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Resting State Functional Connectivity in the Default Mode Network: Relationships Between Cannabis Use, Gender, and Cognition in Adolescents and Young Adults

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RESTING STATE FUNCTIONAL CONNECTIVITY IN THE DEFAULT MODE NETWORK: RELATIONSHIPS BETWEEN CANNABIS USE, GENDER, AND COGNITION IN ADOLESCENTS AND YOUNG ADULTS

by

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ABSTRACT

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Under the Supervision of Professor Krista Lisdahl

Introduction: Cannabis is the most commonly used illicit substance in the United States, and nearly 1 in 4 young adults are current cannabis users. The psychoactive component of cannabis, THC, is active at cannabinoid receptors, type 1, or CB_1 receptors. CB_1 receptors play a critical role in neural development, and chronic cannabis use causes desensitization and downregulation of these receptors. Chronic cannabis use is associated with changes in resting state functional connectivity (RSFC) in the default mode network (DMN) in adolescents and young adults, although results are somewhat inconsistent across studies, likely due to differing methodologies. Additionally, cannabis effects appear to be moderated by gender; while females appear to be more susceptible to receptor-level adverse effects of chronic THC exposure, effects of chronic cannabis use on cognition are inconsistent between males and females. Notably, no study to date has examined gender differences in the effects of cannabis on RSFC in the DMN in adolescents and young adults. **Methods:** Seventy-seven adolescent and young adult subjects underwent an MRI scan (including resting state scan), neuropsychological battery, toxicology screening, and drug use interview. Differences in DMN connectivity were examined between groups and with a group by gender interaction, using a left posterior cingulate cortex seed-based analysis conducted in AFNI. **Results:** Cannabis users demonstrated weaker connectivity than controls between the left PCC seed and various DMN nodes, including the left PCC/precuneus,

right lingual gyrus/precuneus, and right parahippocampal gyrus. Weaker connectivity was also seen in cannabis users between the left PCC and the right Rolandic operculum/Heschl's gyrus. Stronger connectivity was seen in cannabis users between the left PCC and the left and right cerebellum, and the left supramarginal gyrus. The group by gender interaction was not significantly associated with any differences in connectivity between the left PCC and the rest of the brain. Stronger left PCC—cerebellum connectivity was associated with poorer performance on cognitive measures in cannabis users. In controls, intra-DMN connectivity was positively correlated with performance on a speeded selective/sustained attention measure. **Discussion:** Consistent with our hypotheses and other studies, cannabis users demonstrated weaker connectivity between the left PCC and other DMN nodes. Cannabis users had stronger connectivity with the cerebellum, inconsistent with other studies. In the present study, this was related to poorer performance on cognitive measures. One possible mechanism for these findings may be that chronic THC exposure may alter GABA and glutamate concentrations, which relate to altered communication between brain regions. Future studies should be conducted with a larger sample size, examining gender differences, using a longitudinal design, and examining the neurochemical mechanism by which these differences may arise.

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LIST OF ABBREVIATIONS

2-AG	2-arachidonylglycerol
ACC	Anterior Cingulate Cortex
AFNI	Analysis of Functional NeuroImages
BA	Brodmann's Area
BDI-II	Beck Depression Inventory-II
BOLD	Blood-Oxygen-Level Dependent
CB_1	Cannabinoid receptor type 1
CCK	Cholecystokinin
CVLT-II	California Verbal Learning Test, 2nd Edition
D-KEFS	Delis-Kaplan Executive Function System
dlPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
Fcon1000	1000 Functional Connectomes Project
fMRI	Functional Magnetic Resonance Imaging
FSL	FMRIB Software Library
FWE	Family-Wise Error
GABA	γ-aminobutyric Acid
GLM	General Linear Model
LDFR	Long Delay Free Recall
MDD	Major Depressive Disorder
MNI	Montreal Neurological Institute
mPFC	Medial Prefrontal Cortex

MRI	Magnetic Resonance Imaging
PASAT	Paced Auditory Serial Addition Test
PCC	Posterior Cingulate Cortex
PFC	Prefrontal Cortex
PV	Parvalbumin
RSFC	Resting State Functional Connectivity
STAI	State-Trait Anxiety Inventory
THC	Δ_9-tetrahydrocannabinol
TLFB	Timeline Follow-Back
WRAT-4	Wide Range Achievement Test, 4th Edition

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✝AMDG

1. Introduction

1.1 Prevalence of Cannabis Use

Cannabis is the most commonly used illicit substance in the United States (Johnston et al., 2019). In 2018, 22.2% of 12th graders (Johnston et al., 2019) and 24.1% of young adults 19-28 (Schulenberg et al., 2019) reported using cannabis within the past 30 days, while 5.8% of 12th graders and 8.0% of young adults 19-28 reported using cannabis daily (Schulenberg et al., 2019). Given that adolescents and young adults are most vulnerable to initiating substance use (Miech et al., 2019), and the average age of initiation of cannabis use is in the teen years (X. Chen, Yu, Lasopa, & Cottler, 2017; T. T. Clark, Doyle, & Clincy, 2013; Richmond-Rakerd, Slutske, & Wood, 2017), understanding the effects of cannabis on the developing brain is imperative.

1.2 Psychopharmacology of Cannabis

The psychoactive component of cannabis is Δ_9-tetrahyrdocannabinol (THC; Gaoni & Mechoulam, 1964, 1971; Howlett et al., 2002), which is active as a partial agonist (Howlett et al., 2002) on cannabinoid receptors, type 1, also known as CB_1 receptors (Herkenham et al., 1990; Sim-Selley, 2003). CB_1 receptors are present on a variety of cell types, including pyramidal neurons, cholecystokinin (CCK)-expressing interneurons, and cerebellar granule neurons (E. L. Hill et al., 2007; Nogueron, Porgilsson, Schneider, Stucky, & Hillard, 2001; Piomelli, 2003). CB_1 receptors are notably absent from parvalbumin (PV)-expressing interneurons (Caballero & Tseng, 2012; Katona et al., 1999; Marsicano & Lutz, 1999). CB_1 receptors are widely distributed in the cortex, especially in the cingulate gyrus and frontal, secondary somatosensory, secondary motor, and association cortices, and molecular layer of cerebellar cortex (Glass, Dragunow, & Faull, 1997; Herkenham et al., 1990; Mackie, 2005). CB_1 receptors are more concentrated in the neocortex of the left hemisphere compared to the right

(Glass et al., 1997). Additionally, CB_1 receptors are strongly expressed in subcortical structures such as the hippocampus, dentate gyrus, amygdala, and basal ganglia (Glass et al., 1997; Herkenham et al., 1990; Mackie, 2005), while moderate distribution is seen in the periaqueductal gray (PAG), posterior hypothalamus, and ventral tegmental area (Burns et al., 2007). CB_1 receptors are often expressed in axon terminals (Mackie, 2005).

Anandamide and 2-arachidonylglycerol (2-AG) are two endogenous ligands present in the endocannabinoid system that act as agonists of CB_1 receptors (Devane et al., 1992; Sugiura et al., 1995; Wilson & Nicoll, 2002). By way of its endogenous ligands' actions on CB_1 receptors in the brain, the endocannabinoid system acts as a retrograde messenger system (Pertwee, 2008; Wilson & Nicoll, 2002) that modulates release of many neurotransmitters, such as glutamate and GABA (Pertwee, 2008).

Exposure to THC can disrupt the normal modulatory activity of the endocannabinoid system, causing abnormal levels of endocannabinoids and major neurotransmitters (Ellgren et al., 2008; Howlett et al., 2002; Pertwee, 2008; Renard, Rushlow, & Laviolette, 2018; Wilson & Nicoll, 2002). With chronic THC administration, CB_1 receptors desensitize to THC and uncouple from G-proteins (Breivogel et al., 2003). Chronic THC exposure leads to sequestration (Sim-Selley, 2003; Wilson & Nicoll, 2002), desensitization (Breivogel et al., 1999) and downregulation of CB_1 receptors (Breivogel et al., 1999; Oviedo, Glowa, & Herkenham, 1993; Rodriguez de Fonseca, Gorriti, Fernandez-Ruiz, Palomo, & Ramos, 1994). Desensitization and downregulation can be region-specific, including profound decreases in receptor binding in the hippocampus (Breivogel et al., 1999).

1.3 Adolescence/Young Adulthood

1.3.1 Brain Development During Adolescence and Young Adulthood

Adolescence is a time of brain development and maturation, including grey matter pruning (Giedd et al., 1999; Giorgio et al., 2010; Giorgio et al., 2008; Sowell, Thompson, Tessner, & Toga, 2001; Yuan, Cross, Loughlin, & Leslie, 2015) and improvements in white matter microstructure (Giedd et al., 1999; Giorgio et al., 2010; Giorgio et al., 2008; Yuan et al., 2015), which extend into young adulthood (Giedd et al., 1999; Giorgio et al., 2008; Lebel & Beaulieu, 2011; Simmonds, Hallquist, Asato, & Luna, 2014; Sowell et al., 2001). Functional brain networks continue to develop and mature across the lifespan (Betzel et al., 2014; Power, Fair, Schlaggar, & Petersen, 2010).

The endocannabinoid system also undergoes development across the lifespan; CB_1 receptor densities vary by region and gender across developmental periods (Rodriguez de Fonseca, Ramos, Bonnin, & Fernandez-Ruiz, 1993). Cannabinoid receptors are present in the brain from before birth (X. Wang, Dow-Edwards, Keller, & Hurd, 2003), and in the fetal brain, activation of cannabinoid receptors is involved in signaling mechanisms, metabolic regulation, gene expression, and catecholaminergic neuron development (J. Fernandez-Ruiz, Berrendero, Hernandez, & Ramos, 2000; Jager & Ramsey, 2008). Indeed, various neurotransmitters (including dopamine, serotonin, GABA, and opioid peptides) and behaviors (including pain sensitivity, motor activity, stress response, etc.) are impacted by cannabinoid exposure in the perinatal period in rodents (J. Fernandez-Ruiz et al., 2000; J. J. Fernandez-Ruiz, Berrendero, Hernandez, Romero, & Ramos, 1999).

In rats, CB_1 receptor levels increase in adolescence before decreasing to adult levels (Rodriguez de Fonseca et al., 1993). Administration or use of THC and other cannabinoids during development can interfere with typical functioning of the endocannabinoid system (J. Fernandez-Ruiz et al., 2000; Jager & Ramsey, 2008; Viveros, Llorente, Moreno, & Marco,

2005). While the adolescent literature is more sparse (Viveros et al., 2005), research in humans suggests that use of cannabinoids in adolescence is associated with interference in development of GABAergic neurons in the PFC (Renard et al., 2018) and changes in glutamate and n-acetyl aspartate levels in the anterior cingulate cortex (Prescot, Locatelli, Renshaw, & Yurgelun-Todd, 2011).

1.3.2 Effects of Cannabis in the Adolescent/Young Adult Brain

Given the neurodevelopment that is occurring, the adolescent brain appears particularly vulnerable to the effects of chronic THC exposure (Adriani & Laviola, 2004), as preclinical evidence suggests chronic cannabinoid exposure in adolescence produces long-term changes in neural functions (Viveros et al., 2005). Use of cannabis in adolescence and young adulthood is associated with a variety of poorer outcomes. For example, chronic cannabis use is associated with gray matter (Filbey et al., 2014; Gilman et al., 2014), white matter (Filbey et al., 2014; Medina, Nagel, Park, McQueeny, & Tapert, 2007), and subcortical structural (Cousijn et al., 2012; Maple, Thomas, Kangiser, & Lisdahl, 2019) abnormalities in adolescent and young adult users (Batalla et al., 2013; Lisdahl, Shollenbarger, Sagar, & Gruber, 2018), including in areas rich in CB_1 receptors (Mackie, 2005). Early use of cannabis is also associated with greater incidence of psychiatric problems (Chadwick, Miller, & Hurd, 2013) as well as later drug use and dependence (Fergusson, Boden, & Horwood, 2006; Lynskey et al., 2003). Further, regular cannabis use is related to poorer cognitive functioning in this age group, including lower IQ and deficits in processing speed, attention, executive functioning, and memory (Lisdahl, Gilbart, Wright, & Shollenbarger, 2013; Lisdahl et al., 2018; Lisdahl, Wright, Kirchner-Medina, Maple, & Shollenbarger, 2014). However, relatively few studies have examined the impact of chronic cannabis exposure on brain connectivity.

