinn & Fromme, 2010) and substance users exhibit a lesser ability to regulate emotions (Wilcox et al., 2016; Russell et al., 2017). Indeed, poor emotion regulation mediates the relationship between stress and using cannabis as a coping mechanism (Bonn-Miller et al., 2011). Therefore, the literature suggests a relationship between cannabis use, gender, increased perception of stress, poor emotional inhibition, blunted

rACC activation, and increased rACC connectivity. However, no study has examined the relationships between cannabis use, gender, stress, and rACC activation/connectivity during emotional inhibitory processing.

Primary Aims & Hypotheses

Primary Aim 1a. The current study investigated differences in cannabis users relative to non-users in left and right rACC activation during emotional inhibitory processing (during correct Fearful No-go presentation). **Primary Hypothesis 1a.** It was hypothesized that cannabis users relative to non-users would demonstrate blunted activation during correct Fearful No-go trials (Gruber et al., 2009; Wesley et al, 2016).

Primary Aim 1b. The study also examined differences between cannabis users and non-users in functional connectivity between the left and right rACC and the rest of the brain during an emotional inhibitory processing fMRI task (during correct Fearful No-go presentation and, for qualitative control comparison, during correct Calm No-go presentation). **Primary Hypothesis 1b.** It was predicted that cannabis users, compared to non-users, would exhibit increased connectivity between the left and right rACC and both cognitive control regions (e.g., ventrolateral PFC and dmPFC) and emotion-generating regions (e.g., amygdala, insula) during emotional inhibitory processing (Harding et al., 2012; Filbey & Yezhuvath, 2013; Filbey & Dunlop, 2014; Feldstein Ewing et al., 2016; Kelly et al., 2017). It was expected that these connectivity group differences would be more pronounced during Fearful No-go relative to Calm No-go.

Primary Aim 2. The study also investigated whether gender moderated the relationship between cannabis use and left and right rACC activation and functional connectivity (cannabis x gender interaction) during emotional inhibitory processing **Primary**

Hypothesis 2. It was hypothesized that cannabis-using females would exhibit the most pronounced difference (most blunted activation and greatest connectivity) in left and right rACC activation and functional connectivity during emotional inhibitory processing (Rubino et al., 2008; Medina et al., 2009; McQueeny et al., 2011; Crane et al., 2013; Maple et al., under review).

Secondary Aim & Hypothesis

Secondary Aim 1. If a significant relationship was found between cannabis group or cannabis*gender and left or right rACC activation during emotional inhibition (Fearful No-go), then the relationship between rACC activation and perceived stress was investigated.

Secondary Hypothesis 1. It was hypothesized that within the cannabis-using group, aberrant left and right rACC activation during presentation of Fearful No-go trials would predict increased perceived stress.

Secondary Aim 2. For clusters showing a significant relationship between cannabis use or cannabis*gender and left or right rACC functional connectivity during emotional inhibition, the relationship between functional connectivity in the significant clusters and perceived stress (i.e., experienced distress and coping) was investigated in the cannabis-using group.

Secondary Hypothesis 2. It was hypothesized that within the cannabis-using group, aberrant left and right rACC connectivity during presentation of Fearful No-go trials would predict increased perceived stress.

Method

Participants.

Institutional Review Boards at the University of Wisconsin-Milwaukee and the Medical College of Wisconsin approved all components of this study.

Inclusion/Exclusion Criteria. ***Inclusion criteria.*** Participants were individuals ages 16-25, recruited from a larger parent study (R01 DA030354). To be included in the cannabis-using group, individuals were required to have used at least 40 joints in the past year and have at least 50 lifetime uses. To be included as a non-using control, individuals were required to have fewer than 5 past year and 10 lifetime cannabis uses.

Exclusion criteria. Individuals were excluded for magnetic resonance imaging (MRI) contraindications, pregnancy, left-handedness, birth complications, traumatic head injury, neurological disorders, learning and intellectual disabilities, vision or hearing impairments, current psychotropic medication use, independent Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition, Text Revision (DSM-IV-TR) psychological disorder diagnosis (besides substance use disorder), $\geq$10 cigarettes per day, excessive other drug use (>25 lifetime uses of non-cannabis drugs), and failure to show abstinence from all substances on the day of MRI scanning (as demonstrated by positive urine toxicology and/or continuous sweat patch testing).

Procedure.

Individuals were recruited through flyers posted in the community. Phone screening was conducted to determine eligibility of interested individuals. During screening, lifetime substance use history was gathered using the Customary Drinking and Drug Use Record (CDDR) (Brown et al., 1998; Stewart & Brown, 1995). A DSM-IV-

TR semi-structured interview, the Mini International Psychiatric Interview (MINI; Sheehan et al., 1998) was administered to both youth and parents to obtain youth psychiatric history.

Eligible participants completed an informed consent/assent process. For those under age 18, parent permission and minor assent were obtained. Prior to MRI scanning, participants underwent three weeks of monitored abstinence using urine toxicology (One Step Drug Screen Test Dip Card Panel; Innovacon, Inc., San Diego, California) and continuous sweat toxicology (PharmChek Drugs of Abuse Patch; PharmChem Inc., Fort Worth, Texas). Participants also underwent breathalyzer testing (Alco-Sensor IV; Intoximeters, Inc., St. Louis, Missouri) for recent alcohol use. Abstinence was verified at weekly sessions during the three weeks preceding the MRI scan. Participants were compensated $340 for their participation in the study.

Measures.

Demographic Information. Individuals completed a background questionnaire assessing demographic variables including age, gender, ethnicity, and education.

Substance use. Participants were administered the Timeline Follow Back (TLFB; Sobell & Sobell, 1992), a measure of past year substance use that uses holidays and other memory cues. On the TLFB, substance use was measured in standard units (e.g., joints for cannabis) and assessed for each day during the past year. The CDDR was used to measure lifetime and past 3-month substance use.

Perceived Stress. The Perceived Stress Scale-14 (PSS-14; Cohen et al., 1983) was used to measure level of perceived stress. The PSS-14 is a 14-item measure of the

degree to which individuals perceive situations as stressful and measures levels of distress and ability to cope (Hewitt et al., 1992).

MRI Data Acquisition.

Structural. Participants were scanned on a 3T Signa LX MRI scanner (GE Healthcare, Waukesha, Wisconsin) using a 32-channel quadrature transmit/receive head coil. A T1-weighted spoiled gradient-recalled at steady-state (SPGR) 3-D anatomical brain scan was acquired (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. *Functional.* Echo planar (EPI) Images were collected while performing the emotional Go/No-go task using T2*weighted gradient-echo EPI pulse sequence (TR/TE=2500ms/30ms, FOV=200 cm, matrix 64x64 pixels, slice thickness= 3.2 mm., flip angle=90 degrees, 44 contiguous axial slices).

Functional MRI Task.

Left and right rACC activation and functional connectivity were examined in cannabis users versus non-users using an emotional Go/No-Go task previously used with healthy adolescents (Hare et al., 2005; Somerville et al., 2010). Task stimuli included fearful, happy, and calm faces of 12 distinct individuals from the NimStim set of facial expressions (Tottenham et al., 2009). A calm face is similar to a neutral face, but typically interpreted as less negative, especially amongst youth (Tottenham et al., 2009). The task included six functional runs, counterbalanced for order, one for each

combination of emotion (fearful, happy, calm) and Go/No-go. At the beginning of each run, participants were instructed to press a button ("Go") for a particular emotional face (fearful, happy, calm) and to withhold a button press ("No-go") for a different type of face. On each trial, a face was presented for 500 milliseconds, followed by a jittered intertrial interval ranging from 2-14.5 seconds (mean= 5.2 seconds). In sum, 48 trials appeared in a pseudorandomized order (35 "Go" and 13 "No-go"). Given the current study's focus on fearful inhibitory processing, only runs with fearful and calm "No-go" were included in the current analysis (Happy Go/Fearful No-go, Calm Go/Fearful No-go, Happy Go/Calm No-go, Fearful Go/Calm No-go).

MRI Pre-processing.

All images underwent standard preprocessing steps using the Analysis of Functional Neuroimages software package (AFNI; Cox, 1996). Preprocessing included slice time alignment, motion correction, and co-registration of echo-planar (EPI) data to T1 scan with the aid of a cost function. Each voxel's time series was despiked and a spatial smoothing kernel of 4 was used. Each individual's anatomy was warped to standard (Montreal Neurological Institute; MNI) space and the resulting registration matrix was applied to the EPI data. Then a brain mask was created from the EPI imaging data, which was aligned to the volume with the fewest outliers (volume registration). Each individual's activation data was scaled to percent signal change. The first three TR's were removed from each run. To account for motion, TRs with greater than 0.4 mm. of motion were censored from the analysis. Subjects with >18% of TRs exceeding the 0.4 mm. motion threshold on any individual run were removed from the

analysis. Additionally, TRs with intensity outliers greater than 10% of voxels in the automasked brain were censored. For each Fearful and Calm No-go stimuli, two functional runs were concatenated together (Happy Go/Fearful No-go and Calm Go/Fearful No-go for Fearful No-go; Happy Go/Calm No-go and Fearful Go/Calm No-go for Calm No-go). Then a gamma function was used for convolution of the stimuli timing to create a Hemodynamic Response Function (HRF). Finally, the HRF was deconvolved with the acquired MRI signal on a voxel by voxel basis. All images were visually inspected for accuracy and manually edited when appropriate.

Region of Interest (rACC) Measurement.

FreeSurfer's Desikan-Killiany atlas (Desikan et al., 2006) was used to define the left and right rACC for each participant and was visually inspected for accuracy (Figure 1). The left and right rACC were then used as a seed region for (1) task-based ROI activation analysis and (2) task-based psychophysiological interaction (PPI) functional connectivity analysis.

Data Analysis.

Preliminary analysis. Demographic variables were examined with ANOVA and chi-square analyses. Variables that differed between groups were included in the primary analysis as additional covariates.

Primary Aims. *Single subjects analysis (activation).* Using AFNI's 3dROIstats command, mean calm activation was subtracted from mean fearful activation for each the left and right rACC, yielding individual fearful-calm activation values.

Single subjects analysis (connectivity). Single subject analysis included linear modeling consistent with generalized PPI analysis in AFNI. For each subject, four interaction regressors were created (for each combination of left/right rACC and Fearful/Calm) representing the interaction between changes in the blood oxygen level-dependent (BOLD) response to Correct No-go trials and rACC activation. These interaction regressors were each entered into respective linear deconvolution models along with regressors of interest (Correct No-go trials, rACC activation) and no interest (motion, drift effect, go trials, inaccurate No-go trials). The deconvolution models were used to determine connectivity within whole brain, yielding regression coefficients for each subject, which were entered into group analysis. *Group Analysis (activation).* Individual subject fearful-calm activation values for each left and right rACC were entered into SPSS. Multiple regressions were used to determine the relationship between cannabis group status and left and right rACC fearful-calm activation. Main effects and covariates were added into the first block and cannabis x gender interaction was entered into the second block. Gender, past year alcohol use, and past year nicotine use were included as covariates. *Group analysis (connectivity).* ANCOVA via AFNI's 3dMVM was used to perform eight group analyses (for each combination of left/right rACC, Fearful/Calm, and cannabis/cannabis*gender). Gender, past year alcohol use, and past year nicotine use were included as covariates. *Multiple Comparisons.* Monte Carlo simulations using AFNI's 3dClustSim were used to correct for multiple comparisons based on cluster extent (family-wise alpha = .05; voxelwise threshold of p= .01, p= .005, or p= .001).

