Neural Correlates of Hazardous Alcohol Use Examined Via Structural and Functional Neuroimaging

Neural Correlates of Hazardous Alcohol Use Examined Via Structural and Functional Neuroimaging

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Lay Abstract

The aim of this thesis was to add to the existing literature surrounding neuroimaging in alcohol use disorder. First, we sought to expand the structural neuroimaging literature by conducting a study with a large sample size and examining the cortical thickness of a variety of brain regions in relation to characteristics of alcohol use. Second, we aimed to add to the structural neuroimaging literature again by examining a particular brain tissue in chronic alcohol users via a novel MRI pulse sequence. Finally, we sought to add to the functional neuroimaging literature by examining large-scale resting state brain networks in a sample of people who use alcohol alone or in combination with tobacco or other drugs (i.e., polysubstance users). Together, these studies have contributed new findings to the addictions neuroscience literature by revealing anatomical and functional brain correlates of alcohol and other substance misuse.

Abstract

Introduction: Substance use disorders are often associated with widespread structural and functional abnormalities in the brain. The primary aim of this thesis was to reduce existing ambiguity and explore novel topics in the field of addictions neuroscience by conducting three human neuroimaging studies.

Results: In the first study, individuals who used alcohol were found to have significant inverse associations between drinks in past week, frequency of heavy drinking, and cortical thickness in a majority of regions examined via MRI. These regions included the dorsolateral prefrontal cortex, the inferior frontal gyrus, and the precentral gyrus. In the second study, when we employed a novel MRI pulse sequence to examine intracortical myelin (ICM) in people with alcohol use disorder, we found that the alcohol use disorder group in fact had greater ICM signal than the control participants, leading us to hypothesize a potential inflammation response in the brain from the prolonged use of alcohol. Finally, in the third study, when we explored large-scale brain activity in a sample of people who use alcohol alone or in combination with other substances, we found that those who used three or more substances displayed the least amount of activation in the salience and temporal networks of the brain. A peculiar finding, however, was that dual users of alcohol and cannabis were found to have the most activation in these networks.

Conclusions: Results demonstrate that, indeed, alcohol use is associated with structural and functional abnormalities in the brain. These studies have demonstrated cortical thinning and increased ICM signal in relation to alcohol use broadly. As well, this work has shown that polysubstance use is associated with alterations in various large-scale resting state brain networks. Future research should seek to conduct longitudinal work in order to clarify whether structural and functional brain abnormalities are a cause or a consequence of substance use.

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"And tell me this—I must be absolutely sure—this place I've reached, is it truly Ithaka?"

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List of Abbreviations

ACC	Anterior Cingulate Cortex
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
ART	Artifact Detection Tools
ASSIST	Alcohol, Smoking and Substance Involvement Screening Test
AUD	Alcohol Use Disorder
AUDIT	Alcohol Use Disorder Identification Test
BA	Broadman Area
BOLD	Blood Oxygenation Level Dependent
BRAVO	Brain Volume Imaging
CI	Confidence Interval
CON	Control(s)
CONN	Functional Connectivity Toolbox
CT	Computerized Tomography
CUD	Cannabis Use Disorder
CUDIT	Cannabis Use Disorder Identification Test
DICOM	Digital Imaging and Communications in Medicine
DLPFC	Dorsolateral Prefrontal Cortex
DMN	Default Mode Network
DSM	Diagnostic and Statistical Manual of Mental Disorders
DUDIT	Drug Use Disorder Identification Test
EEG	Electroencephalogram
FDR	False Discovery Rate
fNIRS	Functional Near-Infrared Spectroscopy
fMRI	Functional Magnetic Resonance Imaging
FOV	Field of View
FSL	FMRIB Software Library
FTND	Fagerström Test for Nicotine Dependence
FWHM	Full-Width Half-Maximum
GE	General Electric
GIFT	Group ICA fMRI Toolbox
HCP	Human Connectome Project
IC	Independet Component
ICA	Independet Component Analysis
ICM	Intracortical Myelin
IFG	Inferior Frontal Gyrus

ITG	Inferior Temporal Gyrus
IUD	Intrauterine Device
LSD	Lysergic Acid Diethylamide
M1	Primary Motor Area
MDL	Minimum Description Length
MDMA	3,4-Methylenedioxymethamphetamine
MEG	Magnetoencephalography
MMP	Multi-Modal Parcellation
MNI	Montreal Neurological Institute
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
MTG	Middle Temporal Gyrus
NAA	N-acetylaspartate
NIAAA	National Institute on Alcohol Abuse and Alcoholism
NIDA	National Institute on Drug Abuse
NIFTI	Neuroimaging Informations Technology Initiative
NIH	National Institue of Health
OFC	Orbital Frontal Cortex
PCC	Posterior Cingulate Cortex
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PSU	Polysubstance Use / User(s)
ROI	Region of Interest
rs-FC	Resting State Functional Connectivity
SCID	Strucutred Clinical Interview - DSM
SFG	Superior Frontal Gyrus
SPECT	Single-Photon Emission Computed Tomography
SPM	Statistical parametric mapping
SPSS	Statistical Package for the Social Sciences
SSAGA	Semi-Structured Assessment for the Genetics of Alcoholism
STG	Superior Temporal Gyrus
SUD	Substance Use Disorder
T1	Longitudinal Relaxation TIme
T2	Transverse Relaxation Time
TE	Time to Echo
TI	Inversion Time
TR	Relaxation Time
VMPFC	Ventromedial Prefrontal Cortex
WHO	World Health Organization

Declaration of Academic Achievement

Chapter 2: The data used in this project are from the Human Connectome Project, WU-Minn Consortium funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research and by the McDonnell Center for Systems Neuroscience at Washington University in St. Louis. The authors are deeply appreciative to the Human Connectome Project for open access to its data. Data in this chapter was analyzed by V.Morris with aid from M. Amlung and M. Owens. Manuscript composition was carried out by V.Morris with contributions from M. Amlung, and suggestions from S.K. Syan, T. Petker. M. Amlung, L. Sweet, A. Oshri, and J. MacKillop aided with formation of the research questions and data analysis plans.

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Chapter 4: All data presented in this chapter was collected by V. Morris as part of a larger neuroimaging study conducted by M. Amlung. Data analyses were performed by V. Morris with significant aid from S.K. Syan. The manuscript was composed by V. Morris with aid from M. Amlung and S.K.Syan. M. Amlung and J. MacKillop aided in the formation of the research questions and the development of the manuscript.

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Chapter 1: Introduction

1.1 Substance Use Disorders

1.1.1 Clinical Definition

A substance use disorder (SUD) is the continued use of a substance, including alcohol, despite the negative impact and negative consequences that accompany this use (American Psychiatric Association, 2013). In the most recent version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; American Psychiatric Association, 2013), there are ten classes of drugs that SUD's may result from which include: alcohol, caffeine, cannabis, hallucinogens, inhalants, opioids, sedatives, stimulants, tobacco, as well as other or unknown substances. The DSM-5 also states that there are eleven criteria that can be used to diagnose, define, and determine the severity of a substance use disorder. The criteria are as follows: (i) using more of a substance than planned, or using a substance for a longer interval than desired, (ii) inability to cut down despite desire to do so, (iii) spending substantial amount of the day obtaining, using, or recovering from substance use, (iv) cravings or intense urges to use, (v) repeated usage causes or contributes to an inability to meet important social, or professional obligations, (vi) persistent usage despite user's knowledge that it is causing frequent problems at work, school, or home, (vii) giving up or cutting back on important social, professional, or leisure activities because of use, (viii) using in physically hazardous situations, or usage causing physical or mental harm, (ix) persistent use despite the user's awareness that the substance is causing or at least worsening a physical or mental problem, (x) an increase in tolerance (needing to use increasing amounts of a substance to obtain its desired effects), (xi) withdrawal symptoms

(characteristic group of physical effects or symptoms that emerge as amount of substance in the body decreases)(American Psychiatric Association, 2013).

For the diagnosis of a SUD, the DSM-5 guidelines state that an individual must be distressed by their substance use and must also meet a minimum of two of the above criteria in the past twelve months (American Psychiatric Association, 2013). The DSM-5 also includes specifiers which allow for a SUD to be diagnosed as mild, moderate, or severe (American Psychiatric Association, 2013). A mild SUD is classified as the endorsement of two or three criteria, a moderate SUD is classified as the endorsement of four or five criteria, and a severe SUD is classified as an endorsement of six or more criteria (American Psychiatric Association, 2013).

1.1.2 Prevalence and Heritability

It has been reported that roughly 35 million individuals globally struggle with substance use or have a diagnosed SUD (United Nations Office on Drugs and Crime, 2019). It has also been reported that males tend to have higher rates of SUD's than females (Substance Abuse and Mental Health Services Administration, 2014a) and that individuals who begin using substances before the age of 17 will be more likely to develop an SUD (Substance Abuse and Mental Health Services Administration, 2014b). According to a reported published by Statistics Canada in 2018, roughly 20% of Canadians aged 15 and older had experienced an SUD in their lifetime (Pearson, Janz, & Ali, 2013), with alcohol being the most common substance that individuals met SUD criteria for (Pearson et al., 2013). In the United States, it is reported that roughly 8% of Americans aged 12 and older have had an SUD in the past year (McLellan, 2017), with alcohol and tobacco being the most detrimental. The Center for Disease Control has reported that alcohol use accounts for the loss of 95,000 American lives each year (National Center for Chronic

Disease Prevention and Health Promotion, 2020a), while tobacco is responsible for over 480,000 deaths each year in America (National Center for Chronic Disease Prevention and Health Promotion, 2020b).

Substance use disorders also appear to be highly heritable, with heritability estimates of SUD's ranging from 0-87% in males (median of 53%) and 0-77% in females (median of 55%)(Merikangas & McClair, 2012). It has also been reported that heritability rates of alcohol use can range from 40-60% (Schuckit, 2009), for tobacco use can range from 50-60% (MD Li & Burmeister, 2009), and for illicit drug use can range from 30-80% (Agrawal & Lynskey, 2008; MD Li & Burmeister, 2009). Twin and adoption studies have consistently shown that the development of SUD's appears to be the result of both genetic and environmental factors (Volkow, Wang, Fowler, & Tomasi, 2012).

1.1.3 Neurobiological Models of Substance Use Disorder

Substance use disorder, which was once regarded as a character flaw or personal weaknesses, is now understood to be a chronic and debilitating illness rooted in genetic, environmental, behavioral, and social factors (Nelson, Bundoc-Baronia, Comiskey, & McGovern, 2017). A variety of well-supported scientific evidence has shown that SUD's are in fact chronic brain diseases that often follow a three-stage cycle of: (i) intoxication, (ii) withdrawal, and (iii) preoccupation (Longo, Volkow, Koob, & McLellan, 2016; Nelson et al., 2017). This cycle, which is associated with specific regions of the brain, may become stronger and more debilitating until an individual is unable to control their substance use (Nelson et al., 2017). Previous research has found three regions of the brain that appear to be particularly important in the onset and progression of SUD's and the three-stage cycle of use, namely: the basal ganglia, the amygdala, and the prefrontal cortex (Longo et al., 2016; Nelson et al., 2017).

The basal ganglia are a group of structures found deep within the brain that are responsible for a variety of tasks such as motivation, reward, ensuring the body's movements are smooth and coordinated, learning routine behaviours, and the formation of habits (Nelson et al., 2017; Redgrave, Rodriguez Diaz, & Smith, 2010). In the case of SUD's, the basal ganglia include the brains "reward circuitry" which plays an important role in the rewarding and pleasurable effects that accompany substance use (Nelson et al., 2017), which ultimately result in the first stage of the addiction cycle: intoxication (Nelson et al., 2017). Over time as the individual uses the substance more, the "habit circuitry" (also within the basal ganglia) becomes hyperactive and begins to expect and seek the substance compulsively (Nelson et al., 2017).

The amygdala is another one of the brain's deep structures located in close proximity to the basal ganglia (Amunts et al., 2005; Nelson et al., 2017). The amygdala regulates the brain's response to stress and the various behaviours that accompany the feelings of fright, anxiety, or stress (e.g., fight or flight) (Ressler, 2010). In the three-stage cycle of addiction, the amygdala is responsible for the withdrawal stage, whereby an individual begins to experience numerous negative symptoms and significant distress due to the decrease or discontinuation of a substance (Koob & Volkow, 2010). This withdrawal stage arises from both a decrease in activity in the basal ganglia's reward circuitry, as well as from the involvement of various stress-related neurotransmitters in the amygdala (Nelson et al., 2017).