1.4 Default Mode Network

Brain connectivity—or the temporal correlation between measurements (in this case, BOLD responses) in separate parts of the brain (Bijsterbosch, Smith, & Beckmann, 2017)—can be measured with functional MRI (fMRI). Connectivity within and between brain networks can also be examined when at rest (i.e., when not completing a task), termed resting state functional connectivity (RSFC; Biswal, Van Kylen, & Hyde, 1997). The default mode network (DMN) is very active when the brain is at rest (Greicius, Krasnow, Reiss, & Menon, 2003) and may be disrupted by chronic cannabis use during development. The DMN is a functional brain network that matures across the lifespan (Betzel et al., 2014; Power et al., 2010). A "proto-default-mode network" comprised of the precuneus and bilateral parietal cortex is evident in the infant brain (Fransson et al., 2007). When it has largely finished its development by late adolescence (Bluhm et al., 2008), the DMN is composed of the posterior cingulate cortex (PCC), the hippocampal formation, lateral temporal cortex, medial and lateral parietal cortex, precuneus, and medial prefrontal cortex (mPFC; Buckner, Andrews-Hanna, & Schacter, 2008; Fox et al., 2005; Greicius et al., 2003; Raichle et al., 2001). While DMN *regions* appear to be similar between children and adults, *connectivity* between these regions is weaker in childhood but strengthens over time (Fair et al., 2008), although there is some inconsistency across studies (Power et al., 2010).

The DMN is associated with stimulus-independent (i.e. "mind wandering," Mason et al., 2007) and self-referential (Gusnard, Akbudak, Shulman, & Raichle, 2001; Harrison et al., 2008) thought. The PCC specifically is suggested to be involved in attention and monitoring for environmental change (Leech, Braga, & Sharp, 2012). Activation in the DMN is *anti*correlated with activation in the task-positive network (Fox et al., 2005; Fransson, 2005). Sonuga-Barke and Castellanos (2007) posit the "default-mode interference hypothesis," which states that

despite its anticorrelation with the task-positive network, the DMN can intrude upon the task-positive network and thus create instances of attentional lapses and performance deficits. Indeed, poorer deactivation of the DMN is associated with momentary lapses in attention (Weissman, Roberts, Visscher, & Woldorff, 2006) and reaction time variability (Whelan et al., 2012). Additionally, failure to deactivate the default mode network is associated with poorer cognitive functioning, including executive functioning (Bossong et al., 2013) and reaction time during a vigilance task (Drummond et al., 2005), and in disorders such as ADHD (Fassbender et al., 2009) and schizophrenia (Pomarol-Clotet et al., 2008), among others (Broyd et al., 2009). The DMN has also been implicated in attentional control (Small et al., 2003). Moreover, stronger intra-DMN connectivity is associated with better working memory task performance (Sala-Llonch et al., 2012; Sambataro et al., 2010). In individuals with schizophrenia and co-morbid cannabis use disorder, acute THC administration reduces hyperconnectivity within the DMN, and stronger anticorrelation between the DMN and executive control network is positively associated with working memory performance (Whitfield-Gabrieli et al., 2018). Given that the DMN develops during adolescence (Bluhm et al., 2008), the adolescent brain is particularly sensitive to substance use, including cannabis use (Adriani & Laviola, 2004), and areas of the DMN overlap with areas rich in CB_1 receptors (Buckner et al., 2008; Fox et al., 2005; Glass et al., 1997; Greicius et al., 2003; Mackie, 2005; Raichle et al., 2001), it is important to examine how chronic cannabis use in this age group relates to RSFC in the DMN, and potential downstream effects of these relationships.

1.4.1 Cannabis and Resting State Functional Connectivity in the Default Mode Network in Adolescence and Young Adulthood

To date, four studies have been conducted examining the relationship between *chronic* cannabis use and DMN connectivity in adolescents and young adults (Filbey, Gohel, Prashad, & Biswal, 2018; Osuch et al., 2016; Pujol et al., 2014; Wetherill et al., 2015), and one examined time course power spectra in incarcerated male adolescents with a history of cannabis use (Thijssen et al., 2017). Results of these studies are inconsistent, perhaps due to differing methodologies. In a study of 28 chronic cannabis-using young adult males, Pujol et al. (2014) reported that compared to male controls, cannabis users showed *greater* RSFC between a right PCC seed and the bilateral ventral PCC, and weaker connectivity between the seed and the left and right dorsal PCC/precuneus. The latter was associated with poorer verbal recall in cannabis users. These RSFC alterations persisted after 1 month of abstinence, although were lower in magnitude. Filbey et al. (2018) examined the effects of isolated and combined nicotine and cannabis use on an adult/young adult sample of 137 participants (53 cannabis users [71.6% male] and 30 controls [46.7% male]). After 3 days of abstinence from cannabis, the cannabis group demonstrated *lower* RSFC in the posterior cingulate gyrus compared to controls. In a similar study in young adults and adults, Wetherill et al. (2015) found *lower* RSFC in the DMN between the PCC and temporal cortex, medial PFC, cerebellum, and parahippocampus, and *higher* RSFC between the PCC and right anterior insula, in non-abstinent cannabis users (N=19, 53% male) compared to controls (N=21, 67% male).

Two other studies examined DMN connectivity in cannabis users with comorbid psychiatric disorders. In a sample of 16-23 year old participants, Osuch et al. (2016) compared RSFC in the DMN between controls (N=20, 40% male) and presumably non-abstinent cannabis users (N=20, 60% male), and individuals with depression. Cannabis use was associated with lower RSFC in the right medial PFC (BA6), and higher RSFC in the right

caudal/temporal/parahippocampal area (BA30), compared to controls. Additionally, higher RSFC in parts of the DMN was seen in early-onset cannabis users compared to late-onset/non-cannabis users. Early-onset cannabis use was associated with lower total IQ and lower verbal IQ (Osuch et al., 2016). Lastly, in a sample of 180 incarcerated (and thus abstinent) adolescent males, Thijssen et al. (2017) found that longer duration of cannabis use was associated with lower amplitude in lower frequencies (0.00-0.05), which may indicate rapid connectivity and/or poorer connection between the DMN and other networks. Indeed, lower network connectivity was also found between the DMN and the fronto-partietal network (Thijssen et al., 2017). However, while a valuable contribution to the literature, the cannabis-specific effects on time course power spectra would be difficult to disentangle due to possible comorbid psychiatric problems, lack of quantification of substance use, and no information on length of abstinence in the sample.

In summary, results of studies examining RSFC in the DMN between cannabis users and controls to date are inconsistent. In studies with older samples and that excluded (Wetherill et al., 2015) or allowed very light (Filbey et al., 2018) nicotine use in their cannabis groups, RSFC in the DMN is *generally lower* in cannabis users compared to controls. Studies with younger samples find *higher or lower* connectivity depending on the DMN region. Importantly, these studies demonstrate heterogeneity in their methodologies. For example, there appears to be heterogeneity between the studies in terms of their sample ages, e.g. including exclusively adolescents/young adults (Osuch et al., 2016; Pujol et al., 2014), as opposed to adult samples that have average ages in the young adult years (Filbey et al., 2018; Wetherill et al., 2015). While Wetherill et al. (2015) and Filbey et al. (2018) excluded nicotine use in their cannabis groups, Pujol et al. (2014) did not appear to measure nicotine use; Osuch et al. (2016) measured nicotine

use days, which were broadly low but significantly higher in cannabis users than controls. One study (Pujol et al., 2014) had exclusively males in its cannabis-using group, and no study to date has examined gender as a potential moderator of the relationship between cannabis use and RSFC in the DMN. Some studies excluded for psychiatric disorders (Pujol et al., 2014; Wetherill et al., 2015), while others did not (Filbey et al., 2018; Osuch et al., 2016). Given that sex (Bluhm et al., 2008; Hjelmervik, Hausmann, Osnes, Westerhausen, & Specht, 2014), nicotine use (Filbey et al., 2018; Hahn et al., 2007; Wetherill et al., 2015), psychiatric disorders (Broyd et al., 2009; Fassbender et al., 2009; Pomarol-Clotet et al., 2008), and age (Grady, Springer, Hongwanishkul, McIntosh, & Winocur, 2006; Lustig et al., 2003; Sambataro et al., 2010) are associated with differences in DMN connectivity, it is important that these factors are measured and accounted for when examining the relationship between cannabis use and RSFC in the DMN.

1.5 Gender

1.5.1 Cannabis and Gender

While males are more likely to begin using cannabis in late adolescence relative to females (X. Chen et al., 2017), females, particularly during adolescence, appear to be more susceptible to receptor-level adverse effects of chronic THC exposure. Adolescent female rats display greater desensitization of CB_1 receptors in the prefrontal cortex (PFC), PAG, ventral midbrain, striatum (Burston, Wiley, Craig, Selley, & Sim-Selley, 2010), and hippocampus (Burston et al., 2010; Silva et al., 2015) compared to adolescent male rats. Additionally, in the hippocampus, CB_1 receptor downregulation is more widespread and persistent in adolescent female rats (Silva et al., 2015). These sex-specific patterns of desensitization are also present in adult rats (Farquhar et al., 2019). Moreover, adolescent females exhibit greater desensitization compared to adult females in the PFC, PAG, hippocampus, and ventral midbrain, while

adolescent males show lesser desensitization than adult males in the PFC, PAG, and HC (Burston et al., 2010). Taken together, these results suggest that adolescent female rats are particularly susceptible to the CB_1 receptor-desensitizing effects of chronic THC exposure.

While sex differences in receptor-level responses to chronic THC administration are consistent, sex differences in cognition after chronic THC exposure in adolescence and young adulthood are less clear, both in rodents and humans, and may differ across cognitive domain. (See Crane, Schuster, Fusar-Poli, and Gonzalez (2013) for review.) Studies find poorer memory after chronic administration of cannabinoid agonist CP 55,940 exposure in adolescent male (novel object recognition) or female (object location) rodents (Mateos et al., 2011), but poorer memory after chronic THC exposure in female humans (Crane, Schuster, & Gonzalez, 2013; Crane, Schuster, Mermelstein, & Gonzalez, 2015). With chronic CP 55,940 exposure in young adulthood, male (but not female) rats exhibit poorer working memory (O'Shea, McGregor, & Mallet, 2006; O'Shea, Singh, McGregor, & Mallet, 2004). Male humans broadly appear to have poorer psychomotor speed with chronic cannabis use (King et al., 2011; Lisdahl & Price, 2012). Sex differences in the effects of cannabinoids on visuospatial skills (King et al., 2011; Pope, Jacobs, Mialet, Yurgelun-Todd, & Gruber, 1997) and decision making (L. Clark, Roiser, Robbins, & Sahakian, 2009; Crane, Schuster, & Gonzalez, 2013) are inconsistent across studies, and still other studies find no gender differences in adolescent (Solowij et al., 2011) or young adult (Pope et al., 1997; Tait, Mackinnon, & Christensen, 2011) cannabis users' cognition. To our knowledge, no study to date has examined differences in resting state functional connectivity between male and female chronic cannabis users and controls, in any network.

1.5.2 Gender Differences in Resting State Functional Connectivity

Regardless of cannabis use, subtle gender differences exist between males and females in connectivity in various parts of the DMN. Adolescent females show stronger functional connectivity between the medial PFC and right posterior cerebellum than males (Alarcon, Pfeifer, Fair, & Nagel, 2018). Adult females show higher functional connectivity in parts of the DMN, including prefrontal areas, anterior fronto-parietal network (Hjelmervik et al., 2014), and between PCC/precuneus and bilateral medial frontal cortex (Bluhm et al., 2008). Notably, DMN connectivity does not vary with menstrual cycle phase (Hjelmervik et al., 2014).