Secondary Aim 1. Pearson correlations were run to investigate whether left or right rACC activation during emotional inhibition was related to perceived stress scale (PSS) total scores. ***Secondary Aim 2.*** Pearson correlations were run to investigate whether functional connectivity (regression coefficients) in clusters that significantly differed according to group and/or group*gender were significantly associated with perceived stress scale (PSS) total scores. Analyses were conducted in SPSS and statistical decisions were made if $p < .05$.

Behavioral performance. Independent samples t-tests were used to compare differences in fMRI task performance between cannabis users and non-users. Participants who achieved <66% accurate "Go" trials for any given run (e.g., happy Go/fearful No-go) were excluded from the analysis due to performance validity concerns.

Results

I. Participants. After excluding for excessive motion (3 participants) and poor performance validity on "Go" trials (4 participants), 66 individuals (34 cannabis users and 32 non-users) were included in the final analysis.

II. Preliminary Results: Group Differences in Demographics & Drug Use (Table 1)**.**

A. Cannabis Group Status. ANOVAs and chi-square tests revealed no significant difference between cannabis users and non-users in age ($F(1,64)= 0.82$, $p= .37$), race ($\chi^2(6)= 5.63$, $p=.47$), ethnicity ($\chi^2(2)= 1.76$, $p=.42$), gender ($\chi^2(1)= 2.15$, $p=0.14$), education ($F(1,64)= 0.44$, $p= .51$), reading ability ($F(1,64)= .06$, $p= .81$), and PSS-14 total scores ($F(1,64)= .49$, $p= .49$). Cannabis users and non-users significantly differed

on measures of lifetime cannabis use ($F(1,64)= 24.72$, $p<.00001$), past three month cannabis use ($F(1,64)= 29.58$, $p< .000001$), past year cannabis use ($F(1,64)= 29.95$, $p< .000001$), past year alcohol use ($F(1,64)= 14.52$, $p<.001$), and past year nicotine use ($F(1,64)= 5.33$, $p=.02$).

B. Gender. ANOVAs and chi-square tests revealed no significant difference between males and females in age ($F(1,64)= .04$, $p= .84$), race ($\chi^2(6)= 9.84$, $p=.13$), ethnicity ($\chi^2(2)= 1.52$, $p=.47$), education ($F(1,64)= .01$, $p= .92$), reading ability ($F(1,64)= 2.82$, $p= .10$), age of onset of weekly cannabis use ($F(1,32)= .40$, $p= .53$), length of cannabis abstinence ($F(1,36)= 0.07$, $p= .78$), past three month cannabis use ($F(1,64)= 1.84$, $p= .18$), past year cannabis use ($F(1,64)= 3.93$, $p= .052$), past year nicotine use ($F(1,64)=2.82$, $p= .10$), and PSS-14 total scores ($F(1,64)= 2.54$, $p= .12$). Males and females significantly differed on measures of lifetime cannabis use ($F(1,64)= 4.16$, $p= .05$) and past year alcohol use ($F(1,64)= 5.99$, $p= .02$), such that males reported greater use relative to females.

C. Female Cannabis Users vs. Non-Users. No significant difference was observed between cannabis-using and non-using females in age ($F(1,29)= 0.07$, $p= .79$), race ($\chi^2(6)= 7.18$, $p=.30$), ethnicity ($\chi^2(2)= .88$, $p=.64$), education ($F(1,29)= 0.03$, $p= .88$), reading ability ($F(1,29)= 1.00$, $p= .33$), and PSS-14 total scores ($F(1,29)= 2.27$, $p= .14$). Cannabis-using and non-using females significantly differed in lifetime cannabis use ($F(1,29)= 28.50$, $p= .00001$), past three month cannabis use ($F(1,29)= 29.71$, $p< .00001$), past year cannabis use ($F(1,29)= 27.52$, $p<.0001$), past year alcohol use ($F(1,29)= 10.69$, $p<.01$), and past year nicotine use ($F(1,29)= 7.53$, $p= .01$).

D. Male Cannabis Users vs. Non-Users. No differences were observed between cannabis-using and non-using males in age ($F(1,33)= 0.88$, $p= .36$), race ($\chi^2(4)= 3.08$, $p= .54$), ethnicity ($\chi^2(1)= 0.97$, $p= .32$), education ($F(1,33)= 0.49$, $p= .49$), reading ability ($F(1,33)= .04$, $p= .84$), past year alcohol use ($F(1,33)= 4.12$, $p= .051$), past year nicotine use ($F(1,33)= 2.18$, $p=.15$), and PSS-14 total scores ($F(1,33)= 0.002$, $p= .96$). Cannabis-using and non-using males significantly differed in lifetime cannabis use ($F(1,33)= 11.32$, $p< .01$), past three month cannabis use ($F(1,33)= 11.03$, $p< .01$), and past year cannabis use ($F(1,33)= 13.38$, $p= .001$).

III. Primary Results (Table 2)**.**

A. rACC ROI Activation Results. <u>*Cannabis.*</u> Cannabis users, relative to controls, demonstrated significantly less left [t (61) = -3.08, *beta*= -.42, p=.003] and right [t (61) = -3.07, *beta*= -.42, p=.003] rACC activation during Fearful-Calm No-go (Figures 2 & 3). <u>*Cannabis x Gender.*</u> Gender did not moderate the relationship between cannabis group and left [t (60) = .75, *beta*= .09, p=.46] or right [t (60) = .55, *beta*= .07, p=.58] rACC activation. <u>*Covariates.*</u> Greater past year alcohol use significantly predicted stronger right rACC activation [t (61) = 2.13, *beta*= .29, p=.04].

B. rACC Connectivity Results.

1. Left rACC Fearful No-go. <u>*Cannabis & Cannabis x Gender.*</u> Cannabis and gender did not significantly predict clusters functionally connected to the left rACC during successful Fearful No-go trials. <u>*Covariates.*</u> Greater past year alcohol use was significantly related to greater left rACC connectivity with one cluster located in the postcentral gyrus at $p < 0.001$ voxel-level significance (Table 2- Cluster A).

2. Left rACC Calm No-go. *Cannabis & Cannabis x Gender.* Cannabis and gender did not significantly predict clusters functionally connected to the left rACC during successful Calm No-go trials. *Covariates.* Greater past year nicotine use was significantly related to lower left rACC connectivity with three clusters at $p < 0.01$ voxel-level significance (Table 2- Clusters B, C, D).

3. Right rACC Fearful No-go. *Cannabis, Cannabis x Gender, & Covariates.* Cannabis and gender did not significantly predict clusters functionally connected to the right rACC during successful Fearful No-go trials.

4. Right rACC Calm No-go. *Cannabis & Cannabis x Gender.* Cannabis and gender did not significantly predict clusters functionally connected to the right rACC during successful Calm No-go trials. *Gender.* Gender was significantly associated with functional connectivity between the right rACC and a cluster in the posterior cingulate and precuneus at $p < 0.01$ voxel-level significance; males exhibited greater connectivity compared with females (Table 2- Cluster E; Figure 4). *Follow-up Within-Group Contrasts.* Despite no cannabis x gender interaction, within cannabis users, males demonstrated significantly greater connectivity relative to females between the right rACC and a cluster in the right cerebellum at $p < 0.005$ voxel-level significance (Table 2- Cluster F; Figures 4 & 5). Within non-users, gender was not related to right rACC connectivity. *Covariates.* No covariates predicted clusters functionally connected to the right rACC during successful Calm No-go trials.

IV. Secondary Results: Relationship with Perceived Stress.

A. Secondary Aim 1: rACC Activation & Perceived Stress. Within cannabis users, neither left [r= -.001, *p*= .996] nor right [r= -.006, *p*= .97] rACC was associated with Perceived Stress Scale total scores.

B. Secondary Aim 2: rACC Connectivity & Perceived Stress. *rrACC Calm No-go Connectivity (Table 2- Cluster E).* Whole sample. Across the whole sample, precuneus/posterior cingulate (Cluster E) and right rACC connectivity during successful Calm No-go trials was not significantly related to perceived stress [r= -.14, *p*= .25]. Within females, precuneus/posterior cingulate and right rACC connectivity was negatively associated with perceived stress [r= -.47, $p < .01$] (Figure 6). The opposite relationship was observed in males; precuneus/posterior cingulate and right rACC connectivity was positively associated with perceived stress [r= .37, $p = .03$] (Figure 6). *rrACC Calm No-go Connectivity (Table 2- Cluster F).* Whole sample. Right cerebellum (Cluster F) and right rACC connectivity during successful Calm No-go trials was not significantly related to perceived stress across the whole sample [r= -.13, *p*= .31], in neither males [r= .01, *p*= .96] nor females [r= -.13, *p*= .48]. Cannabis users. Similarly, right cerebellum and right rACC connectivity was not significantly related to perceived stress within the cannabis-using group [r= -.20, *p*= .25], in neither males [r= -.17, *p*= .45] nor females [r= -.01, *p*= .97]. Non-users. Within the control group [r= .21, *p*= .24], right cerebellum and right rACC connectivity was not significantly related to perceived stress, in neither males [r= .36, *p*= .20] nor females [r= .05, *p*= .86].

V. Behavioral Performance. There were no group differences in performance during Go trials paired with Fearful No-go [t (42)= 1.02, *p*= .31], Go trials paired with Calm No-

go [t (56)= .84, p= .40], Fearful No-go trials [t (59)= 1.27, p= .21], or Calm No-go trials [t (55)= 1.88, p= .07].

Discussion

To the author's knowledge, the current study is the first to assess relationships between cannabis use, gender, and rACC activation and functional connectivity during an emotional response inhibition task. The primary aims were to investigate whether cannabis use status and cannabis x gender were associated with bilateral rACC activation and connectivity. Additionally, the study examined the relationship between significant rACC activation and connectivity and perceived stress. It was found that abstinent cannabis users, relative to non-using controls, had significantly blunted left and right rACC activation during successful response inhibition upon presentation of fearful faces. Regarding connectivity results, there were no significant differences between abstinent cannabis users and controls in rACC connectivity during fearful or calm response inhibition. However, across the whole sample, during successful response inhibition upon presentation of calm faces, males, relative to females, demonstrated significantly greater connectivity between the right rACC and a cluster in the precuneus and posterior cingulate. Further, greater right rACC and precuneus/posterior cingulate connectivity during successful Calm No-go trials was significantly related to higher levels of perceived stress in males and lower levels of perceived stress in females. No significant cannabis x gender interactions were observed. Yet, follow up contrasts revealed that abstinent cannabis-using males, relative to cannabis-using females, demonstrated greater right rACC and right

cerebellum connectivity during successful Calm No-go trials. Within non-users, gender was not related to rACC connectivity.

The finding that abstinent cannabis users had blunted activation in the right and left rACC during emotional response inhibition complements the ACC structural literature, which has shown relationships between cannabis use and reduced volume and thickness in the ACC (Maple et al., under review; Hill et al. 2016; Jacobus et al. 2014; Lisdahl et al. 2016; Rais et al. 2010; Rapp et al. 2013; Szeszko et al. 2007). These consistent structural differences may be related to the functional findings in the current study. Previous functional studies have also found relationships between cannabis use and reduced ACC activation in response to emotional content and stress (Li et al., 2005; Gruber et al., 2009; Wesley et al., 2016). In contrast, Wetherill and colleagues (2014) showed that cannabis users have *greater* perigenual ACC activation in response to backward masked aversive stimuli. Notably, participants in Wetherill and colleagues' study were slightly older, non-abstinent (mean= 1.5 days abstinence), treatment-seeking cannabis users, which differs from the abstinent adolescent- young adult users in the current study. Previous studies have also demonstrated lower ACC activation or different distribution of ACC activation in cannabis users during response inhibition tasks without an emotional component (Gruber et al., 2012; Hester et al., 2009; Gruber & Yurgelun-Todd, 2005; Eldreth et al., 2004). The present study builds upon these two bodies of literature by showing that cannabis users, following a monitored abstinence period, had rACC hypoactivity during fearful response inhibition after controlling for calm response inhibition.