Finally the prefrontal cortex, located at the forefront of the brain, is involved in the various complex cognitive processes also known as the "executive functions" (Yuan & Raz, 2014) some of which include decision making, attention, organization, self-control, planning, and working memory (Yuan & Raz, 2014). Once again turning to the addiction cycle, the prefrontal cortex is involved in the third and final stage: preoccupation (Nelson et al., 2017). The

preoccupation stage begins after an individual has had a brief period of abstinence (which in the case of severe substance use disorders may be as short as hours) and begins to crave and seek substances again (Nelson et al., 2017) to the point where the individual's thoughts are completely preoccupied by the idea of obtaining the desired substance. The prefrontal cortex along with various subcortical regions (e.g., nucleus accumbens, dorsal striatum) have been described as working together to create a Go system within the brain that directs individuals towards goals and survival-based behaviours (Nelson et al., 2017). The prefrontal cortex is also said to have a Stop system which, when necessary, inhibits the Go system from causing habit-like, or reflexive actions, from being carried out (Goldstein & Volkow, 2011). In the case of SUD's, the prefrontal cortex often exhibits structural damage and abnormal functioning (Goldstein & Volkow, 2011) which is theorized to result in the over activation of the Go system (thereby enforcing substance seeking behaviours), and the under activation of the Stop system, which results in one's inability to control the impulses and desires surrounding substance use (Goldstein & Volkow, 2011; Nelson et al., 2017).

Although the basal ganglia, the amygdala, and the prefrontal cortex are actively involved in the cycle of addiction, there are numerous other brain regions and networks that are involved in the onset and development of SUD's (Nelson et al., 2017). Moreover, the way in which a SUD and this cycle of addiction may begin, develop, or intensify will vary greatly depending on the individual. Ultimately, there is a host of well-supported scientific evidence that suggests that addictive disorders involve a three-stage cycle that may worsen over time and may involve significant changes to the brain with regard to reward, stress, and motivation (Koob, 2013; Nelson et al., 2017).

1.2 Neuroimaging Methods

Structural neuroimaging involves the use of various tools to directly or indirectly image structural and large-scale aspects of the nervous system (Crosson et al., 2010). Structural neuroimaging is able to display contrasts between different tissues such as cerebrospinal fluid, grey matter, and white matter which makes it especially useful in the realm of neuroscience (Crosson et al., 2010). Some of the most commonly used structural neuroimaging methods include computed tomography (CT) and magnetic resonance imaging (MRI).

In the case of functional neuroimaging, there are various tools and methods that allow for the functions and processes of the brain to be viewed. Functional imaging allows for the visualization of brain metabolism, cognitive processes, and time-dependent responses (Chen & Glover, 2015) and often include methods such as: positron emission tomography (PET), electroencephalography (EEG), magnetoencephalography (MEG), functional near-infrared spectroscopy (fNIRS), single-photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI).

In the current thesis, magnetic resonance imaging (MRI) and functional magnetic resonance imaging (fMRI) were the neuroimaging methods that were used and will thus be discussed in more detail below.

1.2.1 Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging (MRI) uses powerful magnets to produce a magnetic field which causes the hydrogen protons in water molecules to align to a particular magnetic field (Berger, 2002). Subsequently a radiofrequency current is applied which causes the protons to spin out of their equilibrium and against the magnetic field (Berger, 2002). When this radiofrequency current is turned off, the protons realign with the magnetic field and release

electromagnetic energy as a result of this change in energy (Berger, 2002). The region where the protons are located within the body will affect the speed in which the protons realign with the magnetic field and will affect the amount of energy that they release (Berger, 2002), thereby allowing physicians to differentiate different tissues within the body.

A particular feature of MRI that allows for the visualization of different bodily tissues, is the use of MRI sequences (Berger, 2002). MRI sequences, which are composed of radiofrequency pulses and gradients, allow for the creation of image sets that have a specific appearance based on the characteristics of the sequence and the ways in which they affect different tissues (Bitar et al., 2006). A commonly used sequence, referred to as T1-weighted, allows for clear anatomical images to be generated based on its ability to demonstrate contrast between different tissues' recovery time (Bitar et al., 2006). Moreover, advances in MRI with regard to image sensitivity, resolution, and accuracy, are now allowing scientists the ability to augment various MRI sequences, such as T1-weighted sequences, in order to better differentiate between relatively minute brain tissues, structures, and regions within the living human brain.

1.2.2 Functional Magnetic Resonance Imaging (fMRI)

Functional Magnetic Resonance Imaging (fMRI) is a tool used for the indirect measure of brain activity and relies on the premise that neuronal activity is related to blood flow (Chen & Glover, 2015). Neurons are unable to store long term energy and therefore require that additional energy be brought in so that they can continue firing (Harris, Jolivet, & Attwell, 2012). The rate at which blood releases oxygen to these active neurons is referred to as the hemodynamic response (Chen & Glover, 2015) and results in a change in the levels of oxygenated and deoxygenated blood within the brain that can be detected via MRI (Chen & Glover, 2015); the

signal detected by the MRI is referred to as the blood-oxygen-level dependent (BOLD) contrast or signal.

Individuals undergoing an fMRI scan are often subjected to many repetitions of actions, signals, or experiences, which are then used in conjunction with statistical methods to determine which areas of the brain are demonstrating more of a BOLD signal and thus which areas of the brain are most active during the associated actions, signals, or experiences (Glover, 2011).

In addition to the detection of the BOLD signal that arises in response to an activity or a stimulus, fMRI is also able to measure the brain while in a state of rest using the BOLD signal (Glover, 2011). Given that brain has networks that are intrinsic, scientists have begun to explore the naturally occurring fluctuations in the BOLD signal that occur synchronously within different neural networks (Cabral, Kringelback, & Deco, 2014). Research has also begun to identify which of these networks appear to be consistent within healthy populations and what they appear to be responsible for, such as the default mode network (DMN), active during wakeful rest or daydreaming (Alves et al., 2019) and the salience network, responsible for directing attention and filtering salient stimuli (Seeley, 2019).

1.2.3 Substance Use and Brain Structure

It has been well documented through structural MRI that substance use is related to significant differences in the brains of those who do and do not use psychoactive substances.

A comprehensive review published in 2011 examined 140 imaging studies of individuals *specifically* with alcohol use disorder and found that chronic alcohol use is consistently associated with reductions in grey and white matter volumes, most prominently throughout the frontal regions of the brain, as well as in regions responsible for reward-related processing (Bühler & Mann, 2011; Makris et al., 2008).

More recently, a mega-analysis by Mackey and colleagues (Mackey et al., 2018) integrated structural MRI data from over twenty studies resulting in a sample of over 3,200 individuals who used either alcohol, nicotine, cocaine, methamphetamine, or cannabis. Overall findings from the analysis revealed that substance use disorder was associated with lower volume or cortical thickness in a variety of brain regions including the insula and the medial orbitofrontal cortex (Mackey et al., 2018). Mackey and colleagues also noted that the largest effect sizes in their analyses were found in individuals with alcohol use disorder (Mackey et al., 2018).

As for the structural brain changes that accompany other specific substances, cocaine users have been found to display less grey matter in regions of the frontal cortex (Matochik, London, Eldreth, Cadet, & Bolla, 2003), and methamphetamine users have been found to demonstrate less grey matter density in the right middle frontal gyrus (SJ Kim et al., 2006). Moreover, methamphetamine users have also been found to have less grey matter in a variety of specific brain structures such as the cingulate cortex, the limbic regions, and in the hippocampus (Thompson et al., 2004). In the case of opioid users, a neuroimaging meta-analysis found that individuals with opioid use disorder had significantly less grey matter in several cognitive processing regions, such as Heschl's gyrus, middle frontal gyrus, temporal pole, and gyrus rectus (Wollman et al., 2017). Opioid users have also been found to exhibit significant volumetric reductions in the amygdala, as well as decreased anisotropy in axonal pathways located within the basal ganglia (Upadhyay, Maleki, Potter, Elman, Rudrauf, Knudsen, Wallin, Pendse, McDonald, Griffin, Anderson, Nutile, Renshaw, Weiss, Becerra, & David Borsook, 2010).

Finally, an important aspect to consider in the field of substance use research, is the combined use of multiple substances and the potential effects that it may have on the brain.

Studies examining structural aspects of polysubstance users' brains have found that they often display smaller prefrontal lobes (X. Liu, Matochik, Cadet, & London, 1998), lower amounts of white matter in the frontal lobes (Schlaepfer et al., 2006), decreased gray matter volume in the ventromedial prefrontal cortex (A. M. Kaag et al., 2018), significantly less volume and surface area of the orbitofrontal cortex (Pennington et al., 2015), and significant thinning of the anterior cingulate cortex (Pennington et al., 2015).

1.2.4 Substance Use and Brain Function

In addition to structural changes, substance use is often associated with various functional brain changes as well. Various research studies have demonstrated that individuals with substance use disorder individuals often display alterations in brain activity and metabolism, differences in response to various cues and stimuli, and differences with regard to resting state activation (Correas et al., 2016; Pennington et al., 2015; Vegara, Lui, Claus, Hutchison, & Calhoun, 2017; Zheng, Kong, Chen, Zhang, & Zheng, 2015).

A systematic review conducted by Bühler & Mann (Bühler & Mann, 2011) found that alcohol using individuals demonstrated increased brain activity in response to alcohol cues in numerous brain regions including the basal ganglia, orbitofrontal cortex, ventromedial prefrontal cortex, dorsolateral prefrontal cortex, visuospatial network, and the temporal lobe (Bühler & Mann, 2011). They also found that this increased activity was not specific to visual cues and that olfactory and gustatory cues produced similar results (Bühler & Mann, 2011). Other studies have reported that alcohol use disorder individuals have lower glucose metabolism in various cortical and subcortical structures, including the medial frontal cortex and the parietal regions of the cortex (Gilman et al., 1990; G. Wang et al., 1993)

A review conducted by Wilcox and colleagues in 2019 (Wilcox, Abbott, & Calhoun, 2019) examined studies of 10 different substances and found three overarching themes: cognitive control and impulsivity were associated with reduced activity in the executive control network; craving and subjective withdrawal were associated with increased connectivity between the executive control network and the reward and limbic networks; and finally that reduced connectivity within the executive control network, and between the executive control network and the salience network, was related to poorer treatment outcomes in longitudinal studies (Wilcox et al., 2019).

With regard to specific effects that substances can have on function and cognition, alcohol has been shown to be associated with deficits in working memory and attention (Moriyama, Muramatsu, Kato, Mimura, & Kashima, 2006), cannabis has been associated with deficits in cognitive flexibility and attention (Pope, Gruber, & Todd-Yurgelun, 1995), and nicotine has been related to memory and learning deficits (Kennedy & Gould, 2008). As for cocaine and amphetamines, these stimulant substances have been associated with impaired cognitive flexibility, attention, and impulse control deficits (Kelley, Yeager, Pepper, & Beversdorf, 2005), as well as less functional activation in the frontal lobes (Wexler et al., 2001) and reduced activity in the medial regions of the anterior cingulate (Kaufman, Ross, Stein, & Garavan, 2003). Moreover, stimulant users have been found to have reduced concentrations of N-acetylaspartate (NAA) in the white matter of frontal regions and the basal ganglia (Ernst, Chang, Leonido-Yee, & Speck, 2000). Finally, with regards to opioids, it has been shown that opioid users display deficits in cognitive flexibility (Lyvers & Yakimoff, 2003), a decrease in functional connectivity in the anterior insula, the amygdala, and the nucleus accumbens (Upadhyay, Maleki, Potter, Elman, Rudrauf, Knudsen, Wallin, Pendse, McDonald, Griffin,

Anderson, Nutile, Renshaw, Weiss, Becerra, & Borsook, 2010) and that these regions often correlate with the duration of opioid use (Upadhyay, Maleki, Potter, Elman, Rudrauf, Knudsen, Wallin, Pendse, McDonald, Griffin, Anderson, Nutile, Renshaw, Weiss, Becerra, & Borsook, 2010). A study examining heroin use specifically, found abnormal connectivity in the prefrontal cortex, the anterior cingulate cortex, the striatum, the insula, the hippocampus, and once again, the amygdala (J. Liu et al., 2009). Lastly, with respect to research surrounding polysubstance users, a limited number of studies have found that polysubstance users often display less activation in the frontal, occipital, and temporal lobes of the brain (Raj et al., 2010), as well as in various resting state networks such as the cerebellum, auditory, sensorimotor, visual, salience, default mode, and executive control network (Vegara et al., 2017).

1.3 Main Aims

Although the field of neuroimaging research examining substance use disorders is plentiful, there remain a variety of topics that warrant initial or further investigation.

Based on the literature discussed in section *1.2.3 Effects of Substance Use on Brain Structure* we can see that there is a great deal of research demonstrating which regions and tissues of the brain appear to be most affected by various substances. One avenue however that would benefit from further investigation is substance use characteristics that may ultimately be responsible for the changes that arise in the brain's structure. These characteristics may include the frequency with which a substance is used, the amount of a substance (i.e., quantity) that may be detrimental to the brain, and the recurrence of heavy drinking episodes (i.e., binge drinking). In order to add to the literature surrounding substance use and examine which use characteristics may be especially impactful on brain structure, we examined continuous associations between

alcohol use quantity and alcohol use frequency in a variety of brain regions within a large sample of participants in Chapter 2.