1.6 Study Aims

The aims of the present study were to examine whether there were differences in resting state functional connectivity between cannabis users and controls using a left PCC seed, and to examine if gender moderated any findings. Additionally, given the relationship between chronic cannabis use and cognitive deficits in young adults (e.g. Lisdahl et al., 2014), we sought to examine relationships among connectivity between the left PCC and significant clusters and performance on select neuropsychological measures in the cannabis users and controls (or by gender and substance use group) in order to further interpret brain-behavior relationships. Although there are heterogenous methodologies between existing studies of RSFC in the DMN in cannabis users and controls, most studies with limited nicotine use find lower RSFC in the DMN in cannabis users. Thus, given the relatively low nicotine use in our sample, we hypothesized that cannabis users will exhibit lower RSFC between the left PCC and other DMN nodes. While females in this age group generally show higher RSFC in parts of the DMN compared to males, it is difficult to hypothesize whether males or females will exhibit higher or lower RSFC between the left PCC and DMN nodes with chronic cannabis use because there is no extant literature addressing this topic. Thus, we hypothesized that there would be a difference

in DMN RSFC between male and female cannabis users, without hypothesizing a direction for either gender. We additionally hypothesized that RSFC would be related to neuropsychological functioning, with stronger connectivity between the left PCC and DMN nodes related to better performance on measures of selective and sustained attention, working memory, inhibition, and verbal memory, or, alternatively, stronger connectivity between the left PCC and areas that are typically anti-correlated with the DMN related to poorer performance on these measures.

2. Methods

2.1 Participants

Participants include 77 young adults (35 female, 42 male) aged 16-26 from a larger neuroimaging study (PI: Lisdahl, R01DA030354). The Institutional Review Boards at the University of Wisconsin-Milwaukee and the Medical College of Wisconsin approved all protocols. Inclusion criteria included: age 16-26, right-handedness, willingness to maintain abstinence from substances for the duration of the study; for the cannabis group: >40 past year cannabis uses or significant lifetime history of cannabis use (500+ lifetime uses) with at least monthly current use; and for the control group: ≤ 20 lifetime uses of cannabis and <5 past year uses. Exclusion criteria included MRI contraindications, pregnancy, left-handedness, birth complications or premature birth (<33 weeks gestation), major medical or neurologic disorders, diabetes, hypertension, hyperlipidemia, hearing or vision impairment, learning or intellectual disability, head injury with loss of consciousness >2 minutes, DSM-IV-TR Axis I disorders independent of substance use, current use of psychotropic medication, heavy other drug use (>25 lifetime uses of substances other than cannabis), use of >10 cigarettes per day, failure to maintain abstinence at session 4 or on the day of MRI scanning (blood alcohol concentration of >.000, positive or increasing continuous sweat patch testing and/or urine toxicology), and WRAT-4

Reading t-score < 80. Eligible participants were divided into cannabis users (n=37, 13 female) and controls (n=40, 22 female).

2.2 Procedure

Individuals were recruited through flyers and advertisements posted in the community. After receiving verbal consent from the participants (or, if under 18, verbal assent from the participant and verbal consent from their parents), interested potential participants were screened by phone for basic eligibility criteria. Potential participants who remained eligible were mailed a written consent form (or an assent form for those under 18, as well as parent consent) prior to a detailed phone screen. The detailed screening included the Customary Drinking and Drug Use Record (CDDR; Brown et al., 1998; Stewart & Brown, 1995) for all participants to assess comprehensive lifetime substance use. For participants aged 18 or older, the detailed screen also included the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) to assess the psychiatric history of the participant. With participants' consent, the MINI was also administered to the participant's parent or guardian to assess the participant's psychiatric history. For participants under age 18 and their parents or guardians, the MINI-Kid (Sheehan et al., 2010) assessed psychiatric history of the participants. For further detail, see Wallace, Wade, and Lisdahl (2020) and Sullivan, Wallace, Wade, Swartz, and Lisdahl (2020).

After obtaining informed consent, all participants (cannabis users and non-users) underwent a minimum of 3 weeks (including 5 in-person sessions) of monitored abstinence via breath samples, urine toxicology, and continuous sweat patch testing. At weekly sessions 1-3, participants completed toxicology testing and a brief neuropsychological and mood battery. One week after session 3, session 4 was conducted in which participants completed toxicology testing, a longer neuropsychological battery, psychological questionnaires, and VO_2 max

treadmill testing. At session 5, which occurred within 24-48 hours of session 4, participants again underwent toxicology testing, a brain MRI scan, and completed questionnaires.

2.3 Measures

2.3.1 Toxicology and Pregnancy Testing

At each study visit, participants provided a urine sample which was examined for adulterants (Specimen Validity Test; DrugTestStrips, Greenville, SC) and tested for cotinine level (a nicotine metabolite; NicAlert strips, Nymox Pharmaceutical Corporation, Hasbrouck Heights, NJ) and recent drug use (One Step Drug Screen Test Dip Card Panel; Innovacon, Inc., San Diego, CA), including amphetamines, barbiturates, benzodiazepines, cocaine, ecstasy, methadone, methamphetamines, opiates, phencyclidine (PCP), THC, and THC-COOH (a THC metabolite). Female participants were administered a urine pregnancy test (HGC Pregnancy Test Card; DrugTestStrips, Greenville, SC). All participants completed a breath alcohol test (Alco-Sensor IV; Intoximeters Inc., St. Louis, MO). Beginning at Session 1, participants also wore a PharmCheck sweat patch that was changed at each weekly visit (discontinued at session 4). The sweat patch was used to monitor substance use between weekly visits that may not be found in weekly urinalysis; substances quantified included 6-monoacetylmorphine (a heroin metabolite), amphetamines, benzoylecgonine (a cocaine metabolite), cocaine, codeine, heroin, methamphetamine, morphine, and THC. If a participant presented to session 2 or 3 with a positive urine screen or breath alcohol sample, or increased levels of THC-COOH on sweat patch testing, they were asked to reschedule their session after 1 week of abstinence. At session 4 or 5, participants were required to have a negative urine and breath alcohol screen, and/or decreasing THC-COOH levels measured via sweat patch testing, in order to participate (Sullivan et al., 2020).

2.3.2 Drug Use

Past year substance use was measured with the Timeline Follow Back (TLFB; Sobell, Maisto, Sobell, & Cooper, 1979). The TLFB is a semi-structured measure in which participants are asked to recall their use of substances week-by-week over the past year using a calendar. They may use days of personal significance as reminders or cues. Substances were measured using standard units (e.g. cannabis in joints, alcohol in standard drinks, cigarettes in number of cigarettes). Lifetime and past 3-month substance use, including assessment of DSM-IV-TR substance abuse and dependence criteria, was measured with the CDDR (Brown et al., 1998; Stewart & Brown, 1995).

2.4 Neuropsychological Assessments

Estimated verbal intelligence and quality of education were assessed for group comparison using the Wide Range Achievement Test-4th Edition (WRAT-4; Wilkinson, 2006) Reading subtest age-scaled score variable. Participants underwent a neuropsychological battery as part of the larger study. Four neuropsychological tests are used in the present study. Selective and sustained attention were measured with the Ruff 2 & 7 Total Speed and Total Accuracy raw scores (Ruff & Allen, 1996). Working memory and sustained attention were assessed with the Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977); total correct score was used. The D-KEFS Color-Word Interference test Condition 3 (Inhibition) was used to assess inhibitory control; total completion time was used (Delis, Kaplan, & Kramer, 2001). Verbal learning and memory was assessed with the California Verbal Learning Test, 2nd Edition (CVLT-II); Trial 1, Total Learning (Trials 1-5), and Long Delay Free Recall (LDFR) raw scores were used (Delis, Kramer, Kaplan, & Ober, 2000).

2.5 Neuroimaging

2.5.1 Acquisition Parameters

Participants were scanned on a 3T MR scanner (GE Healthcare, Waukesha, WI) at Medical College of Wisconsin. 3-dimensional, T-1 weighted anatomical images were obtained using a spoiled gradient-recalled at steady-state (SPGR) pulse sequence (TE = 3.4s, TR = 8.2s, TI = 450ms, flip angle= 12°, FOV = 240mm, resolution = 256x256mm, slice thickness = 1mm, 150 sagittal slices). An 8-minute resting state fMRI scan was conducted with the following parameters: TE = 25ms, TR = 2s, flip angle = 77°, FOV = 240mm, matrix = 64x64, slice thickness = 3.7mm, 40 sagittal slices, 240 repetitions. During the resting state scan, participants were instructed to lie awake with their eyes closed.

2.5.2 Processing

Structural images underwent pre-processing using scripts from the 1000 Functional Connectomes Project (Fcon1000; Biswal et al., 2010), which call upon programs from, primarily, Analysis of Functional NeuroImages (AFNI: Cox, 1996, 2012), and FMRIB Software Library (FSL: Woolrich et al., 2009) software. Pre-processing steps included deobliquing (3drefit: Cox, 2009), reorientation (3dresample: Reynolds, 2014), skull stripping (3dSkullStrip: Saad, 2020; 3dcalc: Cox, 2020), segmentation into white and gray matter structures (fast: Zhang, Brady, & Smith, 2001; flirt: Greve & Fischl, 2009; Jenkinson, Bannister, Brady, & Smith, 2002; Jenkinson & Smith, 2001; fslmaths: Woolrich et al., 2009), registration to MNI space (flirt: Greve & Fischl, 2009; Jenkinson et al., 2002; Jenkinson & Smith, 2001), and white matter segmentation (flirt: Greve & Fischl, 2009; Jenkinson et al., 2002; Jenkinson & Smith, 2001; fslmaths: Woolrich et al., 2009).

Raw functional images were pre-processed using Fcon1000 scripts (Biswal et al., 2010) including dropping the first 4 TRs (3dcalc: Cox, 2020), deobliquing (3drefit: Cox, 2009),

reorientation (3dresample: Reynolds, 2014), motion correction to average of the time series (3dTstat: Hammett & Cox, 2020; 3dvolreg: "AFNI program: 3dvolreg," 2020), skull stripping (3dAutomask: "AFNI program: 3dAutomask," 2020; 3dcalc: Cox, 2020), registration within each subject (3dcalc: Cox, 2020), registration to the anatomical image and to MNI space (flirt: Greve & Fischl, 2009; Jenkinson et al., 2002; Jenkinson & Smith, 2001), spatial smoothing with a 6mm FWHM Gaussian kernel (fslmaths: Woolrich et al., 2009), grand-mean scaling (fslmaths: Woolrich et al., 2009), band-pass filtering (high pass cutoff = 0.005Hz, low pass cutoff = 0.1 Hz; 3dFourier: Ross & Heimerl, 1999), linear and quadratic detrending (3dTstat: Hammett & Cox, 2020; 3dDetrend: "AFNI program: 3dDetrend," 2020; 3dcalc: Cox, 2020), and regression of nuisance variables (including 6 motion parameters, global signal, white matter, and CSF; 3dmaskave: "AFNI program: 3dmaskave," 2020; 3dTstat: Hammett & Cox, 2020; 3dcalc: Cox, 2020; flirt: Greve & Fischl, 2009; Jenkinson et al., 2002; Jenkinson & Smith, 2001, FEAT: Woolrich, Ripley, Brady, & Smith, 2001).

2.6 Data Analysis

ANOVAs and Chi-squares were conducted in SPSS v.25 to examine potential group differences on demographic and other substance use variables between male and female cannabis users and controls. Past year alcohol drinks and Session 5 cotinine (reflecting recent nicotine exposure) were included as covariates in the general linear model (GLM) in AFNI as they differed significantly by group (see Table 1). A seed-based correlation analysis was conducted. A 3mm spherical seed placed in the left PCC at MNI (*x*,*y*,*z*) coordinates (-3, -50, 36; Ernst et al., 2019) was created using AFNI's 3dcalc (Cox, 2020); this region was selected to be consistent with other studies of the DMN (Ernst et al., 2019; Fox et al., 2005; Pujol et al., 2014). Using an Fcon1000 script (Biswal et al., 2010) which called upon specific AFNI programs, the BOLD

timeseries was extracted from the PCC for each subject using 3dROIstats ("AFNI program: 3dROIstats," 2020). The seed timeseries were then correlated with each voxel in the brain using 3dfim+ (B. D. Ward, 2020); these correlations were transformed to Z-scores. The resultant seed-based connectivity maps for each subject were subsequently used in comparison of cannabis vs control groups using a GLM (Bijsterbosch et al., 2017). Thresholding to correct for multiple comparisons was conducted using 10,000 Monte Carlo simulations within AFNI's 3dClustSim ("AFNI program: 3dClustSim," 2020), with individual voxels labeled significant at $p<.001$, corrected for Family-Wise Error (FWE) at cluster thresholds of $p<.05$. These thresholds have been shown to adequately control false-positive rates (Cox, Chen, Glen, Reynolds, & Taylor, 2017; Slotnick, 2017) and replicate, or are more stringent than, thresholding in similar studies using a seed-based analysis (Pujol et al., 2014; Wetherill et al., 2015). The minimum cluster size to meet these thresholds was 8 voxels.