In an emotional Go/No-go task similar to the current one, Dreyfuss and colleagues (2014) found that in healthy individuals, right ACC recruitment was associated with successful inhibition of response to fearful non-targets. The findings from Dreyfuss and colleagues' study are consistent with the present study's finding that controls had greater rACC recruitment during fearful relative to calm inhibition. The current findings extend this literature by demonstrating that controls, compared to cannabis users, recruit the rACC more during fearful relative to calm response inhibition. This suggests that cannabis users do not recruit the rACC to the same extent as controls when successfully inhibiting a motor response to a fearful face. Thus, cannabis users may rely on other networks during emotional response inhibition that are hyperactive relative to controls during response inhibition or emotion tasks. Notably, greater recruitment of the right dorsolateral prefrontal, bilateral medial frontal, bilateral superior and inferior parietal, and right occipital areas has been found in cannabis users during neutral response inhibition tasks (Roberts & Garavan, 2010; Tapert et al., 2007). Further, during emotional processing tasks, greater cannabis use has been related to increased activation in the medial orbital frontal cortex, posterior cingulate, precuneus, and inferior parietal lobule (Aloi et al., 2018; Zimmermann et al., 2018). It is possible that rather than recruiting the rACC during emotional response inhibition, cannabis users recruit areas (e.g., right dorsolateral prefrontal, medial frontal, superior and inferior parietal, right occipital, posterior cingulate, precuneus) that are hyperactive during neutral response inhibition and emotional processing paradigms. A whole brain activation study would be necessary to address which regions cannabis users recruit during emotional response inhibition.

During adolescence and young adulthood, the ACC undergoes significant structural and functional development (Segalowitz & Dywan, 2009; Pfeifer & Peake 2012; Tamnes et al. 2013; Lichenstein et al. 2016). Given the current study's findings, in conjunction with previous literature showing ACC structural and functional differences, chronic cannabis use may interfere with normal ACC development. The ACC may be particularly vulnerable to cannabis due to its high density of CB1 receptors (Glass et al. 1997; Herkenham et al. 1990). Chronic cannabis use causes downregulation of CB1 receptors in the cingulate cortex (Hirvonen et al. 2012). Endocannabinoid signaling via CB1 receptors in the mPFC (including the rACC) regulates the HPA stress response (Micale & Drago, 2018; McLaughlin et al., 2014). Therefore, damage to the endocannabinoid system via long-term cannabis use may result in abnormal or blunted neural response to aversive stimuli. This is consistent with research suggesting that abnormal adolescent development of ACC structure and function is associated with depression and anxiety (Clauss et al. 2014; Swartz et al. 2014; Lichenstein et al. 2016; Ho et al. 2017). Cannabis use during adolescence possibly disrupts normal rACC development, resulting in heightened risk for depression and anxiety. In the current study, contrary to prediction, blunted rACC activation in cannabis users was not associated with perceived stress and coping. It is possible that a more explicit emotion regulation task (e.g., including a simple cognitive intervention for anxious thoughts) would be needed to produce rACC activation differences related to perceived stress and coping. However, it is additionally possible that the neural differences observed in cannabis users during functional MRI precede differences in perceived stress or mood that have yet to emerge, particularly given the study's exclusion for mood disorders. A

longitudinal study would be necessary to address whether blunted rACC activation in abstinent cannabis users predicts emergence into mood disorders.

Despite the blunted rACC activation observed in abstinent cannabis users in the current study, no relationship was found between cannabis group status and rACC connectivity during either fearful or calm response inhibition. Based on previous findings of greater functional connectivity in cannabis users during response inhibition tasks (Harding et al., 2012; Filbey & Yezhuvath, 2013; Filbey & Dunlop, 2014; Feldstein Ewing et al., 2016; Kelly et al., 2017), it was hypothesized that greater connectivity in cannabis users would be necessary to achieve successful response inhibition. Perhaps cannabis users had blunted activation in other areas in addition to the rACC, but to different extents, such that no increase or decrease in rACC connectivity relative to controls was apparent. Additionally, in abstinent cannabis users, other regions might compensate for aberrant rACC activation in a manner that results in similar connectivity and performance across both cannabis users and controls. A whole brain activation study would provide insight into the behavior of other regions in abstinent cannabis users during emotional response inhibition. Regions with significant activation in a whole brain analysis could be more appropriate than the rACC as seeds for an ROI connectivity analysis. Additionally, a whole brain connectivity study would help characterize network functioning in cannabis users during emotional response inhibition.

While gender *did not* significantly moderate the relationship between cannabis use and rACC connectivity during either fearful or calm response inhibition, within only the cannabis-using group, gender was related to rACC connectivity. Specifically, cannabis-using males, relative to females, demonstrated greater connectivity between

the right rACC and right cerebellum during Calm No-go response inhibition. Because no gender interaction was observed, this is considered a marginal finding and should be replicated. On inspection, males' right rACC and right cerebellum connectivity during Calm response inhibition more closely resembles connectivity of male and female controls (Figure 5). This marginal finding suggests that females may be more vulnerable to the effects of cannabis on cognition and affect, consistent with previous research (Maple et al., under review; Rubino et al., 2008; Medina et al., 2009; McQueeny et al., 2011). Further, the cerebellum has a particularly high density of CB1 receptors and female rats have exhibited increased vulnerability to reduced CB1 receptor expression in the cerebellum under repeated stress (Herkenham et al., 1990; Glass et al., 1997; Xing et al., 2011). Therefore, perhaps lower connectivity in females is related to CB1 vulnerability and dysfunction in the cerebellum. Alternatively, it is possible that increased rACC and cerebellum connectivity in cannabis-using males indicates an over-reliance on the cerebellum, which has been observed in substance users during other cognitive tasks (Behan et al., 2014; Bolla et al., 2005; Hester & Garavan, 2004; Desmond et al., 2003). Thus, cannabis use *may* differentially impact male and female rACC-cerebellar circuitry during response inhibition. Again, this finding should be replicated with significant cannabis x gender connectivity results to clarify whether this gender finding is truly specific to cannabis-users.

Gender differences in connectivity were observed across the entire sample during Calm response inhibition. Males, relative to females, demonstrated greater connectivity between the right rACC and posterior cingulate/precuneus during successful Calm No-go response inhibition. In males, greater connectivity between the

right rACC and posterior cingulate/precuneus during Calm No-go response inhibition was related to higher perceived stress. The opposite pattern was observed in females; lower connectivity was associated with higher perceived stress. The precuneus and posterior cingulate are associated with visuo-spatial imagery and self-referential thought (Leech & Sharp, 2014; Cavanna, 2007; Cavanna & Trimble, 2006), while the rACC mediates affective processing, inhibitory control, and emotional regulation (Etkin et al., 2011; Etkin et al., 2015). Greater rACC and posterior cingulate/precuneus connectivity in males compared to females indicates either greater co-deactivation or co-activation during response inhibition. Thus, greater connectivity between these regions in males suggests greater communication between regions involved in self-referential thought and affective processing/inhibitory control. Few studies have investigated gender differences in response inhibition, though stop-signal studies have demonstrated increased global brain activation in males during successful inhibition compared to unsuccessful inhibition (Li et al., 2009; Li et al., 2006). Additionally, males exhibited increased activation in the ACC during inhibition (Li et al., 2006). Unlike men, women had greater brain activation during unsuccessful inhibition relative to successful inhibition (Li et al., 2009). These gender differences in global brain activity during successful inhibition versus errors may explain the current study's findings of greater connectivity in males relative to females during calm response inhibition. The current finding that lower connectivity in females is related to greater perceived stress suggests that females, particularly those with more perceived stress and poorer coping, are less self-referential during success and is consistent with Li and colleagues' (2009) results. These differences in cognitive style (e.g., less mental reflection in women versus men

during success) could contribute to greater prevalence of mood disorders amongst women (Li et al., 2009). Lack of parallel findings during fearful response inhibition suggests that these gender differences in functional connectivity are masked with the addition of an emotional component. Previous literature suggests that females, relative to males, are more sensitive to differences in facial expression, with gender differences heterogeneous across different emotions (Forni-Santos & Osorio, 2015; Lee et al., 2013b). Thus, the current findings suggest that gender differences in rACC connectivity during response inhibition may be moderated by emotional context. However, a study investigating the interaction between emotional valence and gender within a healthy sample would be needed to clarify this relationship.

The current study has some important limitations that possibly contribute to the null connectivity findings. Length of abstinence was relatively long in the current study compared with most studies in the extant literature [mean length of abstinence 31 days in the current study vs. 3 days in most studies of emotion and neurocognition in cannabis users (e.g., Zimmermann et al., 2017; Wesley et al., 2016; Gruber et al., 2009)]. Another limitation is the concatenation of runs with two different Go stimuli (e.g., fearful No-go stimuli were paired with both happy and calm Go stimuli; calm No-go stimuli were paired with both happy and fearful Go stimuli). However, concatenating runs with different Go trial types was done in order to increase the number of No-go trials analyzed and therefore increase power (Huettel & McCarthy, 2001). Further, in the connectivity analysis, a qualitative, rather than quantitative, comparison of fearful inhibition to the experimental control condition, calm inhibition, was used. However, the aim of the connectivity analysis was to compare cannabis users to non-users in

connectivity of the rACC during fearful response inhibition, rather than to parse out response to negative versus neutral stimuli. Additionally, the present study cannot conclude that the observed activation and connectivity results are unique to inhibiting a motor response during presentation of fearful faces. It was decided not to contrast activation to No-go versus Go stimuli in the current study because motor response selection (Go trials) and motor response inhibition (No-go trials) are each active processes with possibly overlapping networks and have been described as “two sides of the same coin” (Simmonds et al., 2008; Mostofsky & Simmonds, 2008). Given the lack of a passive viewing of emotional faces control, it is also possible that the rACC activation and connectivity results in the current study would generalize to passively viewing fearful faces or other negatively-valenced stimuli (Gruber et al., 2009; Wetherill et al., 2014; Wesley et al., 2016). Notably, the current study demonstrated blunted rACC activation during emotional response inhibition even after controlling for calm response inhibition. Thus, the activation results in the current study are consistent with each the emotion processing and response inhibition literatures (Hester et al., 2009; Gruber & Yurgelun-Todd, 2005; Eldreth et al., 2004). Taken as a whole, the present study and the extant literature build the case for lower rACC activation during emotional response inhibition in cannabis users. Additionally, the current study is cross-sectional and cannot determine causality of the relationship between cannabis use and inhibitory control. Response inhibition impairments may be a risk factor for problematic substance use (Nigg et al., 2006; McNamee et al., 2008). Conversely, CB1 downregulation in prefrontal cortical regions underlying inhibitory control likely contributes to deficits observed in cannabis users (Hirvonen et al., 2012). Therefore, further longitudinal research is

warranted on the causal relationship between cannabis use and inhibitory control, as well as the underlying neural mechanisms.