In section *1.2 Neuroimaging Methods and 1.2.1 Magnetic Resonance Imaging (MRI)*, we reviewed the currently available neuroimaging methods and touched on the fact the pulse sequences are continuously being developed and improved in order to allow for different neuroanatomical tissues to be explored in vivo. We also mentioned in section *1.2.3 Effects of Substance Use on Brain Structure* that there is a need for substance specific brain-based biomarkers to be identified to aid in the identification and diagnosis of substance use disorders. In order to expand the neuroimaging and substance use biomarker literature, we utilized a novel MRI pulse sequence to examine the effect of alcohol use on intracortical myelin in Chapter 3.

Finally, in section *1.2.2 Functional Magnetic Resonance Imaging (fMRI)* we discussed the notion that fMRI has more recently begun to identify and investigate large-scale resting-state networks within the brain, and in section 1.2.4 that polysubstance use populations are somewhat understudied within the realm of fMRI, perhaps due to the challenges associated with disentangling the complex results that often follow. Therefore, in Chapter 4 we sought to examine the effect of using alcohol alone or in combination with other substances on resting brain activity.

The overarching aim of this thesis was ultimately to add three studies to the addictions neuroscience literature in order to delineate and ameliorate some of the ambiguity that has developed throughout years of research. We believe that the field of substance use research would benefit from a study with a large sample size to clarify ambiguities on existing topics (Chapter 2), would benefit from a novel imaging method to identify brain-based biomarkers (Chapter 3), and would benefit from a study using a somewhat understudied sample of

polysubstance users (Chapter 4). Therefore, this thesis sought to expand the literature of substance use disorder by conducting the following three studies.

1.4 Objectives

The objectives of this thesis were as follows:

i) To examine associations of cortical thickness in a variety of brain regions with drinking quantity and frequency.
ii) To explore intracortical myelin in a sample of individuals with alcohol use disorder compared to control participants.
iii) To examine resting state functional connectivity in a variety of large-scale brain networks among people who use alcohol alone or in combination with other substances.

1.5 Hypotheses

The hypotheses for each of the objectives were as follows:

i) We expect that increased drinking quantity and frequency will have a negative impact of cortical thickness, predominately in the frontal regions of the brain.
ii) We postulate that individuals with alcohol use disorders will display less intracortical myelin signal via MRI.
iii) We expect that as the degree of polysubstance use increases, that we will observe a decrease in resting state functional connectivity.

1.6 References

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Chapter 2: Associations Between Drinking and Cortical Thickness in Younger Adult Drinkers: Findings from the Human Connectome Project

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2.1 Abstract

Background: Previous neuroimaging studies examining relations between alcohol misuse and cortical thickness have revealed that increased drinking quantity and alcohol-related problems are associated with thinner cortex. Although conflicting regional effects are often observed, associations are generally localized to frontal regions (e.g., dorsolateral prefrontal cortex [DLPFC], inferior frontal gyrus [IFG], and anterior cingulate cortex). Inconsistent findings may be attributed to methodological differences, modest sample sizes, and limited consideration of sex differences.

Methods: This study examined neuroanatomical correlates of drinking quantity and heavy episodic drinking in a large sample of younger adults (N = 706; Mage = 28.8; 51% female) using magnetic resonance imaging data from the Human Connectome Project. Exploratory analyses examined neuroanatomical correlates of executive function (flanker task) and working memory (list sorting).

Results: Hierarchical linear regression models (controlling for age, sex, education, income, smoking, drug use, twin status, and intracranial volume) revealed significant inverse associations between drinks in past week and frequency of heavy drinking and cortical thickness in a majority of regions examined. The largest effect sizes were found for frontal regions (DLPFC, IFG, and the precentral gyrus). Follow-up regression models revealed that the left DLPFC was uniquely associated with both drinking variables. Sex differences were also observed, with significant effects largely specific to men.

Conclusions: This study adds to the understanding of brain correlates of alcohol use in a large, gender-balanced sample of younger adults. Although the cross-sectional methodology precludes causal inferences, these findings provide a foundation for rigorous hypothesis testing in future longitudinal investigations.

2.2 Introduction

Detrimental effects of alcohol on brain structure have been widely reported in the literature (Oscar-Berman & Marinković, 2007; Pfefferbaum, Rosenbloom, Deshmukh, & Sullivan, 2001). These morphological effects include reductions in grey matter volume of cortical and subcortical structures (e.g., Fein et al., 2002; Grodin, Lin, Durkee, Hommer, & Momenan, 2013) and various abnormalities in brain activation patterns revealed via functional neuroimaging (e.g., Chanraud, Pitel, Pfefferbaum, & Sullivan, 2011; Shokri-Kojori, Tomasi, Wiers, Wang, & Volkow, 2017; Zheng, Kong, Chen, Zhang, & Zheng, 2015). In particular, abnormalities in areas of the frontal lobes, including the dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC) and orbitofrontal cortex (OFC), have been emphasized as a neuroanatomical hallmarks of alcohol use disorder (AUD) (Mechtcheriakov et al., 2007; Moselhy, Georgiou, & Kahn, 2001). Functional consequences of alcohol-related decreases in DLPFC volume include impairments in executive functions, behavioral control, and decision-making, among other higher-level neurocognitive processes (Crews & Boettiger, 2009).

Previous research has also shown that lower levels of cortical thickness, most prominently in the frontal regions of the brain, are correlated with greater levels of alcohol use and misuse. However, these findings have not been consistent across all studies. A magnetic resonance imaging (MRI) by Durazzo et al., (2011) compared individuals with AUD (N = 75) to healthy controls (N = 43) and found that the predominately male (96%) AUD group exhibited significantly thinner frontal cortices, including the DLPFC, ACC, anterior insula, and medial and lateral OFC (see also Durazzo, Mon, Gazdzinski & Meyerhoff 2013). Fortier et al., (2011) compared abstinent AUD participants to controls using a more sex balanced sample (38% female). The AUD group exhibited thinner cortex in a variety of frontal regions largely

corresponding to the DLPFC, but there were no significant differences in the additional frontal regions reported by Durazzo et al. (2011; 2013). Momenan et al. (2012) compared cortical gray matter thickness in a large sample of individuals with AUD (N = 130) and controls (N = 69). The AUD group exhibited significantly thinner cortex in the bilateral DLPFC, right insula, precentral gyrus, and precuneus. Significant sex differences were also found with the AUD women exhibiting differences from control women in precentral and postcentral gyri, but none of the classic prefrontal regions. Men with AUD, however, exhibited differences from control men in frontal regions (anterior insula, DLPFC). Pennington et al. (2015) reported that male participants with AUD exhibited less bilateral ACC thickness compared to male control participants. Most recently, a 'mega-analysis' of structural MRI data pooled from 23 research laboratories (Mackey et al. 2018) found that individuals with AUD (N = 898) had lower levels of cortical thickness compared to controls (N = 292) in many of the same regions identified in prior studies, including DLPFC, ACC, insula, OFC, precentral gyrus, precuneus, and posterior cingulate, among others. Sex differences were not reported in this study.

Studies have also investigated sub-clinical samples of drinkers. For example, Mashhoon et al., (2014) examined cortical thickness in a sample of 23 (48% female) emerging adult binge drinkers vs. 31 (48% female) emerging adult light drinkers. In *a priori* region of interest analyses, they found that the rostral ACC and left dorsal posterior cingulate cortex were significantly thinner in the binge drinking group than the light drinking group. Within the binge drinking group, thickness of the rostral ACC and was negatively correlated with alcohol consumption over the last three months, the average number of drinks consumed per drinking period, and the number of drinks consumed per day.

Taken together these studies generally suggest that alcohol misuse, possibly even at levels below clinical threshold for AUD, is associated with less cortical thickness than is typical; however, the specific regions implicated differ widely across studies (see summary of significant findings in Table 1). A number of methodological differences across previous studies may explain these inconsistent results. First, studies have not consistently considered sex effects or included samples that were highly unbalanced between male and female participants (e.g., <10% females; (Durazzo et al., 2011; Pennington et al., 2015). Second, previous research has varied widely in level of alcohol misuse, presence of AUD, and whether participants were currently or in treatment or recovery from AUD. Third, previous studies included relatively small sample sizes, with a few notable exceptions (Mackey et al., 2018; Momenan et al., 2012). Fourth, ages of participants varied widely across studies, from young adults ages 18-24 (e.g., Mashhoon et al., 2014) to adults in their 40-50s (e.g., Durazzo et al., 2011; Pennington et al., 2015). Finally, studies differed widely in the analytic approach used, including conducting whole-brain analyses (Durazzo et al., 2011; Fortier et al., 2011; Momenan et al., 2012) or restricting to a small number of ROIs (Bae et al., 2016; Durazzo et al., 2011; Fortier et al., 2011; Momenan et al., 2012; Pennington et al., 2015). Even within latter group, the specific ROIs examined varied widely (see Table 1). This variation across sample characteristics and analytic methods leads to a lack of consensus and limits direct comparison across studies.

As a result of inconsistent findings and limitations in the current literature, the aims of the current study were two-fold. First, to clarify the inconsistency across studies, we sought to examine cortical thickness in a comprehensive list of ROIs to determine which regions were associated with drinking quantity and heavy drinking. Second, we sought to explore these variables within a sample that was significantly larger, and more sex balanced than samples in

previously published work. The current study examined T1-weighted structural MRI data from active drinkers in the open-source Human Connectome Project (HCP) dataset. The HCP is a multi-site neuroimaging research study that is systematically mapping the structure and function of the human brain and its clinical and neurocognitive correlates (see Van Essen et al. 2013 for an overview of the HCP). We capitalized on this unique resource to examine associations between cortical thickness and two indices of alcohol use—drinking quantity in the past week and frequency of heavy episodic drinking—in the largest sample of participants in a single study to date. Two exploratory aims were also investigated. First, we also examined sex differences in the patterns of association between cortical thickness and the alcohol variables. Second, we explored neuroanatomical correlates of two domains of cognitive functioning from the HCP behavioral assessment that are consistently linked to frontal cortical structures: executive function and working memory. Based on the general trends in previous studies, we hypothesized that cortical thickness would be negatively associated with alcohol consumption and frequency of heavy drinking, particularly in frontal regions (e.g., DLPFC, OFC, ACC, and anterior insula). Given the limited research examining sex differences in the associations between cortical thickness and alcohol use, no specific hypotheses regarding sex effects were made. For the analyses of cognitive processing, we predicted positive associations between cortical thickness and executive function and working memory.

2.3 Materials and Methods

2.3.1 Participants

Structural MRI brain scans were drawn from the 1200 Subjects HCP dataset (released March 1, 2017; available at *http://www.humanconnectome.org/*). The primary HCP participant

pool consisted of community adults between the ages of 22-37. Participants were excluded from the HCP study if they had a history of neurodevelopmental, neuropsychiatric, or neurological disorders, as well as significant medical conditions such as diabetes or high blood pressure. The use of drugs or tobacco were not exclusionary and these variables were included as covariates in all analyses (see below). The current study sample consisted of HCP participants who reported consuming at least one alcoholic drink in the past-week retrospective alcohol assessment (details below), resulting in a sample of 711 participants. An additional 5 participants were excluded due to incomplete data (3 did not complete the drinking assessments, and 2 did not provide full demographic information). The final sample consisted of 706 participants.

2.3.2 Assessments

Access to restricted participant demographic and clinical data was granted via written authorization from the HCP Connectome Coordination Facility. Participants completed the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA, Bucholz et al., 1994). The SSAGA assesses physical, psychological, and social symptoms of alcohol abuse and dependence as well as other psychiatric disorders using DSM-III-R and DSM-IV criteria. The SSAGA also covers general demographic information, medical history, information about tobacco and drug use, and other mental health variables. Participants also completed a seven-day retrospective report of alcohol and tobacco use. Participants provided a commercially available urine drug screen for biochemical testing of recent drug use. Two neurocognitive measures from the HCP behavioral assessment battery were assessed here. These measures were drawn from the NIH Toolbox (http://www.healthmeasures.net/explore-measurement-systems/nih-toolbox), including a measure of executive function/inhibition (flanker task) and a measure of working memory (list

sorting). Full details of the HCP behavioral measures are provided elsewhere (Barch et al., 2013).

2.3.3 Alcohol Variables

Two alcohol variables from the HCP dataset were examined in the current study. The first, "Total drinks in past 7 days", was taken from the retrospective alcohol use assessment. The second, "Frequency of drinking 5+ drinks in past 12 months", was taken from the SSAGA assessment. This variable was coded categorically in the HCP dataset, but the coding for the highest frequency differed for males and females (i.e., the maximum response of 3+ days/week was coded as 1 for males, but 2 for females). The next lowest value (1-2 days/week) was coded as 2 for both males and females. Therefore, no distinction could be made between 1-2 vs. 3+ days/week for females. To standardize the maximum response, the data were recoded as follows (and reverse-scored such that higher values reflect greater frequency): 1 = never; 1-11 days/year = 2; 1-3 days/month = 3; weekly or greater = 4. Selection of these two alcohol variables was based on previous research examining continuous associations between recent drinking quantity and cortical thickness (e.g., Mashhoon et al. 2014) and prior research that focused specifically on structural brain correlates of binge drinking as a unique predictor of cortical thickness differences (e.g., Mashhoon et al. 2014).