AFNI's 3dMVM (G. Chen, Adleman, Saad, Leibenluft, & Cox, 2014) was used for the group analysis, identifying clusters significantly correlated with the left PCC seed by group and in a group*gender interaction. Data from significant clusters from the cannabis group analysis or cannabis*gender analysis were extracted using AFNI's 3dROIstats ("AFNI program: 3dROIstats," 2020) and, using SPSS v.25, correlated with performance on selected neuropsychological measures in order to explore downstream cognitive effects of DMN connectivity differences.

3. Results

Demographic and drug use variables were examined using Chi-squares and ANOVAs with Tukey's HSD post-hoc tests, after dividing participants into male cannabis users (n=24), female cannabis users (n=13), male controls (n=18), and female controls (n=22).

3.1 Demographic and Mood Information

Demographic and drug use information is summarized in Table 1. Groups significantly differed in the Beck Depression Inventory-II (BDI-II) score ($F[3,73]=3.69$, $p=.02$). Female cannabis users had significantly higher BDI-II scores than female controls ($p=.02$). Male cannabis users had marginally higher BDI-II scores compared to female controls ($p=.09$). Ethnicity was marginally different between groups (68% Caucasian, $\chi^2(18)=26.19$, $p=.10$). Groups did not differ in age ($F[3,73]=0.50$, $p=.69$), years of education ($F[3, 73]=0.12$, $p=.95$), WRAT-4 Reading score ($F[3,77]=1.99$, $p=.12$), or state anxiety at Session 1 ($F[3, 73]=1.72$, $p=.17$) or Session 4 ($F[3, 73]=0.04$, $p=.99$).

3.2 Drug Use

Groups significantly differed in past year cannabis use ($F[3,73]=12.40$, $p<.001$), lifetime cannabis use ($F[3,73]=12.51$, $p<.001$), past year cigarettes ($F[3,73]=3.41$, $p=.02$), past year alcohol use ($F[3,73]=6.15$, $p=.001$), age of first cannabis use ($F[3,48]=7.56$, $p<.001$), and cotinine level at Session 5 ($F[3,73]=3.28$, $p=.03$). Post-hoc analysis found that male cannabis users had significantly higher past year cannabis use than male ($p<.001$) and female ($p<.001$) controls. Female cannabis users had marginally higher past year cannabis use than male ($p=.10$) and female ($p=.08$) controls. Male cannabis users had significantly higher lifetime cannabis use than male ($p<.001$) and female ($p<.001$) controls. Female cannabis users had marginally higher lifetime cannabis use than male ($p=.07$) and female ($p=.054$) controls. Male and female cannabis users first initiated cannabis use at significantly younger ages than male ($p<.01$ compared to cannabis-using males; $p<.01$ compared to cannabis-using females) and female ($p=.02$ compared to cannabis-using males; $p=.03$ compared to cannabis-using females) controls who had tried cannabis. Between male and female cannabis users, there was no difference in age of first

cannabis use (p=.99), nor in age of onset of regular cannabis use (F[1,35]=0.24, p=.63). The average length of abstinence from cannabis at the scan day was 37.00 days for male cannabis users, 29.54 days for female cannabis users, 151.20 days for male controls, and 260 days for the one female control who had previously used cannabis.

Male cannabis users consumed significantly more cigarettes in the past year compared to male (p=.04) controls and consumed marginally more cigarettes in the past year compared to female (p=.053) controls. At session 5, male cannabis users displayed significantly higher cotinine compared to male controls (p=.04), and marginally higher cotinine compared to female controls (p=.08). (Of note, one male cannabis user was not administered toxicology testing at Session 5. His Session 5 cotinine level was estimated [6] and included in this analysis, as he smoked cigarettes regularly and had a cotinine level of 6 at each session prior.) Male cannabis users consumed significantly more past year alcohol drinks compared to male (p=.04) and female (p<.001) controls. Male cannabis users consumed significantly more past year other substances compared to male (p=.03) and female (p<.01) controls.

3.3 Primary Findings

DMN Seed Validity Check: In both the CAN and CTL groups, the PCC seed recognized the main nodes of the DMN, including the PCC, precuneus, mPFC, lateral temporal cortex, parahippocampal gyrus, and parietal cortex/angular gyrus.

3.3.1 Main Effect of Group

The coordinates and size of all significant clusters are listed in Table 2. Controlling for recent cotinine and past year alcohol drinks, cannabis users displayed weaker connectivity compared to controls between the left PCC and the right lingual gyrus/right precuneus, left PCC/precuneus, right Rolandic operculum and Heschl's gyrus, and left parahippocampal gyrus.

Cannabis users displayed stronger connectivity between the left PCC and the left and right cerebellum, specifically in the right cerebellum VII/Crus II, left cerebellum Crus I and Crus II, and left cerebellum VIII. Cannabis users also displayed stronger connectivity between the left PCC and the left supramarginal gyrus. See Figures 1 and 2 for images of these clusters.

3.3.2 Group by Gender Interaction

The cannabis group*gender interaction was not significantly associated with any differences in connectivity between the left PCC and the rest of the brain.

3.3.3 Main Effect of Gender

Regardless of cannabis group status, male participants exhibited stronger connectivity between the left PCC and the right temporal pole.

3.3.4 Covariate Findings

Greater cotinine level at Session 5 was associated with weaker connectivity between the left PCC and the right cerebellum (Crus I). Past year alcohol consumption was associated with stronger connectivity between the left PCC and the right precuneus.

3.4 Brain-Behavior Relationships

Connectivity measurements from clusters that were significantly different between cannabis users and controls were correlated with performance on selected neuropsychological measures. In cannabis users, connectivity between the left PCC and the left cerebellum Crus I was significantly negatively correlated with PASAT total correct raw score (p=.04). Additionally, left PCC—left cerebellum VIII connectivity was significantly negatively associated with the CVLT-II Total Learning (Trials 1-5) raw score (p=.04). This means that stronger connectivity between the left PCC and left cerebellum Crus I, and between the left PCC and the left cerebellum VIII, was associated with poorer PASAT and CVLT-II Total Learning

performance, respectively. In controls, connectivity between the left PCC and the left PCC/left precuneus was significantly positively correlated with performance on the Ruff 2 & 7 Total Speed raw score (p=.03), meaning that stronger connectivity between the left PCC seed and the left PCC/precuneus was associated with better speed on this measure. Results are detailed in Table 3 for cannabis users and Table 4 for controls.

4. Discussion

4.1 Discussion of Findings

The aims of the present study were to describe potential differences in resting state functional connectivity in the default mode network, utilizing a seed-based approach, between adolescent and young adult cannabis users and controls and to examine if gender moderated any findings. Additionally, we sought to examine relationships between DMN connectivity in clusters that significantly differed by group or group*gender and performance on select neuropsychological measures in order to further interpret these findings. We found that cannabis users demonstrated weaker connectivity between the left posterior cingulate cortex (PCC) and the right lingual gyrus/right precuneus, left PCC/precuneus, right Rolandic operculum and Heschl's gyrus, and left parahippocampal gyrus, and stronger connectivity with the left supramarginal gyrus, and portions of the left and right cerebellum, compared to controls. There were no significant interactions between group and gender in predicting left PCC connectivity in this study. In cannabis users, stronger connectivity between the left PCC and the cerebellum was correlated with poorer performance on sustained attention/working memory and verbal learning measures. In controls, stronger connectivity between the left PCC and the left PCC/precuneus was correlated with better speed on a selective and sustained attention measure.

Compared to controls, cannabis users exhibited *weaker* connectivity between the left PCC and left PCC/left precuneus, left parahippocampal gyrus, right lingual gyrus/right precuneus, and right Rolandic operculum/right Heschl's gyrus. Lesser intra-network connectivity (i.e. PCC, precuneus, parahippocampal gyrus) is consistent with our hypothesis and with results from similar studies, which find lower connectivity in the PCC (Filbey et al., 2018) or dorsal PCC/precuneus (Pujol et al., 2014) in cannabis users compared to controls, lower connectivity in the posterior DMN, cuneus, and precuneus in cannabis users compared to cannabis/tobacco co-users (Filbey et al., 2018), and lower connectivity between the PCC and parahippocampal gyrus in cannabis users (Wetherill et al., 2015). However, one study found *greater* connectivity between the PCC and the right caudate/temporal/parahippocampal regions (BA30; Osuch et al., 2016); the authors suggested that connectivity between these regions should typically be very low, so the greater connectivity seen in their findings may actually represent lesser anticorrelation between these areas (Osuch et al., 2016). Nevertheless, structural connections exist between the parahippocampal gyrus and the DMN (Lavenex & Amaral, 2000; A. M. Ward et al., 2014), and the parahippocampal gyrus mediates connectivity between the PCC and the hippocampus (A. M. Ward et al., 2014). These areas are rich with CB_1 receptors (Glass et al., 1997; Herkenham et al., 1990; Howlett et al., 2002), and it is possible that repeated activation of these receptors by THC during adolescence and young adulthood may alter PCC—DMN connectivity. In controls, connectivity within the DMN (between the left PCC and the left PCC/left precuneus) was significantly positively correlated with performance a measure of speed within a selective and sustained attention measure. With a similar direction of findings, Pujol et al. (2014) found that weaker connectivity between the right PCC and left and right dorsal PCC/precuneus in cannabis users was associated with poorer verbal recall. Stronger intra-DMN

connectivity is associated with better working memory task performance (Sala-Llonch et al., 2012; Sambataro et al., 2010), and regular cannabis use is associated with poorer memory, executive functioning, processing speed, and attention in this age group (Lisdahl et al., 2013; Lisdahl et al., 2018; Lisdahl et al., 2014).

In cannabis users, weaker connectivity was also seen between the left PCC and the right lingual gyrus, as well as the right Rolandic operculum/Heschl's gyrus. These areas are known to be associated with sensory/perceptual abilities such as visual processing (lingual gyrus; Mechelli, Humphreys, Mayall, Olson, & Price, 2000), hearing and pitch perception (Heschl's gyrus; e.g. Krumbholz, Patterson, Seither-Preisler, Lammertmann, & Lutkenhoner, 2003), and body self-consciousness (Rolandic operculum; Blefari et al., 2017). Thus, the present findings may suggest that cannabis users demonstrate abnormal connectivity between the PCC and sensory/perceptual associative areas. Acute THC administration induces altered perception (D'Souza et al., 2004); it is possible that with chronic THC exposure, CB_1 receptors in these regions underwent downregulation (Breivogel et al., 1999; Oviedo et al., 1993). Indeed, chronic cannabis use is associated with abnormalities in these areas in regular cannabis users, including smaller lingual gyrus and Rolandic operculum volumes (S. Y. Hill, Sharma, & Jones, 2016), and impaired sensory gaiting (Broyd et al., 2013). Interestingly, the generation of the event-related potential associated with sensory gaiting has been localized to Heschl's gyrus (Broyd et al., 2013). Alternatively, it is possible that some of the differences in connectivity seen in these areas may be due to averaging error from connectivity differences in closely related anatomical areas (e.g. the right precuneus for the Heschl's gyrus cluster).