In the current study, cannabis users exhibited blunted right and left rACC recruitment during successful response inhibition to fearful faces compared to calm faces. These findings build upon previous studies demonstrating ACC hypoactivation during emotion processing and inhibitory control tasks (Gruber et al., 2009; Wetherill et al., 2014; Wesley et al., 2016; Hester et al., 2009; Gruber & Yurgelun-Todd, 2005; Eldreth et al., 2004). Chronic cannabis use during adolescence may interfere with typical development of the rACC and other brain regions important for emotion regulation. Abnormal ACC development is related to depression and anxiety (Clauss et al. 2014; Swartz et al. 2014; Lichenstein et al. 2016; Ho et al. 2017). Therefore, rACC functional differences may subsequently emerge into mood differences, predisposing cannabis users to later development of affective disorders. Further, gender differences in right rACC and precuneus/posterior cingulate connectivity during calm response inhibition were related to perceived stress and could be associated with higher prevalence of mood disorders in women (Li et al., 2009). The results from the current study provide evidence for blunted rACC activation, consistent with studies demonstrating smaller rACC volumes (Maple et al., under review) in abstinent cannabis users. Given the significant development of the rACC during adolescence and the potential impact of chronic cannabis use, this region may be important to track structurally and functionally over time in prospective longitudinal studies (e.g., the Adolescent Brain and Cognitive Development (ABCD) study).

Table 1. Participant Demographics

	CAN Females (n=13)	CNT Females (n=18)	CAN Males (n=21)	CNT Males (n=14)
	% or *M* ± *SD* (range)	% or *M* ± *SD* (range)	% or *M* ± *SD* (range)	% or *M* ± *SD* (range)
Race (% Caucasian)	46.2%	66.7%	66.7%	78.6%
Ethnicity (% Non-Hispanic)	76.9%	77.8%	81.0%	92.9%
Age (years)	21.4 ± 2.0 (19-25)	21.2 ± 2.4 (18-25)	21.7 ± 2.0 (18-25)	20.9 ± 2.7 (16-25)
Education (years)	14.1 ± 1.3 (12-16)	14.2 ± 1.8 (12-18)	13.9 ± 1.4 (11-16)	14.4 ± 2.4 (9-17)
WRAT-4 Word Reading (raw score)	59.4 ± 6.2 (41-67)	61.2 ± 4.1 (53-69)	62.6 ± 5.3 (48-69)	62.3 ± 4.1 (55-68)
Age of weekly cannabis use onset (years)	17.8 ± 1.3 (16-21)	-	17.4 ± 1.8 (14-21)	-
Lifetime cannabis use (uses)	782.5 ± 625.0 (101-2314)*	1.3 ± 2.5 (0-10)*	1506.5 ± 1666.0 (125-6000)*	1.1 ± 2.0 (0-6)*
Past year cannabis use (joints)	301.5 ± 245.4 (44.7-879.3)*	0.1 ± 0.24 (0-1)*	408.0 ± 529.6 (54.6-2306)*	0.6 ± 1.3 (0-4.8)*
Number of cannabis joints/month in past 3 months	74.9 ± 58.7 (0.2-194.5)*	0.0 ± 0.0 (0-0)*	95.7 ± 107.1 (0-372)*	0.2 ± 0.6 (0-2)*
Length of cannabis abstinence (days)	25.1 ± 5.6 (20-40)	-	34.9 ± 28.9 (16-149)	-
Past year alcohol use (standard drinks)	271.6 ± 290.5 (0-883)*	45.3 ± 46.1 (0-137.5)*	380.9 ± 312.9 (24-1120.5)	179.6 ± 243.5 (0-698.5)
Past year nicotine use	119.4 ± 176.9 (0-626)*	5.5 ± 10.4 (0-30)*	300.9 ± 588.4 (0-1870)	58.3 ± 207.1 (0-777)
Left rACC fearful-calm no-go activation	-0.066 ± 0.12 (-.3-.1)	0.018 ± 0.14 (-.2-.3)	-0.059 ± 0.23 (-.5-.3)	0.088 ± 0.19 (-.3-.4)
Right rACC fearful-calm no-go activation	-0.050 ± 0.12 (-.2-.1)	0.033 ± 0.17 (-.2-.6)	-0.063 ± 0.17 (-.5-.2)	0.073 ± 0.25 (-.5-.4)
Perceived Stress Scale-14 Total (0-56)	20.9 ± 7.4 (10-34)	17.6 ± 4.8 (8-25)	16.6 ± 6.3 (6-33)	16.7 ± 5.2 (11-30)

Note. WRAT-4= Wide Range Achievement Test -4th edition Word Reading subtest. CAN= Cannabis-using. CNT= Non-using control. *Differences in CAN vs. CNT within gender= $p < .05$.

Table 2. Regions with significant differences in functional connectivity with the rACC for various contrasts. Significant between group differences were determined using a corrected threshold of $p < 0.01$, $p < 0.005$, or $p < 0.001$ determined using a Monte Carlo simulation.

Contrast	MNI Coordinates x,y,z (mm)	Brain Region (s)	Peak T-Score	Voxel-level Significance	Number of Voxels	Direction of Connectivity
Left rACC Fearful No-go						
Alcohol – Cluster A	31.5, 46.5, 73.5	L postcentral gyrus	4.19	$p < 0.001$	36	+alcohol
Right rACC Fearful No-go						
[No significant clusters]						
Left rACC Calm No-go						
Nicotine - Cluster B	-31.5, 31.5, -49.5	R culmen, R cerebellar tonsil	-2.66	$p < 0.01$	217	-nicotine
Nicotine - Cluster C	19.5, 25.5, -37.5	R culmen, L cerebellar tonsil, L temporal lobe, L amygdala	-2.67	$p < 0.01$	214	-nicotine
Nicotine - Cluster D	4.5, 37.5, 10.5	R/L posterior cingulate, R/L thalamus, L parahippocampal gyrus	-2.66	$p < 0.01$	173	-nicotine
Right rACC Calm No-go						
Gender (M vs. F) - Cluster E	-1.5, 64.5, 55.5	R posterior cingulate, R/L precuneus	4.42	$p < 0.01$	169	M > F
Cannabis: M vs. F - Cluster F	-31.5, 82.5, -40.5	R cerebellum: cerebellar tonsil, pyramis, tuber, inferior semi-lunar nodule, uvula	3.88	$p < 0.005$	89	CAN: M > F

Atlas coordinates represent the MNI coordinate system

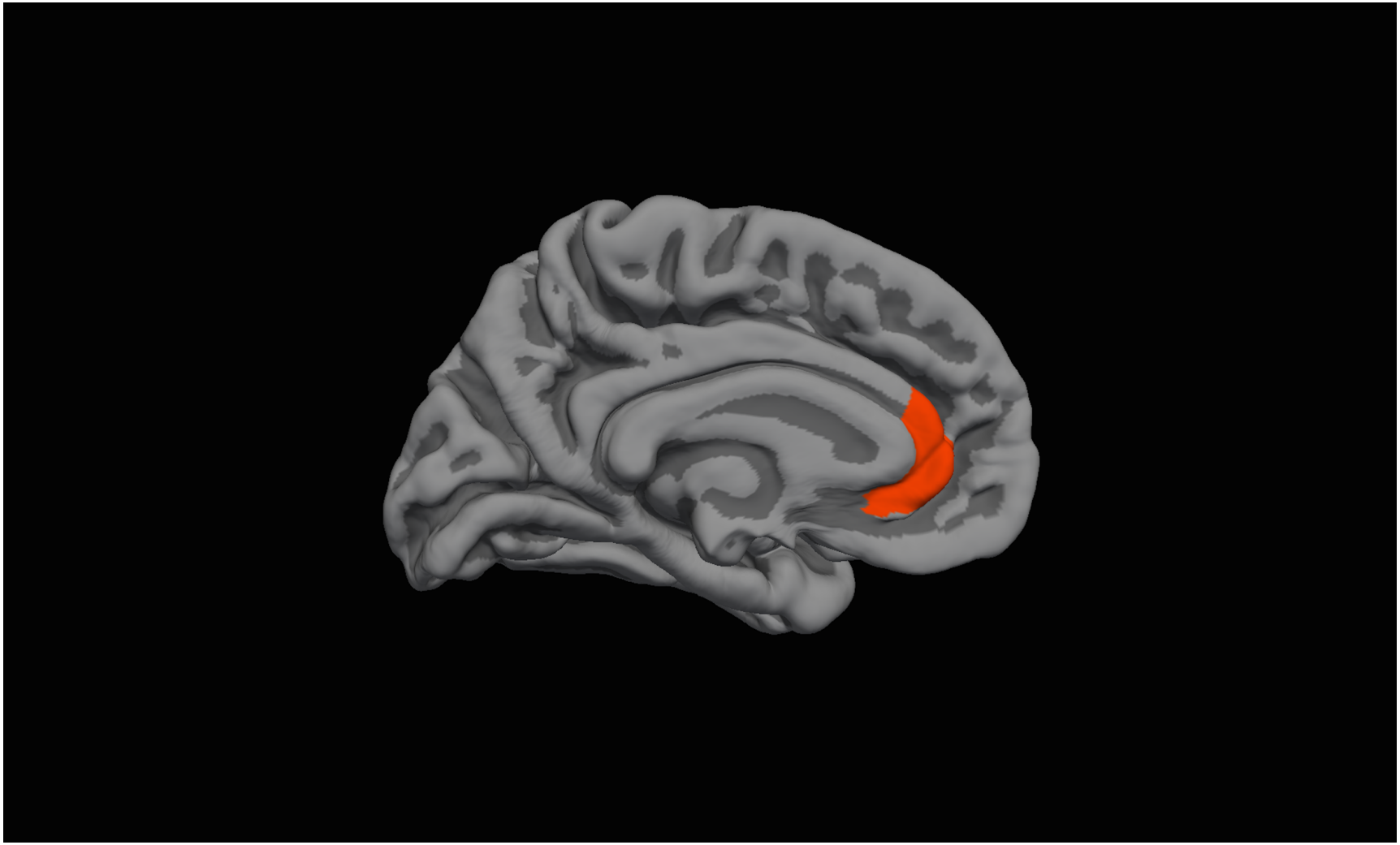

Figure 1. FreeSurfer's Desikan-Killiany atlas (Desikan et al., 2006) was used to define the left (pictured above) and right rACC for each participant. The left and right rACC were used as seed regions for the activation and connectivity analyses.