2.3.4 MRI Data Acquisition and Data Quality Control

High-resolution T1-weighted structural images were collected on a 3T Siemens Skyra scanner (Siemens AG, Erlanger, Germany) with a 32-channel head coil (for full acquisition protocol, see Van Essen et al. 2013). Briefly, images were acquired with a 0.7 mm^3 isotropic resolution (FOV = 224 x 240, matrix = 320 x 320, 256 sagittal slices; TR = 2400 ms and TE =

2.14 ms). Following MRI, each structural scan was examined by a trained rater to assess the overall quality of the scan's contrast, blurring, ringing, and other possible artifacts. Only the scans rated as excellent were released as part of the HCP dataset. For full explanation of HCP quality control procedures, see Marcus et al., 2013.

2.3.5 FreeSurfer Processing Pipelines

Cortical thickness data were generated using the HCP minimal preprocessing pipeline described in Glasser et al., 2013. In the first part of the pipeline, PreFreeSurfer is used to produce a clear structural volume space for each subject, align the images, perform a B_1 correction, and register the subject's structural volume space to the MNI space. The second part of the pipeline is based on FreeSurfer version 5.2 (http://surfer.nmr.mgh.harvard.edu) (Fischl, 2012). This pipeline ensures that the volume is segmented into predefined structures, that the white and pial surfaces are reconstructed, and that FreeSurfer's folding based surface registration (to the surface atlas fsaverage) is performed. Structural data analyzed for the current study came from this second step. This pipeline generates 34 anatomical regions of interest (ROIs) per cortical hemisphere. The mean cortical thickness in each of the 68 ROIs was provided per person in the HCP public dataset.

2.3.6 Selection of Regions of Interest

We examined cortical thickness in a series of *a priori* regions that were chosen based on previous studies on cortical thickness in alcohol use samples (Bae et al., 2016; Durazzo et al., 2013, 2011; Fortier et al., 2011; Mashhoon et al., 2014; Momenan et al., 2012; Pennington et al., 2015). Specifically, we identified 18 bilateral ROIs that have shown significant differences in at least one of these prior studies. Following conventions used in prior studies (e.g., Durazzo et al.,

2013, 2011; Pennington et al., 2015), a subset of these regions were combined into composite regions corresponding to the ACC, OFC, IFG, and DLPFC, reducing the number of regions from 18 to 12. The ACC composite region was created by combining the caudal and rostral ACC segments. The DLPFC composite was created by combining the caudal MFG, rostral MFG, and the SFG segments. Lastly, the OFC composite was created by combining the lateral and medial OFC segments. The only previous study to observe significant results for the IFG (Momenan et al., 2012) did not indicate a specific sub-component of the IFG (*pars opercularis, pars orbitalis, pars triangularis*), so these three regions were combined into a single IFG composite region. The final list of 12 *a priori* ROIs and the studies reporting differences in these areas is provided in Table 1. The anatomical locations of individual ROIs and composite regions are depicted in Figure 1. These ROIs were examined separately for the left and right hemispheres using the average cortical thickness values for each region provided in the HCP dataset.

2.3.7 Data Analytic Plan

Selection of the covariates was based on previous work that has shown that age (e.g., Peters, 2006), sex (e.g., Taki et al., 2011), socioeconomic status (e.g., Piccolo, Merz, He, Sowell, & Noble, 2016), education (e.g., Boller, Mellah, Ducharme-Laliberté, & Belleville, 2017), use of tobacco (e.g., Durazzo et al., 2013) and cannabis and other drug use (e.g., Li et al., 2014; Lopez-Larson et al., 2011) are significantly associated with variation in cortical thickness. Twin status (i.e., monozygotic or not; dizygotic or not) was included given the twin enrichment of the HCP dataset. Estimated total intracranial volume was included to control for differences in overall head size.

Hierarchical multiple linear regression models were conducted to examine associations between cortical thickness indices and alcohol variables. Separate regression models were

calculated for each of the ROIs. Step one of the models included age, sex, education, income, twin status, total intracranial volume, tobacco use, cannabis use, and other drug use as covariates. On the SSAGA, tobacco use was defined as total tobacco use in the past 7 days, cannabis use was defined as the total times participants reported using marijuana on the SSAGA; and other illicit drug use was defined as the total times participants reporting cocaine, hallucinogens, opiates, sedatives or other drugs on the SSAGA. In addition to the self-report drug use variables, a binary variable was calculated based on any positive screen on the urine drug test (1 = any positive; 0 = all negative). Each cortical thickness ROI was added in the second step of the model and change in R^2 was examined. Separate regression models were calculated for drinks in past week and frequency of heavy drinking. Given the relatively large number of ROIs, we applied a two-tailed False Discovery Rate (FDR; Benjamini & Hochberg, 1995) correction of $q < .05$ to reduce inflation of type I error rate in the individual regression analyses.

We then conducted an iterative regression analysis to determine the unique contributions of the ROIs that were significantly associated with the drinking variables in the individual regression models, after correcting for multiple comparisons (similar to the approach used in (Owens, Duda, Sweet, & MacKillop, 2018). In these models, individual ROIs that were found to be associated with alcohol use at FDR $q < .05$ in the previous step were entered sequentially starting with the largest effect size and proceeding to the smallest effect size. At each iteration, ROIs that significantly increased the variance explained by the model (i.e., had a significant ΔR^2) were retained in the model. The iterative regression analysis used a conventional significance level of $p < .05$ and 95% confidence intervals are reported for regression coefficients.

Finally, we conducted two exploratory analyses. First, we examined potential sex difference associations between cortical thickness and the alcohol variables by repeating the

primary analyses (i.e., the hierarchical multiple linear regression models) including an interaction term that was calculated by standardizing each region and sex, then multiplying each region by sex. All 24 ROIs were examined and an FDR of $q < .05$ was used. Continuous associations between cortical thickness in the 24 ROIs and cognitive performance on the flanker and list sorting tasks were explored using Pearson correlations with an FDR of $q < .05$ applied.

2.4 Results

2.4.1 Preliminary Analyses

Complete sample characteristics are provided in Table 2. Participants consumed an average of 7.2 drinks in the past week, and 44.5% engaged in heavy drinking (5+ drinks on an occasion) on a monthly or greater basis. Compared to females, males consumed significantly more drinks in the past week, $F(1,705) = 86.11$, $p < .0001$, $\eta^2 = .11$, and reported significantly higher frequency of heavy drinking, $F(1, 705) = 92.60$, $p < .0001$, $\eta^2 = .12$. See Table 2 for full comparisons between male and female participants.

We examined bivariate correlations among mean cortical thickness values for the 24 ROIs included in the primary analyses. The complete correlation matrix is provided in Supplementary Table 2. The magnitude of the associations between ROIs within the same hemisphere varied widely, with slightly smaller magnitude correlations in the right (rs = .15 - .79) compared to left (rs = .30 - .79) hemisphere. Magnitude of correlations between the hemispheric homologues of bilateral ROIs also varied (rs = .37 - .85), with the largest magnitude associations between left and right DLPFC (r = .85), IFG (r = .73), precentral gyrus (r = .77), postcentral gyrus (r = .77), precuneus (r = .75), and superior temporal gyrus (r = .75).

2.4.2 Cortical thickness and drinking quantity

Multiple regression analyses examining drinking quantity (drinks in past week) are presented in Table 3 (the covariate-only model is presented in Supplementary Table 2). After applying FDR correction, these analyses revealed statistically significant effects for 18 out of 24 ROIs. In each case, lower cortical thickness was associated with greater drinking quantity. Among the significant ROIs, effect sizes were generally small in magnitude, with the largest found for left DLPFC, the left precentral gyrus, and the right superior temporal gyrus. The iterative regression to determine incremental associations of each ROI with alcohol use began with the ROI that had the largest effect size (left DLPFC). Subsequently, we added the remaining significant ROIs individually in order of effect size to determine which ROIs would account for significant variance in drinking quantity. This analysis revealed that after including left DLPFC, no additional ROIs were associated with a statistically significant change in R^2 (ps > .05). To explore whether the observed significant associations were driven by negative impact of other substance use on cortical thickness (e.g., Battistella et al., 2014; Karama et al., 2015; Mackey et al., 2018), we conducted a follow-up regression analysis with cortical thickness in each ROI as the dependent variable and alcohol, cannabis, nicotine, and illicit drug use variables as predictors (along with the same covariates as above). The same regions had significant R^2 change as the original analysis that examined alcohol alone (data not shown), suggesting that the primary results are not solely attributed to effects of other substance use.

2.4.3 Cortical thickness and heavy drinking frequency

Regression results for the heavy drinking frequency variable are presented in Table 4. Compared to the drinking quantity results above, these analyses generally revealed smaller magnitude effects in fewer ROIs following FDR correction (14 out of 24 ROIs). In each case,

higher frequency of heavy drinking was associated with lower cortical thickness. The largest effect sizes were found for the left DLPFC and the left precentral gyrus. Results of the iterative regression analysis were similar to drinking quantity. Beyond left DLPFC, no other ROIs accounted for a significant change in R^2 (*p*s > .05). Similar to the drinking quantity analyses, we conducted a follow-up analysis with cortical thickness as the dependent variable. Once again, the results were identical with the exception of left IFG which was no longer significant in the follow-up model (data not shown).

2.4.4 Exploratory Analyses of Sex Effects

We explored potential sex differences in the relationship between cortical thickness and alcohol variables. In the case of drinks in past week, we found significant region × sex interactions (after FDR correction) in 10 of the 24 ROIs examined (Table 5), including left ACC, left DLPFC, left insula, left OFC, left posterior cingulate, left MTG, and bilateral IFG and STG. In each case, male participants showed a significant negative association between cortical thickness and drinks in the past week which was not observed in female participants. None of region × sex interactions were significant for heavy drinking frequency.

2.4.5 Exploratory Analyses of Cognitive Performance

Results of the exploratory correlations between cognitive performance on flanker and list sorting tasks and the alcohol and cortical thickness variables are presented in Supplementary Table 2. Neither drinks in the past week nor heavy drinking frequency were correlated with flanker or list sorting performance (ps > .17). Flanker task performance was not significantly correlated with cortical thickness in any of the 24 ROIs. Working memory performance on the list sorting task was significantly (after FDR correction) positively correlated with cortical

thickness in 9 ROIs, including bilateral middle temporal cortex and posterior cingulate and right precentral gyrus, insula, precuneus, superior temporal gyrus, and lateral occipital gyrus. However, the magnitude of the correlations was generally small (*r*s .09 - .12).

2.5 Discussion

The current study examined neuroanatomical correlates of alcohol use and heavy episodic drinking in one of the largest sex-balanced samples to date. Consistent with previous studies, we found that thinner cortex in a number of regions was associated with greater alcohol consumption and more frequent heavy drinking. These findings make three important contributions to the literature: 1) they empirically demonstrate the unique association of the left DLPFC with alcohol use compared to other regions, 2) they demonstrate sex differences in associations of cortical thickness with alcohol use, and 3) they indicate significant associations between cortical morphometry and drinking in a relatively young and typical sample of drinkers. These contributions are discussed below.

The first main contribution of these findings is the robust association between the left DLPFC and drinking quantity and frequency of heavy drinking. This finding is consistent with several prior cortical thickness studies showing significantly thinner cortex in DLPFC among individuals with AUD or those who report binge drinking (Bae et al., 2016; Durazzo et al., 2013, 2011; Fortier et al., 2011; Mackey et al., 2018; Pennington et al., 2015). The DLPFC findings are particularly important given the role of this region in cognitive control and other executive functions that contribute to drinking decisions (Niendam et al., 2012). The DLPFC is also commonly targeted via neuromodulation interventions using non-invasive brain stimulation techniques (e.g., Boggio et al., 2008; Coles, Kozak, & George, 2018; Lupi et al., 2017; Mishra,

Nizamie, Das, & Praharaj, 2010) and cognitive interventions such as executive function or working memory training (Duda and Sweet, *In Press*; Olesen, Westerberg and Klingberg, 2004; Takeuchi *et al.*, 2011). Furthermore, by demonstrating that no regions are associated with alcohol use beyond their shared correlations with the DLPFC, the current study highlights the importance of DLPFC in understanding how cortical thickness is linked with alcohol use. There are several possible interpretations of this finding. One interpretation is that reduced DLPFC thickness is causing more problematic alcohol use (perhaps through impaired executive control or other DLPFC-mediated cognitive mechanisms) and all other regional cortical thickness associations with alcohol are solely the result of their association with DLPFC thickness. This would suggest cortical thickness in the DLPFC is a key driver of alcohol use. Another interpretation is that alcohol use is causing cortical thinning across the whole brain through a single mechanism, with the most severe atrophy occurring in the DLPFC. This would suggest that the hierarchical regression results are indicative only of the high magnitude of the correlations between the DLPFC and alcohol. However, the cross-sectional nature of the HCP data does not permit conclusions about causality, and future longitudinal research is needed to tease apart such interpretations.