Contrary to other studies which found weaker connectivity between the PCC and the bilateral cerebellum Crus I and II (Wetherill et al., 2015), or between the cerebellum and the

DMN (Sweigert et al., 2019) in cannabis users, we found that cannabis users demonstrated *stronger* connectivity between the left PCC and the left and right cerebellum, specifically in the right cerebellum VII/Crus II, left cerebellum Crus I and Crus II, and left cerebellum VIII. Studies have shown intrinsic connectivity between the DMN and Crus I, Crus II, and Lobule IX (Bernard et al., 2012; Krienen & Buckner, 2009; L. Wang et al., 2014). However, Crus I and II have also demonstrated functional connectivity with areas that are traditionally not considered part of the DMN, such as the dlPFC (Fox et al., 2005; Krienen & Buckner, 2009). In one study (Habas et al., 2009), Crus I and II participated in activation with areas of the left and right executive control network, and, to a lesser extent, the salience network, but not with the DMN. Cerebellar activations were generally distinct (i.e. nonoverlapping) between networks (Habas et al., 2009). The executive control network and the salience network, considered two parts of the "task-positive network" (Di & Biswal, 2014), are generally *anti*correlated with the DMN (Fox et al., 2005; Greicius et al., 2003; Sridharan, Levitin, & Menon, 2008; Whitfield-Gabrieli et al., 2018; Whitfield-Gabrieli & Ford, 2012), so it is possible that greater connectivity between the left PCC and cerebellar areas seen in cannabis users in the present study is due to reduced anticorrelation between these networks. It is also possible that this stronger connectivity is a compensatory mechanism (Wall et al., 2019) due to downregulation of the CB_1 receptors (Breivogel et al., 1999; Sim-Selley, 2003; Sim-Selley & Martin, 2002) expressed in the cerebellum (Glass et al., 1997; Herkenham et al., 1990; Mackie, 2005; Nogueron et al., 2001). In any case, chronic cannabis use appears to be associated with differences in connectivity from what is "typical" between the DMN and the cerebellum. Indeed, the posterior portion of the cerebellum has increasingly been shown to be involved in cognition (Bernard et al., 2012; Stoodley & Schmahmann, 2009; Stoodley, Valera, & Schmahmann, 2012); presently, stronger connectivity

between the left PCC and the cerebellum was negatively correlated with performance on measures of sustained attention/working memory and verbal learning in cannabis users only, suggesting that stronger connectivity between these regions may have negative performance implications.

Cannabis users also displayed stronger connectivity between the left PCC and the left supramarginal gyrus. This finding was not seen in other studies similar to ours (Filbey et al., 2018; Osuch et al., 2016; Pujol et al., 2014; Wetherill et al., 2015). The supramarginal gyrus is negatively correlated with the PCC/precuneus in a small sample of healthy controls (Fransson, 2005), and, as part of the inferior parietal lobule, could perhaps be considered a part of the task-positive network (Fox et al., 2005). The supramarginal gyrus may contribute modulatory activity between the DMN and the dorsal attention network (Di & Biswal, 2014). Thus, as with the cerebellum, it is possible that the higher connectivity seen here in cannabis users between the left PCC and the left supramarginal gyrus may indicate lesser anticorrelation between the DMN and task-positive/attentional networks.

The lack of significant differences in left PCC connectivity within the group*gender interaction was contrary to our hypothesis. Rodent literature suggests that female rats, especially adolescents, are particularly sensitive to THC at the receptor level (Burston et al., 2010; Farquhar et al., 2019; Silva et al., 2015). Additionally, subtle sex differences do exist regarding functional connectivity in the DMN in healthy controls (Alarcon et al., 2018; Bluhm et al., 2008; Hjelmervik et al., 2014). While it is certainly possible that adolescent and young adult male and female cannabis users and controls simply do not display differences in functional connectivity from the left PCC, it is likely that our study was underpowered to detect these effects given our small sample size. Indeed, in exploratory analyses, male cannabis users had weaker connectivity

between the left PCC and the left caudate nucleus compared to female cannabis users, while male controls displayed significantly stronger connectivity between the left PCC and the right medial temporal pole, and weaker connectivity with the left cerebellum (IV-V), compared to female controls. Future studies should examine potential connectivity differences between male and female cannabis users and controls using a larger sample with more equivalently sized subgroups.

4.2 Possible Mechanism

One possible mechanism by which chronic cannabis use is associated with differences in RSFC between the left PCC and DMN and other brain regions may be by way of THC disrupting the normal modulatory activity of the endocannabinoid system. The endocannabinoid system likely plays a role in brain development (J. Fernandez-Ruiz et al., 2000; Viveros et al., 2005) and undergoes changes throughout adolescence (Ellgren et al., 2008). GABA and glutamate are important neurotransmitters in adolescent brain development and "cortical remodeling" (Crews, He, & Hodge, 2007). GABAergic function in the PFC increases in adolescence (Caballero & Tseng, 2016) but, at least in rodents, can be disrupted in the PFC by a CB_1 agonist (Cass et al., 2014). Through its action at CB_1 receptors, THC can change CB_1-mediated release of endocannabinoids (Ellgren et al., 2008) and neurotransmitters such as GABA and glutamate (Howlett et al., 2002; Pertwee, 2008; Wilson & Nicoll, 2002). Thus, chronic THC administration during adolescence may disrupt the optimal balance of excitatory and inhibitory neurotransmitters (i.e. glutamate and GABA; Renard et al., 2018).

Disruption of this excitatory/inhibitory balance by chronic THC exposure may relate to communication between brain regions by way of disruption of neural oscillations (see Caballero and Tseng (2012) for review). Importantly, synchronization of neural oscillations is primarily

mediated by GABAergic interneurons (Skosnik, Cortes-Briones, & Hajos, 2016), which exhibit and are modulated by CB_1 receptors (Pertwee, 2008; Piomelli, 2003; Skosnik et al., 2016; Wilson & Nicoll, 2002). Acute administration of CB_1 agonists is known to affect neural oscillations, particularly in the theta and gamma bands in both humans and rats (Cortes-Briones et al., 2015; Hajos, Hoffmann, & Kocsis, 2008; Ilan, Smith, & Gevins, 2004; Robbe et al., 2006; Skosnik et al., 2012), including in the mPFC (Kucewicz, Tricklebank, Bogacz, & Jones, 2011). Chronic use has also been associated with lower power in the gamma and beta bands (Edwards, Skosnik, Steinmetz, O'Donnell, & Hetrick, 2009; Skosnik et al., 2012). It makes sense that these bands in particular would be affected, as CB_1 receptors are paired with neurons with fast kinetics, which are thought to facilitate oscillations in the gamma range (20-80Hz; Wilson, Kunos, & Nicoll, 2001; Wilson & Nicoll, 2002). Both CCK- and PV-expressing interneurons may play a role in disruption of oscillations (Caballero & Tseng, 2012; Sherif, Cortes-Briones, Ranganathan, & Skosnik, 2018). Interestingly, while PV-expressing interneurons are broadly devoid of CB_1 receptors (Caballero & Tseng, 2012; Katona et al., 1999; Marsicano & Lutz, 1999), PV- and CCK-expressing interneurons are coupled at least in the hippocampus (Armstrong & Soltesz, 2012, as cited in Caballero & Tseng, 2012). Excitation of PV-expressing interneurons may be decreased by CB_1-mediated reduction of glutamate release by THC, while activation of CB_1 receptors on CCK-expressing interneurons may reduce GABA release, causing disinhibition of glutamatergic pyramidal cells (Sherif et al., 2018).

While these alterations in neural oscillations are seen at much faster frequencies than those examined in BOLD signals using RSFC (Britz, Van De Ville, & Michel, 2010; Fox et al., 2005), differences in GABA and glutamate concentrations have recently been found to relate to RSFC using proton magnetic resonance spectroscopy. In healthy subjects, glutamate and the

glutamate/GABA ratio were positively correlated with intrinsic functional connectivity in the DMN in healthy men, while GABA alone was negatively correlated with this connectivity (Kapogiannis, Reiter, Willette, & Mattson, 2013). Additionally, higher glutamate concentration is associated with stronger RSFC between the mPFC and certain subcortical structures (Duncan et al., 2013). Task-based studies of GABA and/or glutamate concentrations within the DMN also find that strength of BOLD responses (Enzi et al., 2012; Falkenberg, Westerhausen, Specht, & Hugdahl, 2012; Northoff et al., 2007) and DMN deactivation (Hu, Chen, Gu, & Yang, 2013) often related to concentration of these neurotransmitters.

While GABA and glutamate concentrations relate to RSFC within the DMN in healthy controls, far fewer studies exist in cannabis users relating concentrations of these neurotransmitters to RSFC. With chronic cannabis use, lower GABA, glutamate, and neurometabolites are seen in the anterior cingulate cortices of adolescent cannabis users relative to healthy controls (Prescot et al., 2011; Prescot, Renshaw, & Yurgelun-Todd, 2013). Lower glutamate is seen in the basal ganglia of adult users (Chang, Cloak, Yakupov, & Ernst, 2006), and in the dorsal striatum of female (but not male) young adult cannabis users (Muetzel et al., 2013). Monthly cannabis use and dorsal ACC glutamate levels predict dorsal ACC--right nucleus accumbens connectivity in young adults (Newman et al., 2019). To our knowledge, no study to date has directly examined the relationship between GABA concentrations and RSFC in young adult cannabis users.

In summary, it is possible that chronic cannabis use disrupts CB_1 receptors' modulatory activity of neurotransmitters such as GABA and glutamate (Howlett et al., 2002; Pertwee, 2008; Wilson & Nicoll, 2002), and this disruption may cause a change in communication between brain regions and networks (Caballero & Tseng, 2012). However, this mechanism is solely

hypothesis, and much further study needs to be conducted to examine and clarify the relationships between chronic THC exposure, the endocannabinoid system, neurotransmitters, neural oscillations, and RSFC in adolescents and young adults.

While some recovery of cognitive function is seen with abstinence from cannabis in this age group (Lisdahl et al., 2013; Wallace et al., 2020), it appears that subtle differences in communication between brain regions may persist in cannabis users even with 3 weeks of abstinence from cannabis use. In cannabis users, these subtle communication differences are associated with downstream differences in cognition. Given that brain development is still occurring in this age group (Giedd et al., 1999), the adolescent brain is particularly sensitive to the effects of THC (Adriani & Laviola, 2004). Research has repeatedly suggested that earlier exposure to substances is associated with even poorer outcomes in cognition than typically seen in later-onset cannabis users. Thus, encouraging our youth to minimize, eliminate, or delay their onset substance use until after age 18 may reduce some of the exaggerated difficulties seen in early-onset users (Lisdahl et al., 2013). Interventions such as personalized feedback, psychoeducation, and physical activity may help youth delay their onset of substance use, and/or ameliorate some of the cognitive abnormalities seen in adolescent and young adult chronic substance users (Lisdahl et al., 2013).

4.3 Limitations

The present study includes several limitations. The design is cross-sectional in nature and thus precludes discussion of causality. Additionally, the sample size is relatively small, particularly of female cannabis users. Prospective large-scale longitudinal studies such as the Adolescent Brain and Cognitive Development (ABCD) Study™ can address these concerns. The cannabis users present in this sample, on average, used cannabis a few times weekly to roughly

daily. Our goal was to capture the regular, recreational user, and thus the effects seen in the present study may not generalize to lighter or heavier users. These data were collected prior to recent trends of vaping cannabis. Inhalation of cannabis vapor may be safer for the user than inhalation of cannabis smoke from combustion (Giroud et al., 2015; Loflin & Earleywine, 2015), and it is possible that, similar to nicotine cigarettes (Yang & Liu, 2003), compounds in cannabis smoke separate from THC itself may cause damage. As vaping of cannabis is on the rise in youth (National Institute on Drug Abuse, 2019), future studies should examine effects of smoked *and* vaped cannabis on resting state functional connectivity in the DMN. Lastly, the resting state scan length in the present study was 8 minutes. While this is slightly longer than average (Birn et al., 2013), and while the DMN can consistently be identified in resting-state scans (Damoiseaux et al., 2006), reliability of data would likely improve with greater scan time (Anderson, Ferguson, Lopez-Larson, & Yurgelun-Todd, 2011; Birn et al., 2013). Indeed, deeper examination of individual differences requires a minimum of 25 minutes of scan time (Anderson et al., 2011).