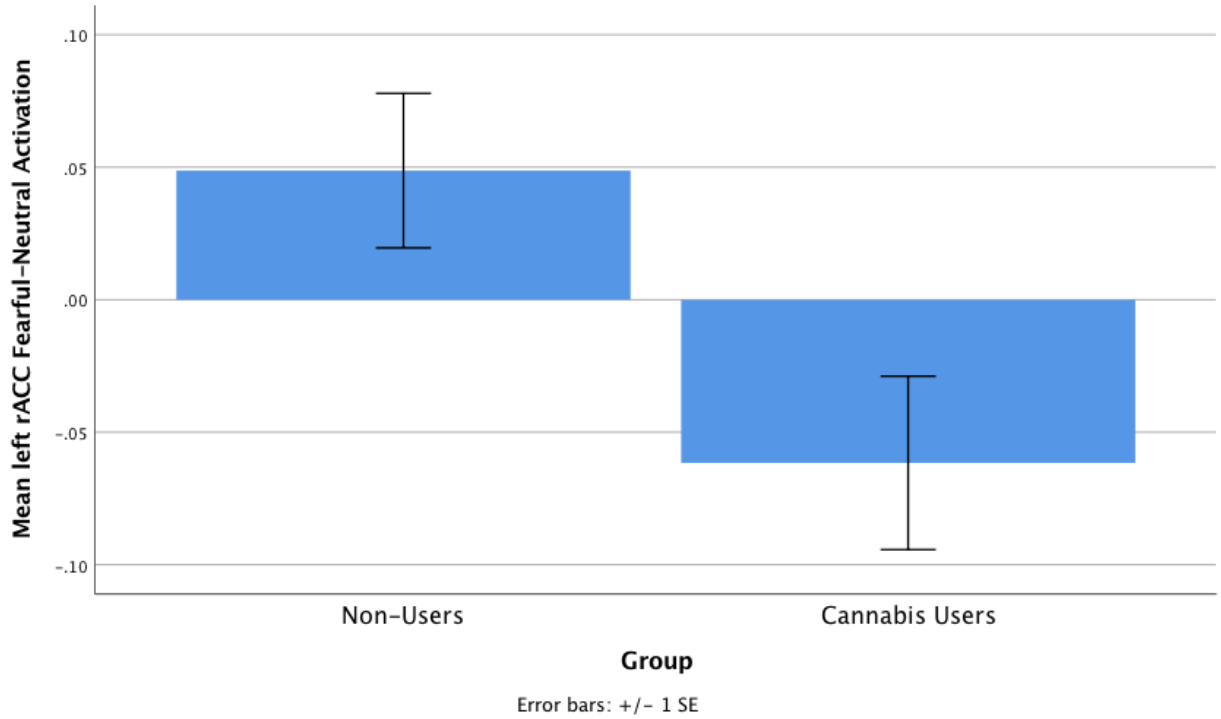

Figure 2. Cannabis users, compared with controls, demonstrated significantly less left rACC activation during Fearful-Calm/Neutral No-go trials. [*t* (48) = -3.08, *beta*= -.42, *p*=.003].

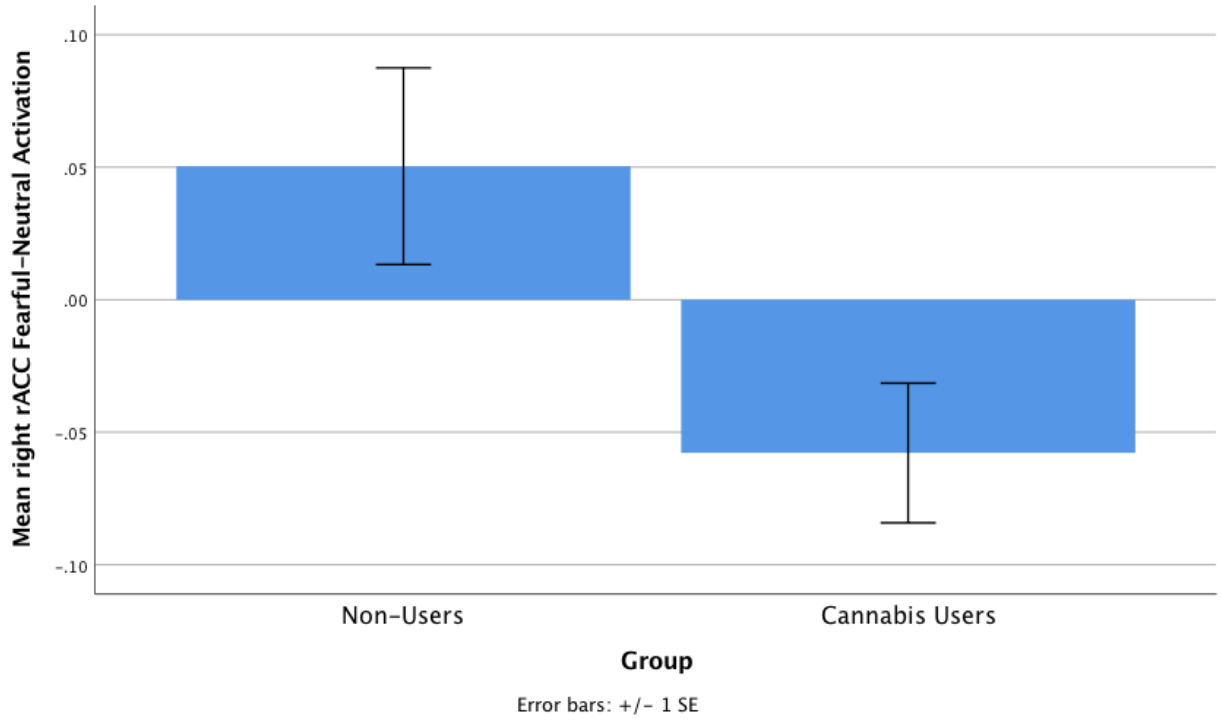

Figure 3. Cannabis users, compared with controls, demonstrated significantly less right rACC activation during Fearful-Calm/Neutral No-go trials. [*t* (48) = -3.07, *beta*= -.42, *p*=.003].

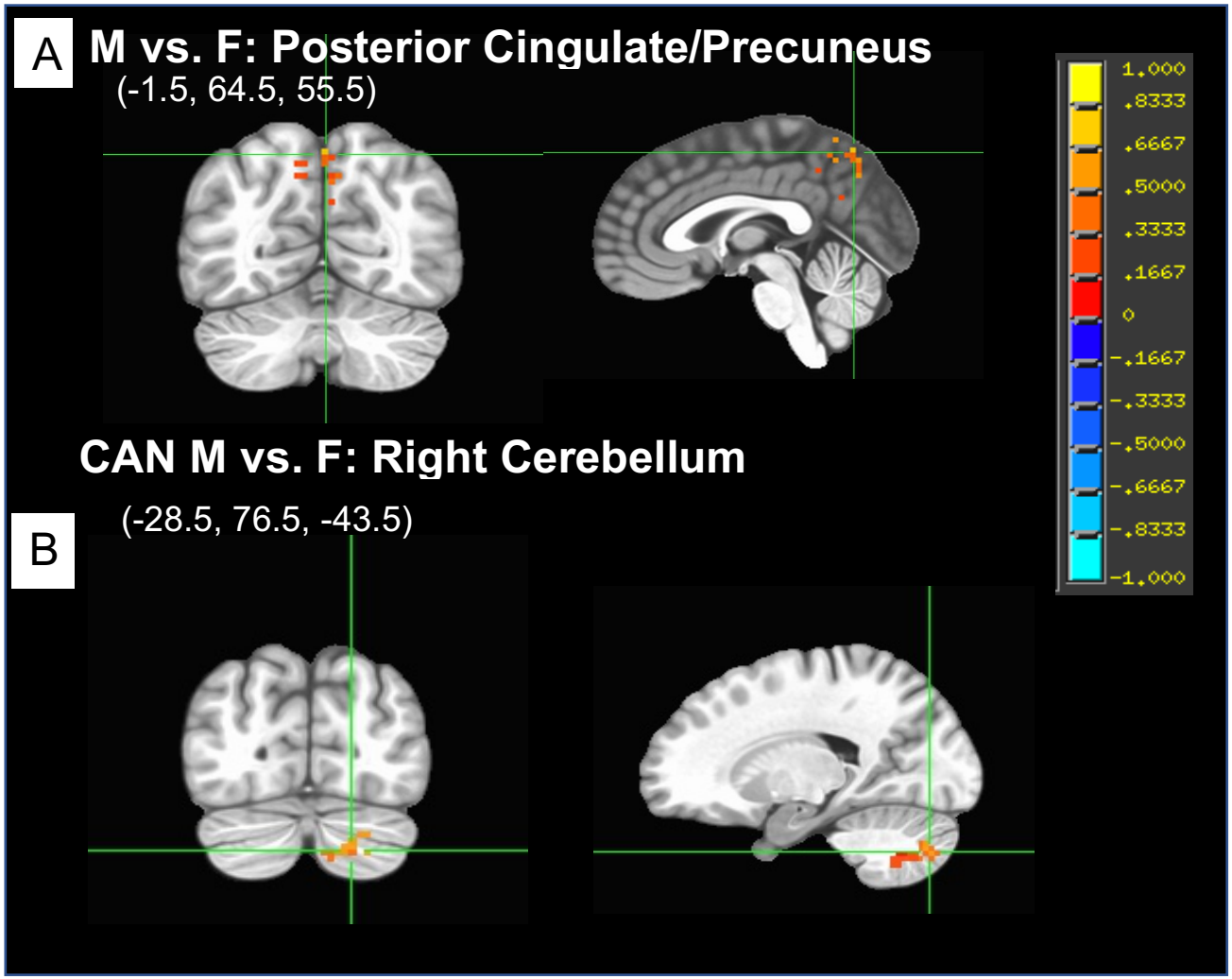

Figure 4. Group analysis of connectivity with the right rACC during Correct Calm No-go trials. A gender group contrast revealed that in males relative to females, the right rACC had significantly greater connectivity with a cluster including the posterior cingulate and precuneus (A; Cluster E). Despite no significant cannabis x gender interaction, within the cannabis-using group, the right rACC had greater functional connectivity with a cluster in the right cerebellum in males relative to females (B; Cluster F). The colors represent areas of significant connectivity; warm colors indicate increased connectivity (voxelwise threshold $p < .01$; family-wise correction $p < .05$).

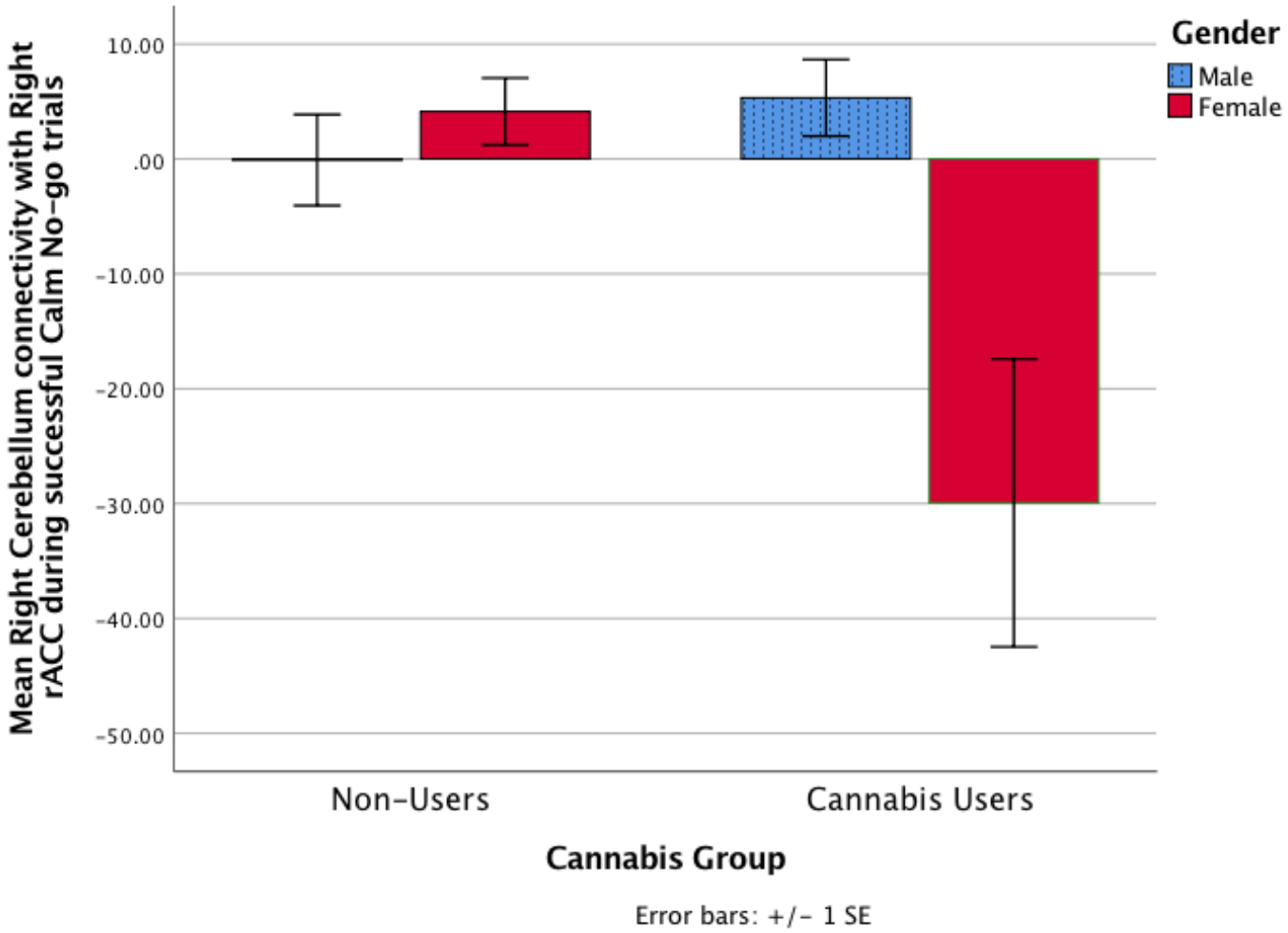

Figure 5. In the cannabis-using group, the right rACC had greater functional connectivity with a cluster in the right cerebellum in males relative to females (Cluster F) during successful Calm No-go trials ($p < 0.005$). Non-users did not exhibit a significant gender relationship. Notably, there was no significant cannabis x gender interaction.