The significant sex differences are also notable. Studies examining differences in the influence of alcohol on the brain between men and women are sparse and discrepant (D. Hommer, 2003). Some studies of AUD samples have reported greater brain shrinkage in women compared to men (e.g., Hommer, Momenan, Kaiser, & Rawlings, 2001), others have reported effects in the reverse direction (Pfefferbaum et al., 2001) or no sex differences (Gescuk, Woods, Mello, Weiss & Mendelson; Pfefferbaum & Sullivan 2002). Although several previous studies examined cortical thickness in relation to alcohol misuse, only one study by Momenan et al.

(2012) reported sex effects. The large sample size and relatively equal sex distribution of the HCP dataset provided us the opportunity to test sex effects sufficient statistical power. Our results suggest that the associations between reduced cortical thickness and drinking in this sample of younger adult drinkers may be driven by effects in the men which differs somewhat from findings in the previous AUD studies (with the exception of Pfefferbaum et al., 2001). The regions implicated were predominately localized in the DLPFC and other frontal regions (e.g, OFC, IFG, ACC), again supporting the important role of frontal regions in drinking behavior. However, associations between drinking quantity and regions of temporal cortex (e.g., MTG, STG) and the posterior cingulate also differed between males and females.

A final important contribution of the current study relates to the nature of the HCP sample, which was notable in its relatively younger age and lack of neurodevelopmental disorders, neuropsychiatric disorders, and neurologic disorders (Van Essen et al., 2013) which may negatively impact cortical thickness. Significant negative associations between reduced cortical thickness and alcohol variables in a sample of young adults without an extensive life-long history of alcohol misuse suggests that low levels of cortical thickness may be a risk factor for engagement in alcohol misuse. However, we emphasize that conclusions regarding causation are outside the scope of a cross-sectional study.

These findings should be considered within the context of several potential limitations. One notable limitation concerns the alcohol measures, which were based on retrospective self-report and, as such, may have been subject to recall bias or demand characteristics. Of note, since the HCP was not primarily focused on alcohol use, the measurement resolution for some of the alcohol variables was somewhat coarse. This is particularly true in the case of lifetime alcohol use and AUD severity which are important variables to consider. Unfortunately, the variables

provided in the HCP dataset do not permit accurate calculation of a continuous measure of AUD severity or an accurate index of lifetime alcohol exposure. Another consideration is that the sample was comprised of adults between the ages of 22–35. Although the younger age range allowed us to infer relationships with brain structure that are presumably independent of extensive neurotoxicity from chronic alcohol misuse, these findings may not generalize to other age groups or individuals with comorbid psychiatric or other health conditions. Additionally, it is possible that effect sizes were smaller in the current results than would be the case if a clinical sample were used with more severe AUD (e.g., Mackey et al., 2018).

In summary, this study further clarifies the structural brain correlates of alcohol use in a large sample of drinkers. The large HCP cohort provided high statistical power and we observed significant effects in a majority of regions reported in prior studies. When considered together, however, the DLPFC was the region most robustly and uniquely associated with the alcohol variables. Our findings are also consistent with the recent 'mega-analysis' of cortical thickness deficits in people with AUD compared to healthy controls (Mackey et al., 2018), but also provide an important extension by demonstrating significant associations in a comparatively younger sample of drinkers. Moreover, our sex balanced sample allowed for the investigation of sex differences in relation to cortical thickness and alcohol misuse; findings demonstrated that male participants exhibited significant negative associations between cortical thickness and drinking quantity in several regions which were not observed in female participants. The consistency between our results and prior studies is an important finding in the context of prominent concerns about reproducibility in addictions (Munafò, 2017) and neuroimaging (Gorgolewski & Poldrack, 2016) research. Although the current study cannot speak to disentangling cause from consequence, these findings provide a foundation for rigorous hypothesis testing in future

longitudinal investigations. Another potentially important future direction is to examine the cognitive and neuropsychological correlates of these associations between cortical thickness and alcohol use. The HCP dataset includes a wide array of cognitive, emotional, and neuropsychological measures that would permit such analyses in future studies.

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Table 1. Region of Interest Selection Based on Previous Findings

Region	**Durazzo (2011)**	**Durazzo (2013)**	**Fortier (2011)**	**Mashhoon (2014)**	**Momenan (2012)**	**Pennington (2015)**	**Bae (2016)**
DLPFC	**X**	**X**	**X**		**X**	**X**	**X**
ACC	**X**	**X**		**X**		**X**	
Anterior insula	**X**	**X**			**X**	**X**	
OFC	**X**	**X**					
IFG					**X**		
Precentral gyrus			**X**		**X**		
Postcentral gyrus			**X**		**X**		
Precuneus					**X**		
Posterior Cingulate				**X**			
Middle Temporal			**X**				
Superior Temporal			**X**				
Lateral Occipital			**X**				

Note. DLPFC = Dorsolateral prefrontal cortex; ACC = Anterior cingulate cortex; OFC = Orbitofrontal cortex; IFG = Inferior frontal gyrus; Regions marked with X indicate statistically significant findings in the respective papers

Table 2. Sample Characteristics

Variable	Overall Mean(SD); %; Median	Males Mean(SD); %; Median	Females Mean(SD); %; Median	Sig.
Sex	51% Female	---	---	
Age	28.77 (3.60) Range 22-37	28.10 (3.58) Range 22-37	29.40 (3.51) Range 22-36	$p < .001$
Education	15.08 (1.74) Range 11-17	15.01 (1.72) Range 11-17	15.08 (1.74) Range 11-17	$p = .37$
Income (median)	$50,000-74,999	$50,000-74,999	$50,000-74,999	$p = .47$
Drinks Last 7 Days	7.22 (6.63); Range 1-28	9.46 (7.75) Range 1-28	5.08 (4.42) Range 1-26	$p < .001$
Heavy Drinking Freq.				$p < .001$
Never	23.4%	13.1%	33.1%	
1-11 days/year	32.2%	25.9%	38.1%	
1-3 days/month	20.0%	25.0%	15.2%	
Weekly+	24.5%	36.0%	13.5%	
Drinks / Drinking Day	1 (30%); 2 (28%); 3 (17%); 4 (8%); 5-6 (13%); 7+ (4%)	1 (15%); 2 (26%); 3 (21%); 4 (12%); 5-6 (18%); 7+ (8%)	1 (45%); 2 (30%); 3 (13%); 4 (4%); 5-6 (8%); 7+ (0%)	$p < .001$
Tobacco Use (7-day)	8.1 (25.60) Range 0 -195	10.78 (27.84) Range 0 -175	5.57 (20.69) Range 0 -195	$p = .005$
Cannabis Use	None (35.7%); 1-5x (22.1%); 6-10x (9.2%); 11-100x (14.4%); 101-999x (7.6%); 1000+ (10.9%)	None (31.1%); 1-5x (18.9%); 6-10x (8.7%); 11-100x (15.7%); 101-999x (10.2%); 1000+ (15.4%)	None (40.1%); 1-5x (25.1%); 6-10x (9.7%); 11-100x (13.3%); 101-999x (5.2%); 1000+ (6.6%)	$p < .001$
Illicit Drug Use	None (73.4%); 1-2x (6.2%); 3-10x (9.3%); 11-25x (4.1%); 25+ (6.9%)	None (66.3%); 1-2x (7.0%); 3-10x (11.0%); 11-25x (5.2%); 25+ (10.5%)	None (80.1%); 1-2x (5.5%); 3-10x (7.7%); 11-25x (3.0%); 25+ (3.6%)	$p < .001$
SSAGA AUD	27.0% Positive	36.3% Positive	18.0% Positive	$p < .001$
SSAGA CUD	11.0% Positive	17.7% Positive	5.8% Positive	$p < .001$

Note: $N = 706$; Illicit drug use included cocaine, hallucinogens, opiates, sedatives, stimulants; SSAGA = Semi-structured Assessment for the Genetics of Alcoholism; AUD = Alcohol use disorder; CUD = Cannabis use disorder

Table 3. Cortical Thickness in Individual Regions of Interest Predicting Drinks in Past Week

Region / Composite	L/R	B	SE	β	t	p	95% CI	ΔR^2	FDR
DLPFC	L	-6.66	1.97	-0.12	-3.37	<.001	-10.53, -2.78	.011	sig.
	R	-5.71	2.09	-0.10	-2.73	.006	-9.81, -1.61	.007	sig.
ACC	L	-4.26	1.54	-0.09	-2.76	.006	-7.29, -1.24	.007	sig.
	R	-1.63	1.27	-0.04	-1.29	.199	-4.13, 0.86	.000	**n.s.**
Insula	L	-4.53	1.57	-0.10	-2.88	.004	-7.61, -1.44	.007	sig.
	R	-2.70	1.72	-0.06	-1.57	.117	-6.09, 0.68	.001	**n.s.**
OFC	L	-4.27	1.85	-0.08	-2.30	.022	-7.90, -0.63	.004	sig.
	R	-4.04	2.01	-0.07	-2.01	.045	-7.99, -0.09	.003	**n.s.**
IFG	L	-5.83	1.91	-0.11	-3.06	.002	-9.57, -2.09	.009	sig.
	R	-6.41	1.97	-0.11	-3.25	.001	-10.28, -2.54	.010	sig.
Precentral gyrus	L	-6.45	1.88	-0.12	-3.42	<.001	-10.15, -2.75	.011	sig.
	R	-6.25	2.06	-0.11	-3.03	.003	-10.30, -2.20	.008	sig.
Postcentral gyrus	L	-5.83	2.25	-0.09	-2.59	.010	-10.24, -1.41	.006	sig.
	R	-5.58	2.27	-0.09	-2.45	.014	-10.04, -1.11	.005	sig.
Precuneus	L	-4.84	1.95	-0.09	-2.49	.013	-8.66, -1.02	.005	sig.
	R	-3.63	2.03	-0.06	-1.79	.074	-7.62, 0.35	.002	**n.s.**
Posterior Cingulate	L	-4.46	1.65	-0.09	-2.70	.007	-7.70, -1.22	.006	sig.
	R	-2.22	1.48	-0.05	-1.50	.134	-5.13, 0.69	.001	**n.s.**
Middle Temporal	L	-4.65	1.73	-0.09	-2.68	.007	-8.05, -1.25	.006	sig.
	R	-4.68	1.81	-0.09	-2.58	.010	-8.25, -1.12	.006	sig.
Superior Temporal	L	-4.74	1.73	-0.10	-2.74	.006	-8.14, -1.34	.007	sig.
	R	-6.73	1.81	-0.13	-3.71	<.001	-10.29, -3.17	.014	sig.
Lateral Occipital	L	-4.83	2.10	-0.08	-2.30	.021	-8.95, -0.72	.004	sig.
	R	-2.22	2.17	-0.04	-1.02	.307	-6.48, 2.04	-.001	**n.s.**

Note: L=left; R=Right; FDR=False discovery rate (sig. indicates q < .05); DLPFC = Dorsolateral prefrontal cortex; ACC = Anterior cingulate cortex; OFC = Orbitofrontal cortex; IFG = Inferior frontal gyrus; ΔR^2 = change in R^2 from covariate model (R^2=.207)

Table 4. Cortical Thickness in Individual Regions of Interest Predicting Heavy Drinking Frequency

Region / Composite	**L/R**	**B**	**SE**	**β**	**t**	**p**	**95% CI**	**ΔR^2**	**FDR**
DLPFC	L	-1.08	0.33	-0.12	-3.28	.001	-1.73, -0.43	.010	sig.
	R	-1.08	0.35	-0.11	-3.11	.002	-1.77, -0.40	.009	sig.
ACC	L	-0.79	0.26	-0.11	-3.07	.002	-1.29, -0.28	.009	sig.
	R	-0.27	0.21	-0.04	-1.25	.210	-0.68, 0.15	.000	**n.s.**
Insula	L	-0.65	0.26	-0.09	-2.48	.014	-1.17, -0.13	.005	sig.
	R	-0.35	0.29	-0.04	-1.20	.230	-0.91, 0.22	.000	**n.s.**
OFC	L	-0.30	0.31	-0.03	-0.96	.339	-0.91, 0.31	-.001	**n.s.**
	R	-0.50	0.34	-0.05	-1.49	.137	-1.16, 0.16	.001	**n.s.**
IFG	L	-0.92	0.32	-0.10	-2.90	.004	-1.55, -0.30	.008	sig.
	R	-0.70	0.33	-0.07	-2.13	.034	-1.35, -0.05	.003	**n.s.**
Precentral gyrus	L	-1.03	0.31	-0.11	-3.27	.001	-1.65, -0.41	.010	sig.
	R	-1.04	0.34	-0.11	-3.01	.003	-1.71, -0.36	.009	sig.
Postcentral gyrus	L	-1.00	0.38	-0.09	-2.67	.008	-1.74, -0.27	.006	sig.
	R	-1.07	0.38	-0.10	-2.82	.005	-1.81, -0.32	.007	sig.
Precuneus	L	-0.60	0.33	-0.06	-1.84	.066	-1.24, 0.04	.002	**n.s.**
	R	-0.60	0.34	-0.06	-1.78	.075	-1.27, 0.06	.002	**n.s.**
Posterior Cingulate	L	-0.66	0.28	-0.08	-2.40	.016	-1.20, -0.12	.005	sig.
	R	-0.70	0.25	-0.10	-2.86	.004	-1.19, -0.22	.008	sig.
Middle Temporal	L	-0.69	0.29	-0.08	-2.37	.018	-1.26, -0.12	.005	sig.
	R	-0.70	0.30	-0.08	-2.32	.021	-1.30, -0.11	.004	sig.
Superior Temporal	L	-0.33	0.29	-0.04	-1.15	.252	-0.90, 0.24	.000	**n.s.**
	R	-0.89	0.30	-0.10	-2.92	.004	-1.49, -0.29	.008	sig.
Lateral Occipital	L	-0.66	0.35	-0.07	-1.87	.061	-1.34, 0.03	.002	**n.s.**
	R	-0.29	0.36	-0.03	-0.80	.423	-1.00, 0.42	-.001	**n.s.**