4.4 Conclusions

In summary, cannabis users demonstrated weaker resting state functional connectivity between the left PCC and various DMN nodes, and stronger connectivity between the left PCC and the supramarginal gyrus and various cerebellar clusters. Stronger connectivity between the left PCC and the left cerebellum was associated with poorer attention and working memory in cannabis users. While the group by gender interaction was not significant, this was potentially due to a small sample size for interaction effects. These differences in connectivity may be due to chronic THC's interaction with GABAergic and glutamatergic neurons, as GABA and glutamate concentrations relate to strength of RSFC (Duncan et al., 2013; Enzi et al., 2012; Falkenberg et al., 2012; Hu et al., 2013; Kapogiannis et al., 2013; Northoff et al., 2007),

including in cannabis users (Newman et al., 2019). These findings suggest that even after 3 weeks of monitored abstinence, brain communication remains abnormal in chronic cannabis users. Future studies should include a larger sample size and examination of mechanisms by which chronic cannabis use is associated with differences in RSFC in the DMN.

Figure 1. Weaker connectivity (in blue) between the left PCC seed and A) left PCC/precuneus, B) right lingual gyrus/right precuneus, C) left parahippocampal gyrus and right Rolandic operculum/Heschl's gyrus observed in cannabis users compared to controls.

1A. **1B.** **1C.**

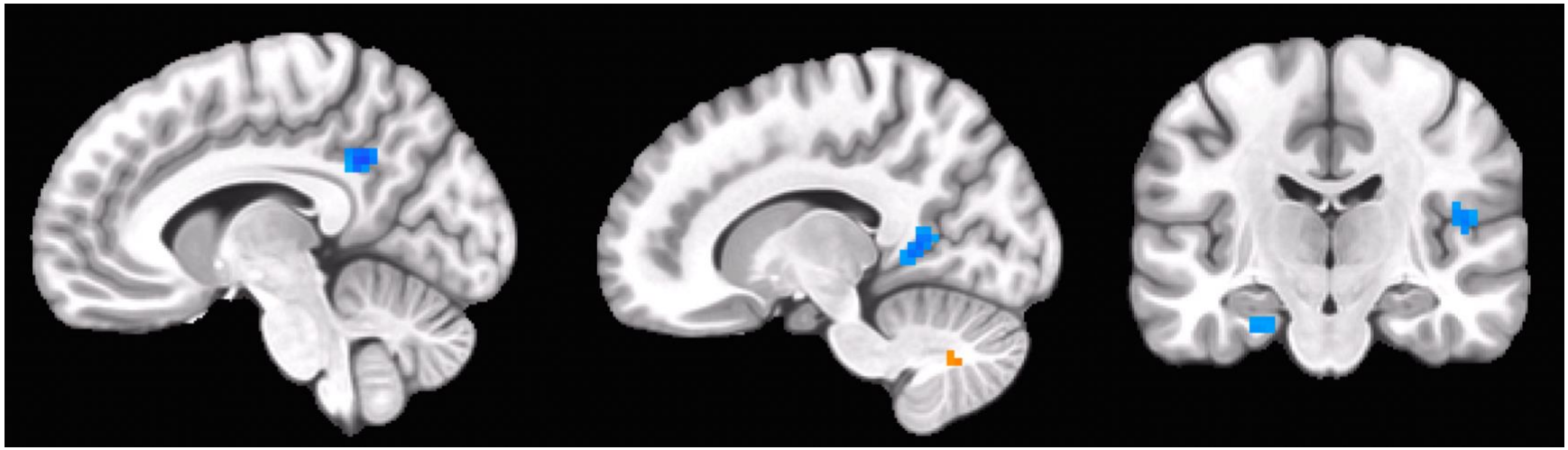

Figure 1A. Weaker connectivity is seen between the left PCC and the left PCC/precuneus.

Figure 1B. Weaker connectivity is seen between the left PCC and the right lingual gyrus/right precuneus.

Stronger connectivity is seen between left PCC and right cerebellum VII/Crus II (pictured in orange, elaborated upon in Figure 2)

Figure 1C. Weaker connectivity is seen between the left PCC and the left parahippocampal gyrus (left), and the right Rolandic operculum/Heschl's gyrus (right).

Figure 2. Stronger connectivity (in orange) between the left PCC seed and A) the left cerebellum Crus II and right cerebellum VII/Crus II, B) left cerebellum Crus I, C) left cerebellum VIII, and D) left supramarginal gyrus observed in cannabis users compared to controls.

2A. **2B.** **2C.** **2D.**

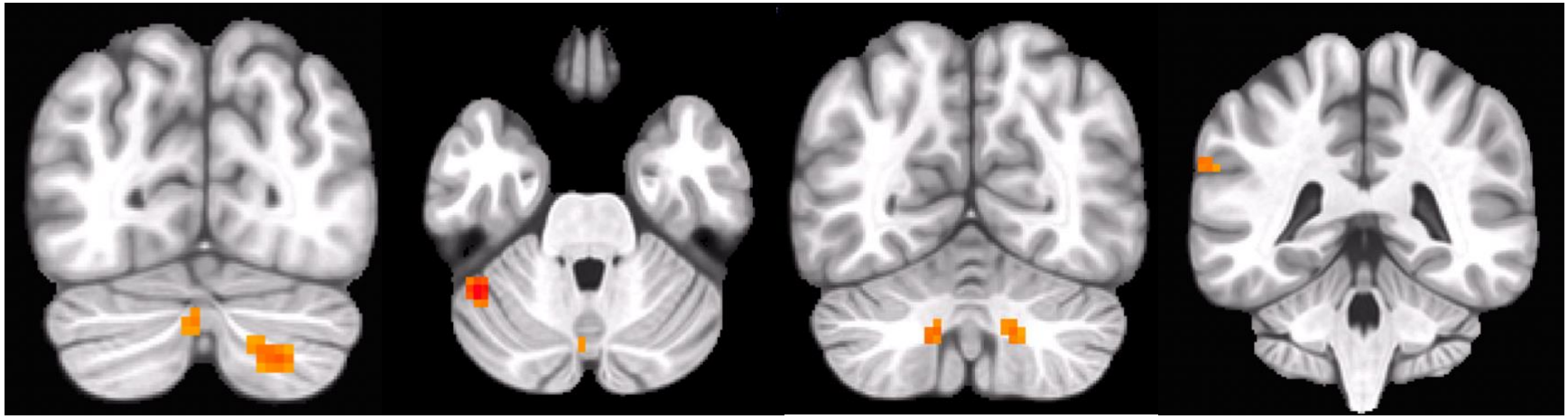

Figure 2A. Stronger connectivity is seen between the left PCC and the left cerebellum Crus II (left) and the right cerebellum VII/Crus II (right).

Figure 2B. Stronger connectivity is seen between the left PCC and the left cerebellum Crus I (left), and Crus II (right, see Figure 2A).

Figure 2C. Stronger connectivity is seen between the left PCC and the left cerebellum VIII (left) and right cerebellum VII/Crus II (right, see Figure 2A).

Figure 2D: Stronger connectivity is seen between the left PCC and the left supramarginal gyrus.

Table 1. Demographic and Drug Use Information

PY = Past Year

M (SD) [Range]	Male Cannabis Users (n=24)	Female Cannabis Users (n=13)	Male Controls (n=18)	Female Controls (n=22)	p
Age	21.71 (2.27) [17-26]	21.62 (2.26) [19-25]	20.89 (2.91) [16-25]	21.09 (2.49) [16-25]	.69
Ethnicity (% Caucasian)	66.67%	53.85%	72.22%	72.73%	.10
Years of Education	14.04 (1.71) [11-18]	14.31 (1.49) [12-17]	14.39 (2.77) [9-19]	14.32 (1.91) [11-18]	.95
WRAT-4 Reading Score	109.25 (13.93) [80-133]	100.77 (7.00) [93-120]	107.89 (8.58) [92-126]	104.64 (10.68) [87-133]	.12
BDI-II Score	5.04 (4.47) [0-19]	6.38 (5.11) [1-18]	3.39 (3.90) [0-10]	2.23 (2.45) [0-8]	**.02**[a]
Session 1 STAI-State Score	28.58 (5.75) [21-44]	31.23 (7.14) [20-45]	25.78 (6.45) [20-46]	28.32 (7.38) [20-51]	.17
Session 4 STAI-State Score	26.13 (4.78) [20-36]	26.69 (7.72) [20-43]	26.72 (5.37) [20-39]	26.41 (7.35) [20-42]	.99
PY Cannabis Use (Joints + Conc)	475.95 (511.07) [24-2306]	260.60 (257.32) [13-879]	0.82 (1.62) [0-5]	0.05 (0.21) [0-1]	**<.001**[b]
Lifetime Cannabis Use (Joints)	1433.50 (1581.92) [125-6000]	837.23 (583.33) [101-2314]	2.33 (4.97) [0-20]	2.52 (5.11) [0-20]	**<.001**[b]
Length of Abstinence from Cannabis at MRI Scan	37.00 (28.69) [18-151]	29.54 (10.53) [20-58]	151.20 (139.66) [32-332]	260.00 (--) [260-260] (N=1)	**<.001**
Age Cannabis Use Onset	15.88 (2.15) [12-20]	15.62 (2.22) [13-21]	19.50 (1.76) [18-22]	18.33 (2.12) [15-22]	**<.001**[c]
Age of Onset Regular Cannabis Use	17.31 (1.90) [14-21]	17.62 (1.56) [15-21]	----	----	.63
PY Cigarettes	253.81 (553.12) [0-1867]	42.37 (68.35) [0-232]	0.28 (0.46) [0-1]	0.80 (2.64) [0-12]	**.02**[d]
Session 5 Cotinine Level	2.17 (2.16) [0-6]	1.23 (0.83) [0-3]	1.00 (0.69) [0-3]	1.18 (0.73) [0-3]	**.03**[e]
PY Alcohol Use (drinks)	353.70 (304.29) [24-1120]	221.58 (242.63) [37-883]	158.08 (224.83) [0-698]	68.43 (97.89) [0-450]	**.001**[b]
PY Other Drug Use	5.73 (8.58) [0-37]	4.74 (7.85) [0-27]	0.56 (2.12) [0-9]	0.05 (0.21) [0-1]	**<.01**[b]

[a] *Female Cannabis Users significantly higher than Female Controls.*

[b] *Male Cannabis Users significantly higher than Male and Female Controls.*

[c] *Male and Female Cannabis Users significantly higher than Male and Female Controls.*

[d] *Male Cannabis Users significantly higher than Female Controls. (Marginally higher than male controls, p=.053)*

[e] *Male Cannabis Users significantly higher than Male Controls.*

Table 2. Significant Left PCC Connectivity Clusters

	Location	# Voxels	MNI Coordinates (x,y,z)	Maximum t
Main Effect of Group (CAN < CTL)	R Precuneus/R Lingual Gyrus	33	12, -51, 6	-4.08
	L PCC/L Precuneus	21	-9, -51, 33	-4.30
	R Rolandic Operculum/R Heschl's Gyrus	14	48, -18, 12	-3.84
	L Parahippocampal Gyrus	12	-21, -15, -24	-3.72
Main Effect of Group (CAN > CTL)	R Cerebellum VII/Crus II	51	24, -74, -45	4.17
	L Cerebellum Crus I	27	-45, -51, -30	4.84
	L Cerebellum VIII	13	-12, -63, -39	4.09
	L Supramarginal Gyrus	11	-66, -42, 30	3.92
	L Cerebellum Crus II	9	-3, -75, -33	3.84
Main Effect of Gender (M > F)	R Temporal Pole	10	54, 9, -18	3.73
Session 5 Cotinine	R Cerebellum Crus I	11	48, -72, -21	-4.19
Past Year Alcohol Drinks	R Precuneus	9	21, -51, 24	4.03

L = Left, R = Right

Table 3. Correlations Between Significant Clusters and Performance on Selected Neuropsychological Measures in Cannabis Users