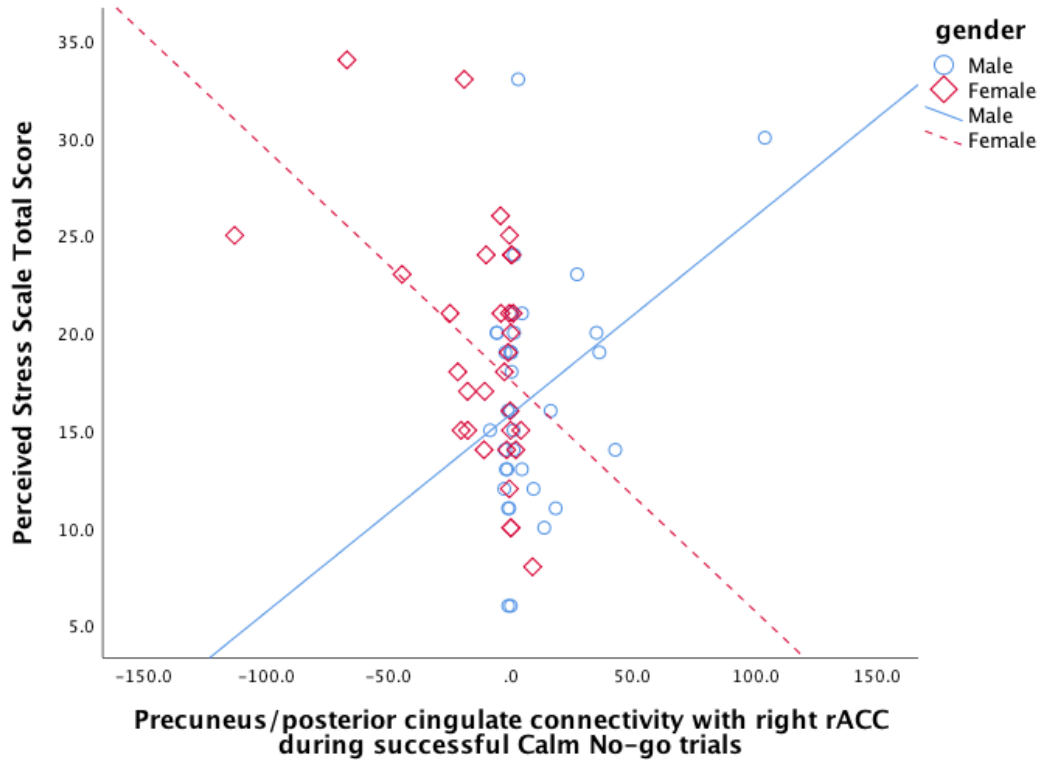

Figure 6. Within females across the entire sample, greater precuneus/posterior cingulate (Cluster E) and right rACC connectivity during successful Calm No-go trials was negatively associated with perceived stress [r= -.47, $p < .01$]. The opposite relationship was observed in males across the sample; greater precuneus/posterior cingulate and right rACC connectivity was positively associated with perceived stress [r= .37, $p = .03$].

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CURRICULUM VITAE

KRISTIN E. MAPLE

University of Wisconsin-Milwaukee
Psychology Department

EDUCATION

Anticipated 2019-2021		**Postdoctoral Fellowship in Clinical Neuropsychology, Minneapolis VA, MN** APA Specialty Accredited Member - Association of Postdoctoral Programs in Clinical Neuropsychology (APPCN)
In Progress (Anticipated August 2019)	Ph.D.	**Psychology (Clinical Psychology Track), University of Wisconsin- Milwaukee, WI** Major Professor: Krista M. Lisdahl, Ph.D. Dissertation: *Cannabis-Using Youth Demonstrated Blunted rACC Activation, but Normal Functional Connectivity, During an Emotional Go/No-go Task* **Successfully Defended:** September 4, 2018
2019	Internship	**Neuropsychology Track, VA Maryland Healthcare System/University of Maryland School of Medicine Internship Consortium, Baltimore, MD** APA-Accredited Member - Academy of Psychological Clinical Science
2016	M.S.	**Psychology, University of Wisconsin-Milwaukee, WI** Major Professor: Krista M. Lisdahl, Ph.D. Thesis: *Cannabis Use and Affective Processing: A Brain Structure Analysis*
2011	B.S.	**Biology, *cum laude* (Psychology Minor, Research Concentration), Gonzaga University, Spokane, WA**

RESEARCH EXPERIENCE

2013- 2018 **Brain Imaging and Neuropsychology (BraIN) Lab, University of Wisconsin-Milwaukee, Milwaukee, WI. Principal Investigator: Krista M. Lisdahl, Ph.D.**

- **Study Title:** *Effects of Physical Activity & Marijuana Use on Frontolimbic Functioning During Adolescence: An fMRI Study* **Funding Source:** NIH/NIDA R01DA030354 (PI: Krista Lisdahl, Ph.D.). **Role:** Graduate Research Assistant. **Duties:** Served as paid research assistant running a protocol examining the relationship between exercise and frontolimbic

function in cannabis using and non-using adolescents and young adults. Moderating factors such as gender, genetics, and alcohol use were also assessed. This study also included a 2-year longitudinal component to investigate the influence of cannabis use and exercise on neurocognitive functioning over time. Personal responsibilities included participant recruitment, clinical assessment (MINI diagnostic interviews), neuropsychological assessment, MRI sessions, VO2 maximum exercise testing, data analysis, conference and manuscript preparation, attending weekly lab meetings, as well as training and mentoring of undergraduates and bachelor-level RAs.

- **Study Title:** *Imaging Data in Emerging Adults with Addiction (IDEAA) Consortium.*
  Funding Source: NIH/NIDA R01DA030354-03S1 (PI: Krista Lisdahl, Ph.D.; IDEAA Consortium P.I.s: Lisdahl, K.M., Gruber, S., Tapert, S., & Filbey, F.). **Role:** Graduate Research Assistant. **Duties:** Quality checked neuroimaging data from five different sites.

- **Study Title:** *Adolescent Brain and Cognitive Development (ABCD) study*
  Funding Source: NIH/NIAAA/NIDA U24 DA041147 (P.I.s: Lisdahl, K.M., Jernigan, T., & Brown, S.A.). **Role:** Lead Graduate Research Assistant for the Adolescent Brain and Cognitive Development (ABCD) study, the landmark longitudinal study that aims to examine child and adolescent brain, cognitive, affective and health development in 10,000 youth over 10 years in the United States. Participants undergo neuroimaging, neuropsychological assessment, interviews, and biospecimen collection. **Duties:** Assisting with UWM site launch, recruitment, phone screening, clinical assessment (KSADS and family history interviews), on-site supervision of suicide risk assessment, training and mentoring of undergraduates and bachelor-level RAs.

- **Study Title:** *Integration of Standing Desks in Elementary Schools to Reduce Sedentary Behavior and Improve Neuropsychological Functioning*, University of Wisconsin-Milwaukee, Kinesiology & Psychology Departments. **Funding Source:** SAFCO Products Company (P.I.: Ann Swartz, Ph.D.; Co-I & Neuropsychology Supervisor: Krista M. Lisdahl, Ph.D.). **Role:** Graduate Research Assistant **Duties:** Assisted in a year-long study in a public elementary school to examine the impact of a standing desk compared to a sitting desk on executive function, postural stability, and physical fitness outcomes. Personal responsibilities included administering select NIH toolbox cognitive subtests to grade-school-aged (4th-6th grade) participants at 3 separate time points. This study also employed teacher and parent behavioral questionnaires, posture and activity line observation, and qualitative reports regarding perceptions of using the standing desk versus sitting desk.

2012-2013 **Developmental Brain Imaging Lab (DBIL), Oregon Health & Science University (OHSU), Portland, OR. Principal Investigator: Bonnie J. Nagel, Ph.D.**

- **Study Title:** *National Consortium of Alcohol on NeuroDevelopment in Adolescence (NCANDA).* **Funding Source:** NIH/NIAAA U01AA021691 (P.I.: Nagel, B.J.). **Role:** Research Assistant **Duties:** Ran protocol for a multi-site consortium study examining the longitudinal effects of alcohol use on structural and functional adolescent brain development. Personal responsibilities included administering clinical interviews and neuropsychological tests.

- **Study Title:** *Timing Effects of Heavy Alcohol Initiation on Adolescent Neurodevelopment* **Funding Source:** NIH/NIAAA R01AA017664 (P.I.: Nagel, B.J.). **Role:** Paid Research Assistant **Duties:** Ran protocol for a longitudinal study examining the longitudinal effects of alcohol use on structural and functional adolescent brain development. Personal responsibilities included recruitment, data collection (clinical interviews, neuropsychological test administration, independent operation of MRI scanner), and data entry.

- **Study Title:** *Sex-Specific Trajectories of Neurobiological Maturation During Adolescence* **Funding Source:** NIH/NIMH R21MH099618 (P.I.: Nagel, B.J.). **Role:** Research Assistant **Duties:** Ran protocol for a longitudinal study investigating the neurocognitive mechanisms underlying gender differences in the development of psychopathology during adolescence. Personal responsibilities included participant recruitment and data collection (including independent operation of MRI scanner and neuropsychological test administration).

- **Study Title:** *Neurobiological Mechanisms of Cognitive Inhibition in Trauma-Exposed Adolescents* **Funding Source:** NIH/NIMH K23MH105678 (P.I.: Mackiewicz Seghete, K.). **Role:** Research Assistant **Duties:** Served as project coordinator for a study investigating the neurobiological mechanisms of cognitive inhibition in trauma-exposed adolescents. Personal responsibilities included database management and IRB management.

2006-2010 **Department of Behavioral Neuroscience, Oregon Health & Science University (OHSU), Portland, OR, Principal Investigator: Kathleen A. Grant, Ph.D.**

- **Study Title:** *INIA Stress and Chronic Alcohol Interactions: Stress and Ethanol Self-Administration in Monkeys* **Funding Source:** NIH/NIAAA U01AA013510 (P.I.: Grant, K.A.) **Role:** High School Apprentice; Undergraduate Fellow **Duties:** This research was funded by the Integrative Neuroscience Initiative on Alcoholism (INIA), a multi-site

consortium study funded by NIAAA. I spent 3 summers assisting in running a protocol investigating ethanol self-administration patterns and HPA axis activity in macaque monkeys. Personal responsibilities included data collection, data analysis, data entry, and animal care.