Note: L=left; R=Right; FDR=False discovery rate (sig. indicates q < .05); DLPFC = Dorsolateral prefrontal cortex; ACC = Anterior cingulate cortex; OFC = Orbitofrontal cortex; IFG = Inferior frontal gyrus; ΔR^2 = change in R^2 from covariate model (R^2=.195)

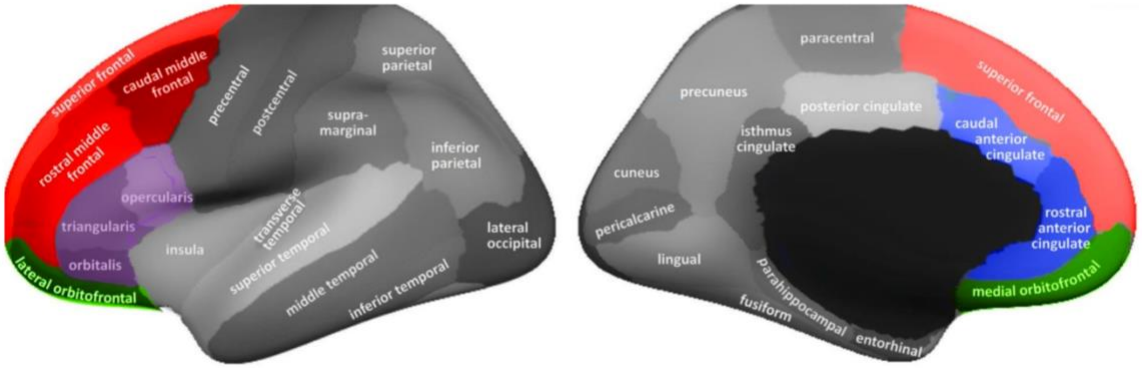
Table 5. Sex × Region of Interest Interactions in Regression Models Predicting Drinks in Past Week

Region / Composite	**L/R**	**B**	**SE**	**β**	**t**	**p**	**95% CI**	**ΔR^2**	**FDR**
DLPFC	L	-1.17	0.45	-0.13	-2.58	.010	-2.06, -0.28	.003	**sig.**
	R	-0.90	0.45	-0.10	-1.99	.047	-1.79, -0.01	.009	n.s.
ACC	L	-1.16	0.45	-0.13	-2.58	.010	-2.04, -0.28	.016	**sig.**
	R	-0.54	0.45	-0.05	-1.19	.234	-1.43, 0.35	.009	n.s.
Insula	L	-1.31	0.46	-0.14	-2.85	.005	-2.22, -0.41	.013	**sig.**
	R	-0.73	0.47	-0.08	-1.56	.118	-1.65, 0.19	.004	n.s.
OFC	L	-1.36	0.45	-0.15	-2.99	.003	-2.25, -0.47	.016	**sig.**
	R	-0.62	0.45	-0.07	-1.37	.170	-1.51, 0.27	.015	n.s.
IFG	L	-1.35	0.45	-0.15	-3.00	.003	-2.23, -0.47	.020	**sig.**
	R	-1.16	0.45	-0.13	-2.56	.011	-2.04, -0.27	.008	**sig.**
Precentral gyrus	L	-0.87	0.45	-0.10	-1.92	.056	-1.76, 0.02	.019	n.s.
	R	-0.44	0.46	-0.05	-0.96	.336	-1.33, 0.46	.023	n.s.
Postcentral gyrus	L	-0.50	0.45	-0.05	-1.10	.273	-1.38, 0.39	.007	n.s.
	R	-0.57	0.45	-0.06	-1.28	.202	-1.46, 0.31	.009	n.s.
Precuneus	L	-0.36	0.45	-0.04	-0.78	.435	-1.25, 0.54	.017	n.s.
	R	0.29	0.45	0.03	0.64	.519	-0.60, 1.18	.010	n.s.
Posterior Cingulate	L	-1.08	0.45	-0.12	-2.41	.016	-1.96, -0.20	.021	**sig.**
	R	0.05	0.45	0.01	0.10	.918	-0.84, 0.93	.018	n.s.
Middle Temporal	L	-1.09	0.45	-0.12	-2.40	.016	-1.97, -0.20	.005	**sig.**
	R	-0.58	0.46	-0.07	-1.28	.203	-1.48, 0.31	.002	n.s.
Superior Temporal	L	-1.35	0.45	-0.15	-2.99	.003	-2.23, -0.46	.011	**sig.**
	R	-1.15	0.45	-0.13	-2.54	.011	-2.04, -0.26	.003	**sig.**
Lateral Occipital	L	-0.86	0.45	-0.09	-1.90	.058	-1.74, 0.03	.018	n.s.
	R	-0.58	0.46	-0.06	-1.27	.203	-1.48, 0.31	.015	n.s.

Note: L=left; R=Right; FDR=False discovery rate (sig. indicates q < .05); DLPFC = Dorsolateral prefrontal cortex; ACC = Anterior cingulate cortex; OFC = Orbitofrontal cortex; IFG = Inferior frontal gyrus; ΔR^2 = change in R^2 from covariate model (R^2=.176).

Figure 1. Anatomical Locations of FreeSurfer Regions of Interest

Lateral (top) and medial (bottom) views of inflated brain surface showing locations of regions of interest produced by cortical segmentation in FreeSurfer. The four composite regions are depicted in color: DLPFC is shown in red (consisting of superior frontal gyrus, and caudal and rostral middle frontal gyrus); ACC is shown in blue (consisting of caudal and rostral anterior cingulate); OFC is shown in green (comprised of lateral and medial OFC); IFG is shown in purple (comprised on *pars opercularis*, *pars orbitalis*, and *pars triangularis* sub-regions).



2.7 Supplementary Material

Supplementary Table 1.
Correlations between cortical thickness values in the *a priori* regions of interest. Part 1 (below) provides region labels that correspond to column and row numbers in Part 2 (next page).

#	Region	L/R
1	DLPFC	L
2	ACC	L
3	Insula	L
4	OFC	L
5	IFG	L
6	Precentral gyrus	L
7	Postcentral gyrus	L
8	Precuneus	L
9	Posterior Cingulate	L
10	Middle Temporal	L
11	Superior Temporal	L
12	Lateral Occipital	L
13	DLPFC	R
14	ACC	R
15	Insula	R
16	OFC	R
17	IFG	R
18	Precentral gyrus	R
19	Postcentral gyrus	R
20	Precuneus	R
21	Posterior Cingulate	R
22	Middle Temporal	R
23	Superior Temporal	R
24	Lateral Occipital	R

Note: L=left; R=Right;
DLPFC = Dorsolateral prefrontal cortex;
ACC = Anterior cingulate cortex;
OFC = Orbitofrontal cortex;
IFG = Inferior frontal gyrus

Supplementary Table 1 (continued)

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
1	--																							
2	.46	--																						
3	.41	.38	--																					
4	.63	.47	.47	--																				
5	.79	.45	.51	.66	--																			
6	.79	.41	.44	.49	.70	--																		
7	.62	.35	.39	.42	.60	.67	--																	
8	.67	.37	.40	.48	.62	.67	.63	--																
9	.48	.44	.30	.36	.43	.43	.34	.45	--															
10	.62	.37	.48	.51	.67	.63	.55	.64	.41	--														
11	.62	.47	.53	.56	.68	.62	.61	.63	.40	.71	--													
12	.54	.37	.45	.48	.58	.59	.64	.69	.37	.65	.63	--												
13	.85	.37	.31	.51	.68	.68	.53	.60	.36	.53	.53	.46	--											
14	.25	.39	.24	.25	.25	.19	.13	.18	.24	.22	.19	.12	.28	--										
15	.29	.24	.44	.38	.32	.26	.25	.24	.13	.33	.35	.28	.36	.22	--									
16	.56	.38	.38	.65	.57	.43	.35	.44	.27	.45	.48	.40	.65	.31	.39	--								
17	.68	.38	.39	.56	.73	.57	.50	.55	.32	.57	.60	.50	.79	.27	.44	.68	--							
18	.66	.32	.34	.36	.57	.77	.55	.58	.30	.51	.51	.50	.75	.22	.35	.49	.65	--						
19	.50	.25	.29	.30	.47	.53	.77	.52	.23	.44	.48	.53	.60	.15	.30	.43	.56	.57	--					
20	.55	.26	.31	.32	.51	.56	.51	.75	.34	.54	.51	.56	.64	.23	.29	.47	.59	.65	.57	--				
21	.33	.25	.20	.23	.30	.26	.21	.29	.37	.28	.23	.23	.35	.55	.19	.29	.31	.30	.24	.35	--			
22	.55	.28	.37	.44	.55	.52	.49	.54	.29	.68	.58	.55	.65	.19	.43	.55	.69	.60	.57	.62	.30	--		
23	.51	.36	.41	.42	.55	.52	.52	.50	.29	.56	.75	.52	.60	.23	.44	.52	.66	.59	.58	.59	.27	.69	--	
24	.40	.25	.32	.33	.45	.45	.53	.55	.23	.52	.48	.71	.51	.15	.35	.46	.55	.56	.60	.62	.28	.63	.57	--

Note: Color scale denotes effect size (r): Red = < .30; Orange = .30 - .49; Light green = .50 - .69; Dark green = .70 – 1.0

Supplementary Table 2.
Covariate Models Predicting Drinks per Week and Frequency of Heavy Drinking

Covariate	B	SE	β	t	p	95% CI	R^2
Drinks per Week							.207
Sex	-3.13	0.60	-0.24	-5.21	<.0001	-4.31, -1.95	
Age	-0.07	0.07	-0.04	-1.07	.283	-0.20, 0.06	
Income	0.04	0.12	0.01	0.35	.729	-0.19, 0.27	
Education	0.25	0.15	0.07	1.75	.081	-0.03, 0.54	
Tobacco Use	0.02	0.01	0.06	1.62	.106	0.00, 0.04	
Cannabis Use	0.68	0.18	0.18	3.74	<.0001	0.32, 1.04	
Other Drug Use	0.80	0.23	0.15	3.51	<.0001	0.35, 1.25	
Urine Screen (Pos/Neg)	0.09	0.77	0.00	0.12	.901	-1.41, 1.06	
MZ Twin Status	-0.74	0.54	-0.05	-1.36	.174	-1.80, 0.33	
DZ Twin Status	0.19	0.66	0.01	0.29	.772	-1.10, 1.48	
Total ICV	0.00	0.00	0.03	0.75	.456	0.00, 0.00	
Heavy Drinking Frequency							.144
Sex	-0.53	0.10	-0.24	-5.26	<.0001	-0.72, -0.33	
Age	-0.04	0.01	-0.14	-3.75	<.0001	-0.06, -0.02	
Income	0.02	0.02	0.04	1.03	0.304	-0.02, 0.06	
Education	0.00	0.02	0.00	0.02	0.981	-0.05, 0.05	
Tobacco Use	0.00	0.00	0.07	1.78	0.076	0.00, 0.01	
Cannabis Use	0.16	0.03	0.25	5.26	<.0001	0.10, 0.22	
Other Drug Use	0.00	0.04	0.00	-0.07	0.941	-0.08, 0.07	
Urine Screen (Pos/Neg)	-0.06	0.13	-0.02	-0.43	0.665	-0.31, 0.20	
MZ Twin Status	-0.10	0.09	-0.04	-1.13	0.259	-0.28, 0.08	
DZ Twin Status	-0.03	0.11	-0.01	-0.27	0.790	-0.24, 0.19	
Total ICV	0.00	0.00	0.04	0.87	0.384	0.00, 0.00	

Note: MZ = monozygotic; DZ = dizygotic; ICV = intracranial volume; Sex (0 = male; 1 = female)

Supplementary Table 3
Exploratory Correlations between Cognitive Performance, Alcohol Variables, and Cortical Thickness