		R Crblm VII	R Lingual Gyr/R Precuneus	L Crblm (Crus I)	L PCC/L Precuneus	R RO/R Heschl's Gyr	L Crblm VIII	L paraHC Gyr	L Supra-marginal Gyr	L Crblm (Crus II)
PASAT Total Correct Raw Score	Pearson Correlation	-0.051	0.091	**-.346***	0.001	-0.068	0.016	-0.104	-0.095	0.019
	Sig. (2-tailed)	0.764	0.593	**0.036**	0.994	0.691	0.926	0.539	0.577	0.912
DKEFS Color-Word Interference Inhibition Condition Completion Time Raw Score	Pearson Correlation	0.087	-0.178	-0.082	0.258	-0.072	0.072	0.146	0.025	0.042
	Sig. (2-tailed)	0.607	0.292	0.627	0.123	0.671	0.671	0.388	0.885	0.803
CVLT-II Trial 1 Raw Score	Pearson Correlation	-0.225	0.124	-0.112	0.088	0.059	-0.299	-0.154	-0.278	-0.156
	Sig. (2-tailed)	0.180	0.464	0.510	0.605	0.731	0.073	0.364	0.096	0.356
CVLT-II Total Correct (Trials 1-5) Raw Score	Pearson Correlation	-0.236	0.039	-0.097	0.156	0.055	**-.345***	-0.005	-0.127	-0.315
	Sig. (2-tailed)	0.159	0.819	0.567	0.356	0.744	**0.036**	0.979	0.455	0.057
CVLT-II Long Delay Free Recall Raw Score	Pearson Correlation	-0.133	-0.050	0.247	0.129	-0.108	-0.143	-0.082	-0.135	-0.283
	Sig. (2-tailed)	0.433	0.768	0.140	0.447	0.526	0.399	0.628	0.426	0.090
Ruff 2 & 7 Total Speed Raw Score	Pearson Correlation	-0.229	-0.006	-0.053	0.009	-0.221	-0.298	0.140	-0.170	-0.321
	Sig. (2-tailed)	0.172	0.972	0.756	0.958	0.189	0.074	0.409	0.316	0.052
Ruff 2 & 7 Total Accuracy Raw Score	Pearson Correlation	0.027	0.074	0.220	0.102	0.055	0.047	-0.120	-0.039	0.185
	Sig. (2-tailed)	0.873	0.663	0.191	0.547	0.747	0.782	0.479	0.819	0.272

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

Abbreviations: Crblm = Cerebellum, Gyr = Gyrus, L = Left, R = Right, paraHC = parahippocampal, RO = Rolandic operculum

Table 4. Correlations Between Significant Clusters and Performance on Selected Neuropsychological Measures in Controls

		R Crblm VII	R Lingual Gyr/R Precuneus	L Crblm (Crus I)	L PCC/L Precuneus	R RO/R Heschl's Gyr	L Crblm VIII	L paraHC Gyr	L Supra-marginal Gyr	L Crblm (Crus II)
PASAT Total Correct Raw Score	Pearson Correlation	-0.119	-0.101	0.013	-0.003	-0.152	0.133	-0.176	-0.026	0.027
	Sig. (2-tailed)	0.466	0.536	0.938	0.984	0.351	0.415	0.277	0.872	0.868
DKEFS Color-Word Interference Inhibition Condition Completion Time Raw Score	Pearson Correlation	-0.033	0.028	0.052	-0.009	0.283	0.020	0.117	0.102	-0.217
	Sig. (2-tailed)	0.842	0.862	0.748	0.956	0.077	0.901	0.472	0.533	0.179
CVLT-II Trial 1 Raw Score	Pearson Correlation	0.147	0.047	0.116	0.109	0.101	0.304	0.215	-0.054	-0.106
	Sig. (2-tailed)	0.365	0.772	0.477	0.504	0.536	0.056	0.183	0.738	0.514
CVLT-II Total Correct (Trials 1-5) Raw Score	Pearson Correlation	0.041	-0.006	-0.166	0.005	0.097	0.066	0.033	-0.094	-0.039
	Sig. (2-tailed)	0.803	0.969	0.305	0.974	0.553	0.684	0.842	0.564	0.812
CVLT-II Long Delay Free Recall Raw Score	Pearson Correlation	0.065	-0.071	-0.157	0.081	0.034	0.046	0.190	0.002	0.051
	Sig. (2-tailed)	0.689	0.663	0.334	0.618	0.833	0.776	0.241	0.988	0.754
Ruff 2 & 7 Total Speed Raw Score	Pearson Correlation	-0.140	-0.137	-0.184	**.342***	-0.086	-0.087	0.000	-0.100	-0.089
	Sig. (2-tailed)	0.389	0.401	0.255	**0.031**	0.596	0.595	0.999	0.541	0.585
Ruff 2 & 7 Total Accuracy Raw Score	Pearson Correlation	-0.089	0.033	0.042	-0.243	-0.238	-0.039	-0.242	-0.276	0.046
	Sig. (2-tailed)	0.584	0.841	0.797	0.130	0.138	0.813	0.132	0.085	0.780

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

Abbreviations: Crblm = Cerebellum, Gyr = Gyrus, L = Left, R = Right, paraHC = parahippocampal, RO = Rolandic operculum

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Megan M. Ritchay

(formerly Megan M. Kangiser)
University of Wisconsin-Milwaukee

Education

In progress	Ph.D.	Psychology, Clinical Psychology Track University of Wisconsin-Milwaukee (UWM) Dissertation (Oral Defense Passed May 2020): *Resting State Functional Connectivity in the Default Mode Network: Relationships Between Cannabis Use, Gender, and Cognition in Adolescents and Young Adults* Advisor: Krista M. Lisdahl, Ph.D. Current GPA: 3.97
2018	M.S.	Psychology University of Wisconsin-Milwaukee (UWM) Thesis: *Nicotine Effects on White Matter Microstructure in Male and Female Young Adults* Advisor: Krista M. Lisdahl, Ph.D. Cumulative GPA: 3.97
2015	B.A.	Psychology, Magna Cum Laude Creighton University Advisor: Dustin J. Stairs, Ph.D. Cumulative GPA: 3.73; Psychology GPA: 3.95

Research Experience

2015 – Present **Graduate Research Assistant**, Brain Imaging and Neuropsychology (BraIN) Lab, UWM. *PI*: Krista M. Lisdahl, Ph.D.

- Assist on the Adolescent Brain and Cognitive Development (ABCD; abcdstudy.org), a landmark longitudinal NIH initiative to examine the impact of various health behaviors on the developing brain in a cohort of 10,000 children over 10 years.
    - Duties include: recruiting children and families at local community events, screening parents for study eligibility, running research sessions including psychiatric interview (K-SADS) and psychological symptom questionnaires (e.g. CBCL, ASR), engage in suicide risk assessment, supervise and train staff and undergraduate students with the ABCD protocol.

Funding source: U01 DA041025, NIH/NIDA; PI: Lisdahl, K.M.

- Assist on a study examining the effects of marijuana use on adolescent and emerging adult neurocognition as well as the potential influence of factors such as gender, alcohol use, life stress, and exercise. Longitudinal effects at 2-year follow-up are also assessed.
    - Responsibilities include: participant recruitment and screening (including semi-structured interview), neuropsychological testing, bioassays, and VO_2 aerobic fitness testing.

Funding source: R01 DA030354, NIDA; PI: Lisdahl, K.M.

2016 – 2017 **Research Assistant**, Integration of Standing Desks in Elementary Schools to Reduce Sedentary Behavior and Improve Neuropsychological Functioning. UWM, Kinesiology and Psychology Departments
PI: Ann Swartz, Ph.D.; *Co-I and Neuropsychology Supervisor*: Krista M. Lisdahl, Ph.D.

- Conducted assessments of 3rd-6th grade children using NIH Toolbox at baseline, 4 months, and 8 months over a year-long study examining the effects of use of standing desks in school on neuropsychological functioning, posture, and physical activity.

Funding source: SAFCO Products Company

2012 – 2015 **Research Assistant**, Psychopharmacology Lab, Creighton University. PI: Dustin J. Stairs, Ph.D.

- Conducted experiments with rodents using behavioral pharmacology techniques, including self-administration and conditioned place preference procedures.
    - Other skills include injections in awake rodents, heart catheterization surgeries, and preparation of psychoactive drugs. Responsible for daily care and handling of animals, including catheterized animals.
- Submitted a competitive proposal for a summer research fellowship in 2013 and 2014; awarded in 2014.

Funding source (2014): **Ferlic Undergraduate Summer Research Scholarship** (PI: Kangiser, M.M.; Mentor: Stairs, D.J.)

Clinical Training and Experience

2020 – 2021 (Anticipated) Doctoral Internship, Clinical Psychology, Neuropsychology Track; Clement J. Zablocki VA Medical Center, Milwaukee, WI

2019 – 2020 Neuropsychology Practicum Extern at the Clement J. Zablocki VA Medical Center, Milwaukee, WI

- DCT: James Hart, Ph.D. Supervisors: Angela Gleason, Ph.D., ABPP-CN, Eric R. Larson, Ph.D., ABPP-CN, Kathleen M. Patterson, Ph.D., ABPP-CN, Leia Vos, Ph.D. Post-doctoral supervisors: Allison Midden, Ph.D., Jared Rensberger, Ph.D.

- Conduct and score neuropsychological testing for male and female Veterans diverse in age and disability status at the Milwaukee VAMC in an outpatient setting.
- Types of cases seen include various memory disorders (e.g. MCI vs. dementia vs. pseudodementia; potential etiologies including vascular, Lewy body, Alzheimer's), TBI, movement disorders, ADHD, psychiatric, and complex vascular cases.
- Completed one full assessment per week; write reports under faculty supervision.
- Attend neuropsychology case conferences.

2018 – 2019 Neuropsychology Extern at the Medical College of Wisconsin (MCW), Wauwatosa, WI

- DCT: Laura Umfleet, PsyD. Supervisors: Julie Bobholz, Ph.D., ABPP-CN, Julie Janecek, Ph.D., ABPP-CN, Michael McCrea, Ph.D., ABPP-CN, Sara Swanson, Ph.D., ABPP-CN, and Laura Umfleet, PsyD. Post-doctoral mentor: Katherine Reiter, PhD.
- Conducted and scored neuropsychological testing at MCW for clientele diverse in age (adolescent, adult, older adult), ethnicity, and referral question.
- Types of cases seen included memory disorders, neuro-oncology, TBI (outpatient and in interdisciplinary clinic), pre- and post-surgical epilepsy, normal pressure hydrocephalus, learning difficulties, ADHD, congenital heart disease, and movement disorders.
- Wrote 27 comprehensive reports under faculty supervision.
- Attend didactic experiences such as case conferences, neuropsychology didactics, awake brain surgery, and Wada test.

2017 – 2019 Therapy Practicum at the University of Wisconsin-Milwaukee Psychology Clinic

- Perform cognitive-behavioral therapy (CBT) with clients on eating disorder specialty and generalist teams in adolescents and adults. Supervisors: Stacey Nye, Ph.D. FAED and Robyn Ridley, Ph.D.

2016 – 2017 Assessment Practicum at the University of Wisconsin-Milwaukee Psychology Clinic

- Conducted learning disability and psychodiagnostic assessments using a range of cognitive, achievement, and neuropsychological measures, as well as symptom and behavioral questionnaires in adolescents and adults.
- Completed clinical interviews, reports, and feedback sessions. Supervisors: Hanjoo Lee, Ph.D. and Kristin Smith, Ph.D.

2016 – 2017 Consultant, Comprehensive Clinical and Consulting Services, Milwaukee, WI

- Conduct assessments, including cognitive and visual-motor measures, with individuals at the clinic.
  Supervisor: Pamela Schaefer, Ph.D.

2014 Undergraduate Internship – CHI Health Immanuel, Omaha, NE
Behavioral Services, Child/Adolescent Partial Hospitalization Program

- Observed formal intake assessments, daily charting, group therapy, and individual therapy. Provided support in group therapy and education groups. Assisted therapists with daily tasks and play with children.
  Faculty Supervisor: Amy Badura Brack, Ph.D.

Grants & Fellowships

2017 – Present Advanced Opportunity Program Fellowship Recipient, University of Wisconsin-Milwaukee.

- Total costs: full cost of tuition; stipend; travel funding; benefits package.
- Renewed for 2018-2019 and 2019-2020 school years.
- A state-funded fellowship for underrepresented minority or non-minority graduate students at UWM.
  - Classification - Underrepresented non-minority

2018 Department of Psychology Summer Graduate Research Fellowship, University of Wisconsin-Milwaukee. Total costs: $4,266.