- 2006- Earned a competitive funded summer high school apprenticeship in Dr. Grant's lab. I completed a research project through this program, which I presented at the Apprenticeships in Science & Engineering summer symposium.
- 2009- Personally funded through the Oregon Health & Science University Undergraduate Research Fellowship. I completed a 10-week fellowship program, which culminated in presenting my summer research, "Baseline measures of HPA activity in non-human primates related to social hierarchy and alcohol consumption," at the Oregon National Primate Research Center summer symposium.

PEER-REVIEWED PUBLICATIONS

1. Lisdahl, K.M., Wright, N.E., Kirchner-Medina, C., **Maple, K.E.**, & Shollenbarger, S. (2014). *Considering Cannabis*: The impact of regular cannabis use on neurocognition in adolescents and young adults. *Current Addiction Reports, 1*, 144-156.

2. **Maple, K.E.**, McDaniel, K.A., Shollenbarger, S.G., & Lisdahl, K.M. (2016). Dose-dependent cannabis use and depressive symptoms predict sleep quality in emerging adults: A pilot study. *The American Journal of Drug and Alcohol Abuse, 13,* 1-10.

3. **Maple, K.E.,** Thomas, A., Kangiser, M.M., & Lisdahl, K.M. (In Revision). Anterior cingulate volume reductions in adolescent and emerging adult cannabis users: Association with affective processing deficits.

4. Wallace, A.L., **Maple, K.E.**, Thomas, A., & Lisdahl, K.M. (Under Review). BOLD Responses to Inhibition in Cannabis Using Adolescents and Emerging Adults after Two Weeks of Monitored Cannabis Abstinence.

5. **Maple, K.E.,** & Lisdahl, K.M. (In Preparation). Independent and interactive contributions of alcohol and cannabis use to affective processing in adolescents and emerging adults.

6. **Maple, K.E.,** Thomas, A., Wallace, A., & Lisdahl, K.M. (In Preparation). Cannabis-using youth demonstrate blunted superior & medial frontal, anterior cingulate, and dorsal striatal activation during an emotional go/no-go task.

BOOK CHAPTERS

1. **Maple, K.E.**, Wright, N.E., & Lisdahl, K.M. (2017). Cannabis Use and Attention-Deficit/Hyperactivity Disorder: Potential Moderators. In *The Handbook of Cannabis and Related Pathologies: Biology, Diagnosis, Treatment, and Pharmacology.* Philadelphia: Academic Press.

2. Wright, N.E., **Maple, K.E.**, & Lisdahl, K.M. (2017). Effects of Cannabis Use on Neurocognition in Adolescents and Emerging Adults. In *The Handbook of Cannabis and Related Pathologies: Biology, Diagnosis, Treatment, and Pharmacology.* Philadelphia: Academic Press.

PRESENTATIONS

(Chaired Oral Presentations)

1. **Maple, K.,** Thomas, A., & Lisdahl, K. (2017, June). *Associations between cannabis use, gender, and frontolimbic white matter integrity in adolescents and emerging adults.* **(Session Chair: Maple, Kristin).** Oral presentation at the annual meeting of the College on Problems of Drug Dependence (CPDD), Montreal, Canada.

(Oral Presentations)

1. **Maple, K.E.,** & Grant, K.A. (2009, August 13). *Baseline measures of HPA activity in non-human primates related to social hierarchy and alcohol consumption.* Oral presentation given as part of the Undergraduate Fellowship Research Program at Oregon Health & Science University, Beaverton, Oregon.

2. **Maple, K.E.,** & Grant, K.A. (2010, August 12). *Is medical history related to alcohol self-administration in male rhesus monkeys?* Oral presentation given as part of an undergraduate summer internship at Oregon Health & Science University, Beaverton, Oregon.

3. Lisdahl, K.M., Shollenbarger, S.G., & **Maple, K.E.** (2014, February). *Potential moderators of marijuana effects: Age of onset, gender, body mass, and genetics*. Presented as part of symposium (Sifting Through the Smoke: Uncovering the Impact of Marijuana Use on Neurocognition. Chair: Gonzalez, Raul) presented at the annual meeting of the International Neuropsychological Society, Seattle, WA.

4. Lisdahl, K.M., Price, J.S., Shollenbarger, S. & **Maple, K.** (2015, August). *Neurocognitive effects of cannabis use on youth: Genetic moderators.* Paper presented in a symposium *Marijuana on the Adolescent Brain? Exploring Neurodevelopment and Behavior* at the annual APA convention.

5. Lisdahl, K., Shollenbarger, S., **Maple, K.**, & Thomas, A. (2016, December). *Cannabis use is associated with frontoparietal structural and functional abnormalities and executive dysfunction in young adults with and without ADHD.* American College of Neuropsychopharmacology, Hollywood, FL.

(Poster Presentations)

1. **Maple, K.E.**, & Grant, K.A. (2009, October 31). *Baseline measures of HPA activity in non-human primates related to social hierarchy and alcohol consumption.* Poster presented at the Murdock Undergraduate Research Conference, Spokane, Washington.

2. **Maple, K.E.**, Wright, N.E., & Lisdahl, K.M. (2014, June). *Marijuana use and FAAH genotype predict sleep quality in adolescents and emerging adults.* College on Problems of Drug Dependence (CPDD), San Juan, Puerto Rico.

3. Wright, N.E., Padula, C.B., **Maple, K.E.**, Anthenelli, R.M., Nelson, E.G., & Lisdahl, K.M. (2014, June). *Alcohol dependence, gender, and cortisol response predict amygdala response pattern to fMRI stress task.* College on Problems of Drug Dependence (CPDD), San Juan, Puerto Rico.

4. Shollenbarger, S.G., **Maple, K.**, & Lisdahl, K. (2015, February). *Impact of sleep quality on prefrontal gyrification in cannabis using emerging adults.* International Neuropsychological Society (INS), Denver, CO.

5. **Maple, K.E.**, Shollenbarger, S.G., Gilbart, E.R., & Lisdahl, K.M. (2015, June). *Sleep quality does not predict frontolimbic white matter integrity in young marijuana users.* College on Problems of Drug Dependence (CPDD), Phoenix, AZ.

6. Shollenbarger, S.G., Price, J.S., **Maple. K.E.**, & Lisdahl, K.M. (2015, June). *Correlation between PFC gyrification and underlying white matter integrity in young cannabis users.* College on Problems of Drug Dependence (CPDD), Phoenix, AZ.

7. **Maple, K.E.**, Gilbart, E.R., Hatcher, K.F., & Lisdahl, K.M. (2016, June). *Independent and interactive contributions of alcohol and cannabis use to affective processing in adolescents and emerging adults.* Research Society on Alcoholism (RSA), New Orleans, LA.

8. **Maple, K.E.,** Thomas, A., Kangiser, M.M., Gilbart, E.R., & Lisdahl, K.M. (2017, February). *Anterior cingulate volume reductions in adolescent and emerging adult cannabis users: Association with affective processing deficits.* International Neuropsychological Society (INS), New Orleans, LA.

9. Hatcher, K., **Maple, K.**, Kaiver, C., Wade, N., & Lisdahl, K. (2018, June). *Increased Executive Dysfunction and Disinhibition in Marijuana and MDMA users Compared to Controls.* College on Problems of Drug Dependence (CPDD), San Diego, CA.

10. **Maple, K.E.**, Thomas, A., Wallace, A., & Lisdahl, K. (2019, February). *Blunted Rostral Anterior Cingulate Activation During an Emotional Inhibition Task in Chronic Cannabis Users.* International Neuropsychological Society (INS), New York, NY.

11. Wallace, A.L., **Maple, K.E.**, & Lisdahl, K.M. (2019, June, *submitted*). *Does Gender Moderate the BOLD Response to Inhibition in Cannabis-Using Adolescents and Emerging Adults?* College on Problems of Drug Dependence (CPDD), San Antonio, TX.

INVITED TALKS

Maple, K.E. & Lisdahl, K.M. (2018, April). *The Adolescent Brain & Cognitive Development (ABCD) Study: An Overview of Methods & Expected Impact.* Invited talk to undergraduates, graduate students, and clinicians at the Wisconsin Council on Family Relations, Wisconsin Dells, WI.

CLINICAL TRAINING AND EXPERIENCE

June 2018-Present **Neuropsychology Intern**, **VA Maryland Healthcare System, Baltimore, MD**

APA-Accredited Internship (Neuropsychology track) consisting of: 2 major rotations in Neuropsychology; 1 major rotation in Gero-neuropsychology; year-long minor in Neuropsychology; Intern Seminar (2.5 hours/week); Research Project (*Investigating the relationship between substance use and neuropsychological performance in HIV-positive Veterans*; supervised by Moira Dux, Ph.D.).

Major Rotations:

- 1 of 3: Neuropsychology (Baltimore VA Medical Center; July-October 2018):
  - Worked with Veterans with the following diagnoses: ADHD, Alzheimer's, vascular dementia, Parkinson's Disease, TBI, HIV, Hepatitis C, diabetes, chronic kidney disease, B12 deficiency, bipolar disorder, and other psychiatric comorbidities. Patients were both genders (primarily male), ranged in age from 38 to >90, and were approximately 67% Black/African American.
  - 11 Geriatric Assessment Clinic neuropsychological evaluations (~1/week) (interdisciplinary team with Geriatric Medicine; interviewed caregivers, presented chart reviews, tested patients, provided feedback, wrote reports)
  - 13 Outpatient neuropsychological evaluations (~1/week) (interviewed and tested patients, provided feedback, wrote reports).
  - 1 Inpatient medical decision-making capacity evaluation
  - Maintained 3 individual therapy/cognitive rehabilitation patients
  - Co-facilitated bi-weekly support group for caregivers of individuals with dementia
  - Neuropsychology Treatment Group Supervision (.5 hours/week)
  - Neuropsychology Case Conference (1 hour/week)
    Supervisors: Jeremy Carmasin, Ph.D., Anjeli Inscore, PsyD, ABPP-CN, Patricia Ryan, Ph.D., Megan Smith, Ph.D., ABPP-CN

- 2 of 3: Gero-neuropsychology/Community Living Center (CLC; Perry Point VAMC; October 2018- February 2019):
  - Worked with Veterans with the following diagnoses: Neurosyphilis, Alzheimer's, vascular dementia, fronto-temporal dementia (behavioral variant), Parkinson's Disease,

Huntington's disease, TBI, normal pressure hydrocephalus, Lewy Body dementia, multiple sclerosis, diabetes, chronic kidney disease; 50% of residents have a history of serious mental illness in addition to their medical and cognitive conditions. Patients were of both genders (primarily male), primarily over age 55, and of all races and ethnicities.