Variable	L/R	Executive Function (Flanker)	Working Memory (List Sorting)
Drinks per Week	-	.034	.046
Heavy Drinking Frequency	-	.052	.013
DLPFC	L	-.011	.010
ACC	L	.002	.036
Insula	L	.070	.084
OFC	L	.005	.060
IFG	L	.002	.021
Precentral gyrus	L	.006	.054
Postcentral gyrus	L	.021	.063
Precuneus	L	.020	.054
Posterior Cingulate	L	-.013	.117*
Middle Temporal	L	.070	.115*
Superior Temporal	L	.061	.082
Lateral Occipital	L	.053	.087
DLPFC	R	.031	.037
ACC	R	.010	.041
Insula	R	.073	.116*
OFC	R	.071	.078
IFG	R	.049	.066
Precentral gyrus	R	.052	.090*
Postcentral gyrus	R	.061	.087
Precuneus	R	.041	.112*
Posterior Cingulate	R	.018	.111*
Middle Temporal	R	.084	.102*
Superior Temporal	R	.060	.110*
Lateral Occipital	R	.070	.108*

Note: *Statistically significant after FDR $q < .05$;
L=left; R=Right; DLPFC = Dorsolateral prefrontal cortex; ACC = Anterior cingulate cortex; OFC = Orbitofrontal cortex; IFG = Inferior frontal gyrus

Chapter 3: An Initial Investigation of Disrupted Intracortical Myelin as a Novel Brain Marker of Alcohol Use Disorder

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3.1 Abstract

Introduction: Although disruption of cortical gray matter and white matter tracts are well-established markers of alcohol use disorder (AUD), this is the first study to examine the specific role of intracortical myelin (ICM; i.e., highly myelinated gray matter in deeper cortical layers) in AUD. The current study used a 3T MRI sequence optimized for high intracortical contrast to examine patterns of ICM-related MRI signal in 30 individuals with AUD and 33 healthy social drinkers. Secondary aims included exploring continuous associations with alcohol problem severity and examining sex differences.

Methods: Surface-based analytic techniques were used to quantify ICM-related MRI signal for *a priori* region of interest analyses (20 bilateral regions) and exploratory vertex-wise analyses (using Cohen's d).

Results: Although the distribution of ICM-related signal was generally comparable between groups, the AUD group exhibited significantly (p<.05) greater ICM-related MRI signal in precuneus, ventromedial prefrontal cortex, posterior cingulate, middle anterior cingulate, middle/posterior insula, dorsolateral prefrontal cortex, and posterior cingulate, among other regions (Cohen's d = .50-.75, indicating medium magnitude effects). Significant positive correlations between ICM signal and AUD severity were found in several frontal, parietal, cingulate, and temporal regions (rs .25-.34). No sex differences in ICM were observed.

Discussion: These findings provide initial proof-of-concept for examining ICM in relation to AUD. Understanding the pathophysiological mechanisms of these associations (e.g., neuroinflammation) and the clinical relevance of ICM is warranted.

3.2 Introduction

Structural and functional disruptions of the cerebral cortex are well-established indicators of alcohol use disorder (AUD) (Fritz, Klawonn, & Zahr, 2019; Sullivan, Harris, & Pfefferbaum, 2010). People who meet criteria for AUD have been found to exhibit reduced cortical thickness (Durazzo et al., 2011; Fortier et al., 2011), reduced white and grey matter volume (Bühler & Mann, 2011), as well as reduced volume in the frontal cortex and other cortical and sub-cortical regions (Durazzo et al., 2011; Momenan & Grodin, 2017; Yang et al., 2016) relative to people without an AUD. Cortical thickness deficits are related to a number of clinical indicators in AUD, including associations with degree of alcohol use and misuse (Fortier et al., 2011; Mashhoon et al., 2014), poor AUD treatment outcomes (Durazzo et al., 2011), and impaired inhibitory control in people with AUD (Pennington et al., 2015). Although it has been theorized that the brain reaches peak development at roughly twenty-five years of age (Arain et al., 2013), some literature suggests that white matter may have a more prolonged trajectory (Bartzokis, 2011; Haroutunian et al., 2014). Various studies have found that while grey matter may peak in one's mid-twenties, heavily-myelinated white matter on the other hand, may not fully develop until the third, fourth, or fifth decade of one's life (Haroutunian et al., 2014; Sowell et al., 2003). As a result of this deferred development, white matter remains inherently sensitive and susceptible to damage from the use of addictive substances, environmental effects, and physical insults (Filley, McConnell, & Anderson, 2017). Reasons for the extended vulnerability in white matter include its low level of blood supply (Bartzokis, 2011; Filley et al., 2017; Haroutunian et al., 2014) and the extensive energy requirements of oligodendrocyte function (Bartzokis, 2011; Filley et al., 2017; Haroutunian et al., 2014). Increased focus on studying associations between brain myelination and substance use disorders is an important and clinically-significant priority.

Although cortical deficits in AUD are generally well-established, the cerebral cortex is highly heterogenous with respect to types of neuronal tissue (Nieuwenhuys, 2013). In particular, there is growing interest in characterizing the role of myelin in the cortex. Myelin serves many functions, including increasing action potential transmission speed, improving neuronal synchrony, increasing brain connectivity, decreasing refractory time, and supporting cognitive functions (Haroutunian et al., 2014). Although primarily concentrated in neuronal tracts in the white matter, myelinated axons are also found in the cortex, with deeper layers (IV-VI) being more heavily myelinated than the superficial layers (I-III) (Rowley et al., 2015). These deeper, myelinated layers of the cortex represent what has been termed *intracortical myelin* (ICM) (Rowley et al., 2015). Similar to myelin in white matter, ICM reaches peak development between the third to fifth decade of one's life (Haroutunian et al., 2014; Sowell et al., 2003) and thus remains vulnerable to toxins and damage (Haroutunian et al., 2014; Unterrainer et al., 2019). Intracortical myelin is thought to play a central role in synchronizing and speeding of neuronal signals through the cortex in support of cognitive processing. For example, research has shown that decreased ICM in posterior cingulate cortex in healthy individuals is correlated with decreased error processing and cognitive control (Grydeland, Westlye, Walhovd, & Fjell, 2015) and reduced ICM in insula and superior temporal gyrus is associated with increased performance variability (Grydeland, Walhovd, Tamnes, Westlye, & Fjell, 2013).

Since the magnetic resonance imaging (MRI) signal is very sensitive to the presence of myelin, several MRI protocols have been developed to image ICM content *in vivo* (Bock et al., 2013; Glasser & Van Essen, 2011). In the protocol developed by Bock et al. (Bock et al., 2013), the T1-weighted MRI contrast was optimized for differentiating cortical regions with low and high myelin content. This T1 image is commonly divided by a proton-density-weighted image to

generate a ratio image that is strongly T1-weighted with high intracortical contrast. Image processing tools are then applied to generate a whole-brain map of the ICM ratio signal that is projected on the middle-depth cortical surface. Various studies have confirmed these *in vivo* MRI measurements of ICM by comparing the MRI maps to histological samples of nonhuman primate brain tissue (Bock, Kocharyan, Liu, & Silva, 2009), as well as samples of post-mortem human brain tissue (Fracasso et al., 2016). The results of these histological studies confirm that MRI-generated ICM maps provide an accurate representation of underlying myeloarchitecture across the cortex.

The MRI protocol developed by Bock et al. has been used in multiple studies of ICM in healthy (Rowley et al., 2015; Manpreet Sehmbi et al., 2019a) and clinical populations (Rowley et al., 2015; M. Sehmbi et al., 2018a; Manpreet Sehmbi et al., 2019a). For example, it has been suggested that disruptions in ICM may partially underlie susceptibility to the development of mental health disorders such as bipolar disorder and schizophrenia (Haroutunian et al., 2014). Rowley et al., (2015) used MRI with high intracortical contrast in a sample of healthy adult females and female participants with bipolar disorder. They examined total cortical thickness, as well as myelinated (ICM) and unmyelinated cortical thicknesses. The healthy participants displayed the greatest degree of myelination in the precentral gyrus, postcentral gyrus, Heschel's gyrus, posterior cingulate gyrus, as well as visual cortex, which is consistent with other research demonstrating that the human motor cortex (located on the precentral gyrus) displays the highest degree of myelinated fiber density (Miller et al., 2012). The comparison of healthy participants to those with bipolar disorder revealed that total cortical thickness was significantly reduced in the bipolar disorder group, and that there was a trend towards less cortical myelination in the bipolar disorder group (Rowley et al., 2015). Additional research examining white matter in

bipolar disorder has found that patients have fewer oligodendrocytes, reduced myelin-related genes, and significant age-related deficits in ICM development (Lewandowski et al., 2015; Öngür, Drevets, & Price, 1998; Tkachev et al., 2003; Uranova, Vostrikov, Orlovskaya, & Rachmanova, 2004). Moreover, impairments in neurocognitive performance (i.e., verbal memory) have been associated with ICM in patients with bipolar disorder (M. Sehmbi et al., 2018a). In the context of schizophrenia, ICM has been shown to be dysregulated in the frontal lobes (Bartzokis et al., 2012). More recently, Tishler et al. (Tishler et al., 2018) found that patients with schizophrenia displayed a significantly different age-related ICM trajectory compared to healthy controls.

The studies reviewed above suggest that ICM may be an important neural marker of psychiatric disorders; however there has yet to be a study examining ICM in addictive disorders even though there is evidence to suggest that myelin and ICM are inherently sensitive and vulnerable to neurotoxins, such as alcohol (Filley et al., 2017). One study found that mice subjected to maternal binge-drinking in utero, exhibited reductions in multiple myelin-related proteins that were associated with various neurocognitive impairments (motor coordination, spatial awareness, etc.) (Cantacorps et al., 2017). As mentioned previously, there is a variety of evidence demonstrating cortical thickness and brain volume deficits in AUD, but these studies have largely examined indices of total cortical thickness or gray matter volume which do not take into account the rich neurobiology of the cortex. Fortunately, the ability to image ICM-related signal *in vivo* with the optimized MRI pulse sequences described above affords a unique opportunity to explore differential effects in cortical sub-units. This research may elucidate whether the overall cortical reductions and disruptions are attributable its myelin content.

The current study examined ICM in adults with AUD compared to social drinkers without AUD using the Bock et al. (Bock et al., 2013) optimized MRI protocol for imaging ICM *in vivo* and a post-processing protocol for investigating changes over the cortical surface (Glasser et al., 2013). Being the first study to examine ICM in relation to AUD, we refrained from composing a directional hypothesis and instead assumed that there would be some degree of change in ICM signal between the two groups. We also examined continuous associations between ICM and alcohol problem severity as assessed by the Alcohol Use Disorders Identification Test (AUDIT) questionnaire (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993). We selected nine bilateral *a priori* regions of interest (ROIs) based on theoretical models implicating frontal lobe circuitry (Crews & Boettiger, 2009; Koob & Volkow, 2010; Longo et al., 2016), cortical thickness findings from previous AUD studies (Durazzo et al., 2011; Fortier et al., 2011; Lawyer et al., 2010; Mashhoon et al., 2014; Momenan et al., 2012; Morris et al., 2019), and studies of neurocognitive correlates of ICM (Grydeland et al., 2013, 2015). The ROIs examined included: middle frontal gyrus (MFG), superior frontal gyrus (SFG), inferior frontal gyrus (IFG), anterior cingulate (ACC), posterior cingulate (PCC), anterior insula, superior temporal gyrus (STG), middle temporal gyrus (MTG), and precuneus, orbital frontal gyrus (OFG), and dorsolateral prefrontal cortex (DLPFC). A whole-brain vertex-wise analysis examined effect size differences outside of the a priori ROIs. An exploratory aim of the current study was to examine ICM differences between male and female participants. A number of studies have identified differences between males and females with addictive disorders in relation to epidemiology, treatment outcomes, and effects on brain structure and function (for review see McHugh, Votaw, Sugarman, & Greenfield, 2018). Significant sex disparity still exists in structural brain imaging studies, with many studies not routinely reporting sex differences.

3.3 Materials and Methods

3.3.1 Participants

Participants were recruited from the Hamilton, Ontario, Canada community including four addiction treatment centers in the region. All participants had to be between the ages of 25-55, have no contraindications against MRI, no history of severe head or brain trauma with loss of consciousness, neurological disorder, or severe psychiatric disorder (schizophrenia, bipolar disorder, post-traumatic stress disorder), and meet criteria for current AUD or non-hazardous social drinking. Specifically, participants in the AUD group (*N*=30) met DSM-5 criteria for AUD and did not meet DSM-5 for any substance use disorder other than nicotine dependence. Participants in the social drinker (control) group (*N*=33) reported drinking on at least a weekly basis, but did not exceed NIAAA weekly drinking limits of ≥14/7 drinks per week for males/females and did not meet DSM-5 criteria for AUD or SUD, except for nicotine dependence. For full demographics, please see Table 1.