2014 Ferlic Undergraduate Summer Research Scholarship, Creighton University. Total costs: $5000.

- A competitive in-house grant for undergraduate research in the sciences

Honors and Awards

2018 CPDD Travel Award for Early Career Investigators to the annual meeting of the College on Problems of Drug Dependence, San Diego, CA, $1525

2017 NIDA Women & Sex/Gender Differences Junior Investigator Travel Award to the annual meeting of the College on Problems of Drug Dependence, Montreal, QC, Canada, $1000

2015 – 2017 Chancellor's Graduate Student Award, University of Wisconsin-Milwaukee, $3500/year

- A University of Wisconsin-Milwaukee Graduate School merit-based award

2015	Department of Psychology Award for Outstanding Scholarship, Creighton University
2011 – 2015	Creighton University Academic Scholarship Recipient, $14,000/year
2011	Creighton University Magis Scholarship Recipient

Peer-Reviewed Publications

1. **Kangiser, M.M.,** Thomas, A.M., Kaiver, C.M., & Lisdahl, K.M. (2020). Nicotine effects on white matter microstructure in young adults. *Archives of Clinical Neuropsychology, 35*(1), 10-21. doi: 10.1093/arclin/acy101.
2. **Kangiser, M.M.,** Lochner, A.M., Thomas, A.M., & Lisdahl, K.M. (2019). Gender moderates chronic nicotine effects on verbal memory in young adults. *Substance Use and Misuse, 54*(11), 1812-1824. doi: 10.1080/10826084.2019.1613432.
3. Maple, K.E., Thomas, A.M., **Kangiser, M.M.**, & Lisdahl, K.M. (2019). Anterior cingulate volume reductions in adolescent and young adult cannabis users: Association with affective processing deficits. *Psychiatry Research: Neuroimaging, 288*, 51-59. doi: 10.1016/j.pscychresns.2019.04.011.
4. **Kangiser, M.M.,** Dwoskin, L.P., Zheng, G., Crooks, P.A., & Stairs, D.J. (2018). Varenicline and GZ-793A differentially decrease methamphetamine and food self-administration under a multiple schedule of reinforcement in rats. *Behavioural Pharmacology, 29*(1), 87-97. doi: 10.1097/FBP.0000000000000340
5. Stairs, D.J., Ewin, S.E., **Kangiser, M.M.,** & Pfaff, M.N. (2017). Effects of environmental enrichment on d-amphetamine self-administration following nicotine exposure. *Experimental and Clinical Psychopharmacology, 25*(5), 393-401. doi: 10.1037/pha0000137
6. Ewin, S.E., **Kangiser, M.M.,** & Stairs, D.J. (2015). Effects of Environmental Enrichment on Nicotine Conditioned Place Preference. *Experimental and Clinical Psychopharmacology, 23*, 387-394. doi: 10.1037/pha0000024

In Preparation

7. Kaiver, C.M., Wallace, A.L., **Ritchay, M.M.,** Mulligan, D.J., Messman, G.M., & Lisdahl, K.M. (In preparation). Association between binge drinking and prefrontal and parietal gyrification in young adults.
8. **Ritchay, M.M.**, Kaiver, C.M., Jennette, K.J., Knecht, B.M., & Lisdahl, K.M. (In preparation). Gender moderates the impact of binge drinking on cognition in young adults.
9. **Ritchay, M.M.,** Huggins, A.A., Wallace, A.L., Larson, C.L., & Lisdahl, K.M. (In preparation). Resting state functional connectivity in the default mode network: Relationships between cannabis use, gender, and cognition in adolescents and young adults.

Book Chapters

1. Stairs, D.J., **Kangiser, M.M.,** Hickle, T., & Bockman, C.S. (2016). Environmental Enrichment and Nicotine Addiction. In V.R. Preedy (Ed.), Neuropathology of Drug Addictions and Substance Misuse; Volume 1: Common Substances of Abuse/Tobacco, Alcohol, Cannabinoids and Opioids (246-253). London: Academic Press.

Presentations

Oral Presentations

1. **Kangiser, M.M.,** Thomas, A.M., Kaiver, C.M., & Lisdahl, K.M. (2018 April). *Nicotine effects on white matter microstructure in male and female young adults.* Talk at the 20th Annual Research Symposium of the Association of Graduate Students in Psychology, University of Wisconsin-Milwaukee, Milwaukee, WI.
2. Stairs, D.J., **Kangiser, M.M.**, Pfaff, M.N., Ewin, S.E., & Dwoskin, L.P. (2015 June). *Effects of varenicline and GZ-793A on methamphetamine and food self-administration under a multiple schedule of reinforcement in rats.* Talk at the annual meeting of the College on Problems of Drug Dependence (CPDD), Phoenix, AZ.
3. **Kangiser, M.M.,** Pfaff, M.N., Ewin, S.E., Dwoskin, L.P., & Stairs, D.J. (2015 April). *Effects of varenicline and GZ-793A on methamphetamine and food self-administration under a multiple schedule of reinforcement in rats.* Honors Day at Creighton University, Omaha, NE.
4. Stairs, D.J., **Kangiser, M.M.,** Ewin, S.E., Salvatore, C.A., Pfaff, M.N., Daugherty, K.A. & Schroeder, M.K. (2014 August) *Effects of environmental enrichment on d-amphetamine self-administration following nicotine exposure.* Talk at the annual meeting for American Psychological Association (APA), Washington, DC.
5. Stairs, D.J., Ewin, S.E., **Kangiser, M.M.**, Salvatore, C.A., & Pfaff, M.N. (2014 June) *Effects of environmental enrichment on amphetamine self-administration under a fixed-ratio and progressive ratio schedule following nicotine exposure.* Talk at the annual meeting for College of Problems of Drug Dependence (CPDD), San Juan, PR.

Poster Presentations

1. Leclaire, K.N., **Kangiser, M.,** Hase, E., & Lisdahl, K. (2020 June). *Interaction effects of nicotine and alcohol on white matter microstructure in young adults.* Virtual poster presentation at the 43rd annual Research Society on Alcoholism Conference.
2. Bernal, E. S., **Kangiser, M.M.**, & Lisdahl, K.M. (2019 Apr). *Effects of gender and binge drinking on hippocampal structure of young adults.* Poster presented at the annual meeting of University of Wisconsin-Milwaukee's Undergraduate Research Symposium, Milwaukee, WI.
3. Kaiver, C.M., Wallace, A.L., **Kangiser, M.M.,** Mulligan, D., Messman, G.M., & Lisdahl, K.M. (2019 Feb). *Binge drinking impacts prefrontal gyrification index in young adults.* Poster presented at the annual meeting of the International Neuropsychological Society (INS), New York, NY.
4. **Kangiser, M.M.,** Jennette, K.J., Knecht, B.M., Kaiver, C.M., & Lisdahl, K.M. (2019 Feb). *Gender moderates the impact of binge drinking on cognition in young adults.* Poster presented at the annual meeting of the International Neuropsychological Society (INS), New York, NY.

5. Pfaff, M.N., Ramsey, W.S., Wunsch, C.N., **Kangiser, M.M.**, Ewin, S.E., Chacho, N.M., & Stairs, D.J. (2018 Aug). *Effects of amphetamine and ketamine on responding under an IRT>t schedule of reinforcement.* Poster presented at the annual meeting of the American Psychological Association (APA), San Francisco, CA.
6. **Kangiser, M.M.**, Thomas, A.M., Kaiver, C.M., & Lisdahl, K.M. (2018 June). *Nicotine effects on white matter integrity in male and female young adults*. Poster presented at the annual meeting of the College on Problems of Drug Dependence (CPDD), San Diego, CA.
7. Jennette, K.J., **Kangiser, M.M.**, Knecht, B., & Lisdahl, K.M. (2018 Feb). *The influence of binge drinking behavior on verbal learning and memory strategy in young adults.* Poster presented at the annual meeting of the International Neuropsychological Society (INS), Washington, DC.
8. **Kangiser, M.M.**, Thomas, A.M., Lochner, A.M., Jennette, K.J., & Lisdahl, K.M. (2017 June). *Gender moderates chronic nicotine effects on cognition in young adults.* Poster presented at the annual meeting of the College on Problems of Drug Dependence (CPDD), Montreal, QC, Canada.
9. Maple, K.E., Thomas, A.M., **Kangiser, M.M.,** Gilbart, E.R., & Lisdahl, K.M. (2017 Feb). *Anterior cingulate volume reductions in adolescent and emerging adult cannabis users: Association with affective processing deficits.* Poster presented at the annual meeting of the International Neuropsychological Society (INS), New Orleans, LA.
10. Wright, N.E., **Kangiser, M.M.,** Vitucci, S., Gill, E., & Lisdahl, K.M. (2016 June). *Adolescent and young adult alcohol, marijuana use, and gender effects on depression, anxiety, and apathy*. Poster presented at the annual meeting of the Research Society on Alcoholism (RSA), New Orleans, LA.
11. Pfaff, M.N**. Kangiser, M.M.**, Ewin, S.E., Salvatore, C.A., Daugherty, K.A., Chacho, N.M., Lee, S.S. & Stairs, D.J. (2015 May) *Effects of amphetamine and ketamine on responding under a differential-reinforcement-of-low-rates schedule of reinforcement*. Poster presented to the annual meeting of the Midwestern Psychological Association (MPA), Chicago, IL.
12. **Kangiser, M.M.**, Pfaff, M.N., Ewin, S.E., & Stairs, D.J. (2015 May) *Effects of varenicline and GZ-793A on methamphetamine and food self-administration under a multiple schedule of reinforcement in rats.* Poster presented at the annual meeting of the Midwestern Psychological Association (MPA), Chicago, IL.
13. **Kangiser, M.M.**, Pfaff, M.N. & Stairs, D.J. (2014 Sept) *Effects of varenicline and GZ-793A on methamphetamine and food self-administration under a multiple schedule of reinforcement in rats.* Undergraduate poster presented at the Creighton University, Ferlic Summer Research Program Poster Presentation, Omaha, NE.
14. Ewin, S.E., **Kangiser, M.M.,** Salvatore, C.A., Daugherty, K.A., Pfaff, M.N., Schroeder, M.K., & Stairs, D.J. (2014 May). *Effects of environmental enrichment on d-amphetamine self-administration following nicotine exposure*. Poster presented at the annual meeting of the Midwestern Psychological Association (MPA), Chicago, IL.
15. Angsten, K., Bragdon, A.K., **Kangiser, M.M.,** Salvatore, C.A. Giordano, D.A., Ewin, S.E., Lange, R.C. & Stairs, D.J. (2013 May). *Effects of environmental enrichment on nicotine conditioned place preference.* Poster presented at the annual meeting of the Midwestern Psychological Association (MPA), Chicago, IL.

Teaching Experience

2015 – 2017	Teaching Assistant, *Psychological Statistics* (PSYCH 210), University of Wisconsin-Milwaukee. Instructor: Pamela Schaefer, Ph.D.
2013 – 2014	Teaching Assistant, *Introductory Psychology* (PSY 111), *Research Methods and Statistics I* (PSY 313), *History and Systems of Psychology* (PSY 424), *Physiological Psychology* (PSY 437), *Drugs and Behavior* (PSY 481), Creighton University. Instructor: Dustin J. Stairs, Ph.D.

Professional Memberships

2019 – Present	APA Division 12 – Society of Clinical Psychology Student Member
2018 – Present	APA Division 28 – Psychopharmacology and Substance Abuse Student Affiliate
2018 – Present	Wisconsin Psychological Association Student Affiliate
2017 – Present	APA Division 40 – Society for Clinical Neuropsychology Student Affiliate
2018 – 2019	President – Health Psychology Graduate Students Club, University of Wisconsin-Milwaukee
2018 – 2019	Vice-President – Association of Graduate Students in Neuropsychology, University of Wisconsin-Milwaukee
2016 – 2018	Treasurer – Health Psychology Graduate Students Club, University of Wisconsin-Milwaukee
2013 – Present	Member of Psi Chi
2012 – 2015	Member of the Honors Program, Creighton University