- Will conduct at least 8 neuropsychological assessments
- Provide 2x/week consultation on CLC interdisciplinary team (with physicians, nurse practitioners, nurses, nursing assistants, dieticians, occupational therapists, recreation therapists)
- Provide individual psychotherapy and behavioral interventions using:
  - Cognitive Behavioral Therapy for depression and anxiety
  - BE-ACTIV! (for nursing home residents with depression)
  - Life Review Psychotherapy
- Assist nursing staff in identifying and implementing behavioral/environmental interventions to address challenging and disruptive behaviors displayed by residents. Implement Staff Training in Assisted Living Residences in the Veterans' Administration (STAR-VA; evidence-based approach to addressing disruptive behaviors secondary to dementia; see Karlin et al., 2017).
- Neuropsychology Case Conference (via phone; 1 hour/week)
- ***Maintained Neuropsychology minor- 1 Geriatric Assessment Clinic or Outpatient evaluation per week***
  Supervisors: Jodi French, PsyD, Anjeli Inscore, PsyD, ABPP-CN, Patricia Ryan, Ph.D., Megan Smith, Ph.D., ABPP-CN

- 3 of 3: Neuropsychology (Baltimore VA Medical Center; February-June 2019):
  - Worked with Veterans with the following diagnoses: Epilepsy, Alzheimer's, vascular dementia, Hepatitis C, diabetes, chronic kidney disease, bipolar disorder, and other psychiatric comorbidities. Patients were both genders (primarily male), ranged in age from 38 to >90, and were approximately 67% Black/African American.
  - Geriatric Assessment Clinic neuropsychological evaluations (~1/week) (interdisciplinary team with Geriatric Medicine; interviewed caregivers, presented chart reviews, tested patients, provided feedback, wrote reports)
  - Outpatient neuropsychological evaluations (~1/week) (interviewed and tested patients, provided feedback, wrote reports).
  - Neuropsychology Treatment Group Supervision (.5 hours/week)
  - Neuropsychology Case Conference (1 hour/week)

Supervisors: Jeremy Carmasin, Ph.D., Moira Dux, Ph.D., Kristen Mordecai, Ph.D.

July 2017- May 2018 **Neuropsychology Extern, Clement J. Zablocki VA Medical Center, Milwaukee, WI**

- Completed outpatient and inpatient (including transplant, pre-surgical, and capacity evaluations) neuropsychological assessments of Veterans who served during a wide range of conflicts. Diagnoses included learning disability, ADHD, Alzheimer's, vascular dementia, multiple sclerosis, Parkinson's Disease, Lewy Body dementia, TBI, normal pressure hydrocephalus, diabetes, end stage renal disease, schizophrenia, and other psychiatric comorbidities. Patients were of both genders (primarily male), ranged in age from 24 to >90, and were of all races and ethnicities.
- Conducted brief dementia evaluations as part of an interdisciplinary team with neurology and geriatric medicine
- Attended and presented in weekly neuropsychology fact-finding case conference.
- Completed one full assessment per week (including interview, testing, scoring, interpretation, report writing, and feedback)
- Wrote 27 comprehensive reports

Supervisors: Angela Gleason, Ph.D., ABPP-CN, Melissa Lancaster, Ph.D., Eric Larson, Ph.D., ABPP-CN, Kathleen Patterson, Ph.D., ABPP-CN

May 2016- July 2017 **Neuropsychology Extern, Medical College of Wisconsin Neuropsychology (Adult Track)**

- Completed outpatient neuropsychological assessments of adults and occasionally adolescents. Diagnoses included epilepsy, learning disability, ADHD, autism spectrum disorder, multiple sclerosis, TBI, normal pressure hydrocephalus, vascular dementia, Alzheimer's, Lewy Body dementia, fronto-temporal dementia (behavioral and language variants), sleep disorders, diabetes, and psychiatric comorbidities. Patients were balanced for gender, ranged in age from 16-80, and were of all races and ethnicities.
- Conducted brief evaluations as part of the mild TBI interdisciplinary team with physical medicine and rehabilitation
- Observed multiple Wada tests
- Attended mandatory 2 hours of neuropsychology didactics per week (including seminar for ABPP-CN prep, journal club, fact-finding case conference, and neurology grand rounds)
- Completed two assessments per week (including interview, testing, scoring, interpretation, and feedback)
- Wrote 34 comprehensive reports

Supervisors: Julie Bobholz, Ph.D., ABPP-CN, Michael McCrea, Ph.D., ABPP-CN, Lindsay Nelson, Ph.D., David Sabsevitz, Ph.D., ABPP-CN, Sara Swanson, Ph.D., ABPP-CN, Laura Umfleet, PsyD

2013-2017 **Clinical Psychology Trainee, UWM Psychology Clinic**

2015-2017 *Therapy Practicum.*
- Utilized evidence-based outpatient treatments for:
  - Couples therapy (Integrative Behavioral Couples Therapy)
  - Children's anxiety disorders (Coping Cat- cognitive behavioral treatment for anxiety)
  - Adult anxiety (Exposure and Response Prevention)
  - Adult depression (Behavioral Activation Therapy)
- Obtained in-depth experience with two individual adult clients, two individual child clients, and one couple.
- Met weekly with faculty supervisors for individual supervision in addition to six hours of group supervision per week.

Supervisors: Shawn Cahill, Ph.D., Bonnie Klein-Tasman, Ph.D., Christopher Martell, Ph.D., ABPP, Robyn Ridley, Ph.D.

2015-2017 *Supervised Assessments in the UWM Psychology Clinic.*
- Live observed and provided supervision for child and adult psychodiagnostic assessment sessions for second year clinical psychology graduate students.

Supervisors: Hanjoo Lee, Ph.D., Kristin Smith, Ph.D.

2014-2015 *Assessment Practicum.*
- Conducted four psychodiagnostic assessment cases during the year. Worked with faculty supervisors to determine battery, administer battery, interpret results, write a comprehensive report, and provide recommendations. Also completed clinical interviews and feedback sessions with supervision.

Supervisors: Hanjoo Lee, Ph.D., Kristin Smith, Ph.D.

2013-2014 *First Year Clinical Psychology Practicum.*
- Gained experience conducting unstructured and structured diagnostic interviews (SCID-I & SCID-II). Also obtained neuropsychological test administration experience.

Supervisors: Bonnie Klein-Tasman, Ph.D., Hanjoo Lee, Ph.D.

TEACHING EXPERIENCE

Student Coordinator

2017-2018 *Cases in Clinical Neuropsychology Seminar* (PSYCH 711), University of Wisconsin-Milwaukee
-Recruited neuropsychologists from the community (e.g., Medical College of Wisconsin, Milwaukee VA) to present cases to neuropsychology students in a fact-finding format.

-Selected complementary review articles and chapters for students to read.

Teaching Assistant

2015-2017 *Graduate Clinical Assessment Practicum* (PSYCH 821), University of Wisconsin-Milwaukee, Instructors: Hanjoo Lee, Ph.D. & Kristin Smith, Ph.D.

Spring 2015 *Child Psychology* (PSYCH260), UWM, Instructor: Kristin Smith, Ph.D.

Fall 2014 *Research Methods* (PSYCH325), UWM, Instructor: Katie Mosack, Ph.D.

Spring 2014 *Research Methods* (PSYCH325), UWM, Instructor: Marcellus Merritt, Ph.D.

Fall 2013 *Research Methods* (PSYCH325), UWM, Instructor: Susan Lima, Ph.D.

Spring 2011 *Research Methods* (PSYCH207), Gonzaga University, Instructor: Mark Bodamer, Ph.D.

Fall 2009 *Cell Biology* (BIOL201), Gonzaga University, Instructor: Marianne Poxleitner, Ph.D.

Guest Lecturer, University of Wisconsin-Milwaukee, Milwaukee, WI.

Fall 2016 PSYCH433 Neuropsychology, *The Parietal Lobes.* Instructor: Natasha Wright, M.S.

Spring 2016 PSYCH205 Personality, *The Anatomy and Physiology of Personality.* Instructor: Kristin Smith, Ph.D.

Fall 2015 PSYCH260 Child Psychology, *Physical Development in Adolescence.* Instructor: Kristin Smith, Ph.D.

Spring 2015 PSYCH260 Child Psychology, *Heredity and Environment.* Instructor: Kristin Smith, Ph.D.

ACADEMIC AWARDS, HONORS, AND FELLOWSHIPS

2017 Distinguished Dissertation Fellowship, a merit-based award from the UWM Graduate School. Includes full tuition waiver, living stipend, plus $1,000 travel expenses for conferences.

2017 Summer Research Fellowship, a merit-based award from the UWM Psychology Department. Includes summer living stipend.

2017 The College on Problems of Drug Dependence (CPDD) NIDA Women & Sex/Gender Differences Junior Investigator Travel Award (*declined*), for the 2017 CPDD Conference. Competitive, merit-based travel fellowship.

2017 The College on Problems of Drug Dependence (CPDD) Travel Award for Early Career Investigators, for the 2017 CPDD Conference. Competitive, merit-based travel fellowship that includes registration waiver and $1,000 in travel expenses.

2016 Research Society on Alcoholism Student Merit Award, for the 2016 RSA Conference, funded by the National Institute on Alcohol Abuse and Alcoholism (NIAAA).

2009 Oregon Health & Science University Undergraduate Research Fellowship, 10-week funded summer fellowship in addiction neuroscience research.

2008-2009 Gonzaga University: Howard Hughes Medical Institute (HHMI) Undergraduate Research Award, received competitive undergraduate funding for two semesters to conduct research.

2009-2011 Gonzaga University President's List, 3 semesters

2007-2011 Gonzaga University Trustee Scholarship, 8 semesters, recipient of highest merit-based financial award, Gonzaga University

2008-2010 Gonzaga University Dean's List, 3 semesters

2007 American Association of University Women Scholarship, recipient of local AAUW Branch merit-based scholarship.

2006 Apprenticeships in Science & Engineering (ASE), 10-week funded summer apprenticeship in addiction neuroscience research.

STUDENT AND PROFESSIONAL AFFILIATIONS

2015-present Student Affiliate- American Psychological Association (APA) Division 40 (Clinical Neuropsychology)

2014-2018 President (2016-2018), Vice-President (2014-2016), Health Psychology Graduate Students Club, UWM

2015-2018 President (2017-2018), Treasurer (2015-2017), UWM Chapter of Association of Neuropsychology Students in Training (ANST); Association of Graduate Students in Neuropsychology (AGSIN), UWM

2015-2016 Student Representative on the Clinical Training Committee- UWM

2010-2011 President, Gonzaga University Science Club

VOLUNTEER/COMMUNITY OUTREACH

2013 Presenter, Oregon Museum of Science and Industry (OMSI)'s Annual Brain Fair

2011-2013 Volunteer Crisis Worker, Lines for Life (formerly Oregon Partnership). Answered calls on six hotlines: Drug & Alcohol Helpline, National Suicide Prevention Lifeline, Portland Suicide Hotline, Military Helpline, Veteran's Crisis Line, Oregon Youthline.

ADDITIONAL WORKSHOPS, TRAININGS, & CERTIFICATIONS

2018 Basic Life Support Certification, VA Maryland Healthcare System

2017 Issues in Mental Health Assessment & Service for Transgender Students Workshop, given by Barry Schreier, Ph.D., University of Iowa, presented at UWM

2017 Title IX Training, University of Wisconsin-Milwaukee

2016 Behavioral Activation for Depression Workshop, given by Christopher Martell, Ph.D., ABPP, UWM.

2014 Responsible Conduct of Research Course, UWM

2013* MRI Safety Training, Medical College of Wisconsin

2013* CITI Training, Medical College of Wisconsin & UWM

2013 MRI Operator certification, Oregon Health & Science University (OHSU), Portland, OR. Certified by OHSU Advanced Imaging Research Center (AIRC) Safety Officer to independently operate the MRI scanner.

2011 Applied Suicide Intervention Skills Training (ASIST) certification, Oregon Partnership/Lines for Life, Portland, OR. Completed 2-day training in suicide intervention skills.

*With additional training and continuing education sought in subsequent years