3.3.2 Procedures

The Hamilton Integrated Research Ethics Board approved the study (Project #1747) and participants provided informed consent. Individuals who were interested in participating were first screened to determine their eligibility. Individuals who met all eligibility criteria were then scheduled for the first of two in-person sessions. The first session took place at our laboratory or at the participant's respective treatment centers. During the first session, participants completed a battery of self-report questionnaires, a clinical interview, and neurocognitive measures. Upon completion of the first session, participants received a $25 gift card to local stores. Those who were eligible and interested in continuing were then scheduled for an MRI at the Imaging

Research Centre at St. Joseph's Healthcare Hamilton. All participants completed MRI safety screening with the MRI technologist. The MRI scan lasted roughly 40 minutes, after which participants were debriefed, received a $25 gift card, and the session concluded.

3.3.3 Measures

Participants completed a variety of clinical and individual differences measures during the first session. These measures were administered either on the computer, one-on-one with a researcher, or individually using paper and pencil forms.

Structured Clinical Interview DSM-5 (SCID-5). Diagnoses of current (i.e., in last 12 months) alcohol use disorder and substance use disorder were obtained via the Structured Clinical Interview for DSM-5 (SCID-5; First, Williams, Karg, & Spitzer, 2015). All participants completed the alcohol use disorder module and participants who reported using drugs also completed the substance use disorder module for their most often used substance.

Alcohol-related Problems. The AUDIT (Saunders et al., 1993) was used as a self-report measure of drinking behavior and alcohol-related problems. The AUDIT is a 10-item self-report scale with total scores ranging from 0-40. Scores of 8 or greater are typically considered to be indicative of hazardous alcohol drinking.

Alcohol and Substance Use Frequency. The timeline follow-back interview was used to assess participants' daily alcohol consumption on for the thirty days prior to the assessment (Sobell & Sobell, 1992). The primary dependent measure was the number of drinks consumed per week, however, given that 27 of 30 participants in the AUD group were recruited from treatment

centers, there was a high percentage of participants who reported no drinking in the last 30 days. Thus, the drinks per week variable was for descriptive purposes only and not used in the primary analyses. The modified version of the National Institute on Drug Abuse Alcohol, Smoking and Substance Involvement Screening Test (NIDA Modified ASSIST, https://www.drugabuse.gov/sites/default/files/pdf/nmassist.pdf) assessed frequency of use of ten substances (cannabis, cocaine, prescription stimulants, methamphetamine, inhalants, sedatives, hallucinogens, street opioids, and prescription opioids). Participants rated their use in the past three months, with responses ranging from Never to Multiple Times Daily.

Nicotine Dependence. Participants who reported current smoking completed the Fagerström Test for Nicotine Dependence (FTND; (Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991), a validated self-report assessment of cigarette consumption and nicotine dependence severity.

Demographics. A demographic questionnaire asked participants to provide information on their age, sex assigned at birth, ethnicity, years of education, smoking status, income, and handedness.

3.3.4 Imaging Methods

Image Acquisition. MRI images were acquired on a 3T General Electric Discovery scanner using a 32-channel receive-only radio frequency coil for the head and a transmit radio frequency body coil. All images were acquired with 1mm isotropic resolution using a scan protocol developed by Bock and colleagues (Bock et al., 2013) and used in several prior studies of ICM (Rowley et al., 2015; M. Sehmbi et al., 2018b; Manpreet Sehmbi et al., 2019b). Full details of

the MRI scanning protocol are provided in Supplementary Materials. The total scanning protocol was roughly 40 minutes.

Image Preprocessing and Data Analysis. Image processing was performed predominately in FSL (v6.0.0), Freesurfer (v5.3.0) and Connectome Workbench (Human Connectome Project, v1.3.2). Preprocessing and ICM quantification closely followed published procedures (Glasser et al., 2013; Rowley et al., 2015; Manpreet Sehmbi et al., 2019b). The complete preprocessing pipeline is described in Supplementary Materials. Briefly, preprocessing included motion correction, registration to MNI space, spatial smoothing (5x5x5mm 3D median filter). A strongly T_1-weighted ratio image was created by dividing the T_1-weighted high intracortical contrast image by the filtered proton-density-weighted image. This removed radiofrequency receive field (B_1-) inhomogeneities, some radiofrequency transmit field (B_1+) inhomogeneities, and T_2*-weighting arising from the gradient echo readout in the inversion-recovery image. Freesurfer segmentation was performed using *recon-all*. The remaining processing steps closely followed the Human Connectome Project's minimal processing pipeline using custom scripts for myelin mapping adapted from the HCP scripts (Glasser et al., 2013). Each participant's ratio image signal is projected onto the ½ cortical depth surface (HCP midthickness surface) using Matlab's SurfStat toolbox.

Group comparisons were performed using an *a priori* anatomical ROI approach and a whole-brain vertex-wise analysis. ROIs were generated using the multi-modal parcellation atlas (MMP) (Glasser et al., 2017). To reduce inflation of type-1 error due to many small regions, we consolidated neighboring ROIs into composite regions corresponding to our *a priori* ROIs. The 40 ROIs examined (20 symmetrical regions per hemisphere) are provided in Table 2 and anatomical locations are visualized in Figure 1 (see Supplementary Table 1 for MPP region numbers).

The mean ICM signal within each ROI was extracted and exported to SPSS Version 26 for group analyses using analysis of covariance models. Covariates were selected based on a two-step process. Demographic and substance use variables that differed significantly between groups were subsequently examined in bivariate correlations with overall ICM-related ratio signal (sum of 20 ROIs per hemisphere). Only covariates that were significantly correlated at $p<.05$ were included. An exploratory vertex-wise analysis was conducted by calculating effect size (Cohen's d) for differences between groups at each vertex. Finally, sex differences were explored by repeating the primary group comparisons including sex as a between-subjects factor. Given that this is the first study to characterize ICM in AUD, we elected to be comprehensive and report statistical significance at $p<.05$.

3.4 Results

3.4.1 Sample Characteristics

The AUD group (N=30) did not differ significantly from the control group (N=33) with regard to sex, age, race, or handedness (Table 1). By nature of the case-control design, the AUD group had a higher AUDIT score and drinks per week. Compared to the AUD group, the control group reported higher education and higher median income. Finally, a greater percentage of participants in the AUD group reported weekly use of cannabis (although no participants met DSM-5 criteria for cannabis use disorder) or being a current cigarette smoker.

3.4.2 ICM Group Maps

Surface visualization maps depicting ICM-related ratio signal for both the AUD and the control group are shown in Figure 2, Panels A-B. The pattern of anatomical distribution of ICM across groups was generally similar with the highest concentrations present throughout the visual

cortex, primary motor and primary sensory regions, medial regions such as the anterior cingulate cortex (ACC), and the temporal pole. Visual comparison of the AUD and control maps suggests greater ICM-related MRI signal in the AUD group (indicated by darker or more extensive red areas in the maps), particularly in medial frontal regions in the left hemisphere, the cingulate gyrus in both hemispheres, and the anterior temporal lobe in the right hemisphere.

3.4.3 Region of Interest Analysis

Mean ICM-related ratio signal was extracted from the 40 *a priori* ROIs and group differences were examined using ANOVA. Although there were significant differences in a number of potential covariates (see Table 1), none of these variables were significantly correlated with overall ICM in left or right hemisphere (rs<.15) although the correlation between smoking status and right hemisphere ICM was marginally significant (r=.25, p=.053). Thus, we elected to conduct the primary analyses with no covariates and then examine whether covarying for smoking impacted the statistical results.

The AUD group exhibited significantly increased ICM-related ratio signal in ten regions (see Figure 3 for ICM signal by group and Table 3 for statistical results). These included precuneus, ventromedial prefrontal cortex, posterior cingulate, and middle ACC in the left hemisphere; and middle/posterior insula, dorsolateral prefrontal cortex (Brodmann areas 8 and 46), posterior cingulate, temporal pole, and primary motor cortex in the right hemisphere. Of note, effect sizes (Cohen's d) for these significant group differences ranged from .50-.75, reflecting medium magnitude effects. When smoking was covaried, four of these effects remained significant, including precuneus, ventromedial prefrontal cortex and posterior cingulate in the left hemisphere and dorsolateral prefrontal cortex (BA8) in the right hemisphere.

3.4.4 Exploratory Whole-Brain Analysis

We also characterized group differences outside of the *a priori* regions of interest (ROIs) by generating a whole-brain vertex-wise map of effect sizes (Cohen's d) (See Figure 2, Panel C). Here, the largest effect sizes (d's > .70) were located in the temporal pole, the ACC, and various medial and lateral frontal regions.

3.4.5 Associations with Alcohol Problem Severity

Bivariate correlations were conducted to examine whether ICM-related ratio signal was significantly associated with alcohol problem severity as assessed by the AUDIT total score. Significant positive correlations between greater ICM-related signal and greater alcohol problems were found for precuneus and middle ACC in the left hemisphere, and dorsolateral prefrontal cortex (BA8), posterior cingulate, temporal pole, and primary motor cortex in the right hemisphere.

3.4.6 Sex Differences in ICM

Sex differences in ICM-related MRI signal were examined by repeating the primary ANOVA models including sex at birth as an additional between-subjects factor. These analyses did not reveal any significant main effects of Sex (ps > .08) or Sex × Group interactions (ps > .11). Thus, the group differences observed above do not appear to be significantly impacted by participant sex.

3.5 Discussion

The current study is the first to use an optimized MRI pulse sequence to characterize ICM in a sample of participants with AUD and examine potential differences from a sample of healthy social drinkers. Previous research in healthy samples has reported the distribution of

ICM across the cortex and provided initial clues about its role in neurocognitive processing. Prior studies with clinical samples have also indicated significant ICM disruption in people with bipolar disorder (Rowley et al., 2015; M. Sehmbi et al., 2018a; Manpreet Sehmbi et al., 2019b), schizophrenia (Bartzokis et al., 2012; Tishler et al., 2018), and other major mental health disorders (Luo et al., 2019). Despite the increasing use of optimized MRI methods (e.g., Bock et al., 2013), the role of ICM in the pathophysiology of AUD remains unclear. Our results indicated that global distribution of ICM appears to be generally similar between people with AUD and controls; however, a finer-grained analysis among specific ROIs reveals significant differences between groups with small-to-medium effect size magnitudes. In all cases, the AUD group exhibited significantly greater ICM-related ratio signal compared to controls. These initial results provide important proof-of-concept for mapping ICM *in vivo* in people with AUD and, more importantly, offer a foundation for several future directions.

The primary finding was, although ICM does not appear to be globally disrupted in the AUD group, it does appear to differ in specific ROIs. Comparing the two groups, we found significantly higher ICM-related ratio signal in ten regions, including DLPFC, VMPFC, PCC, ACC, posterior insula, and precuneus, among others. When covarying for smoking status, differences in DLPFC, VMPFC, precuneus, and PCC remained significant. Another important finding was the small magnitude positive correlations between higher AUDIT score and greater ICM-related signal in DLPFC, ACC, PCC, precuneus, temporal pole, among other regions. Although we refrained from constructing hypotheses related to directionality, the finding that the AUD group had *more* ICM signal than the control participants was somewhat unexpected. Unfortunately, the cross-sectional design of this study and the relatively large number of participants who were currently engaged in alcohol treatment limit our ability to make inferences

about why ICM was increased or whether differences would remain in participants who were not actively trying to reduce their drinking. Nevertheless, comparing the present results with previous ICM studies in healthy and clinical populations reveals some overlap in key regions. The PCC region in the current study is in the same general location as the Grydeland et al. study in healthy participants that reported associations between ICM in PCC and error processing(Grydeland et al., 2015). Exploring whether increased ICM in PCC in people with AUD is related to neurocognitive performance is an important next step. Differences in DLPFC / Brodmann Area 46 have also been reported in previous studies with patients with bipolar disorder (M. Sehmbi et al., 2018a).

One potential explanation for our somewhat counterintuitive results may be that the increase in ICM signal is a compensatory response to neurotoxic effects or inflammatory responses to extended and excessive alcohol consumption. Alcohol has neurotoxic and inflammatory effects in both humans (Leclercq, De Timary, Delzenne, & Stärkel, 2017; H. J. Wang, Zakhari, & Jung, 2010) and rodents (Pascual, Pla, Miñarro, & Guerri, 2014). As well, neuroinflammation can lead to the initiation of myelin repair (Glezer, Simard, & Rivest, 2007; Tang & Le, 2016), and oligodendrocyte precursor cells may differentiate into remyelinating oligodendrocytes when demyelination is present in the case of an injury or lesion (Setzu et al., 2006). Additionally, the biproducts of neuroinflammation, such as loss of tissue, demyelination, swelling (i.e., edema), can lead to various changes in T1 relaxation times (Albrecht, Granziera, Hooker, & Loggia, 2016) which may also be a possible explanation for the unexpected elevation in of ICM signal in the AUD group relative to controls. Importantly, much of this work is at the cellular level in animal models and should be interpreted with caution when translating findings to humans. However, it is reasonable to speculate that the increased ICM-related signal may stem

from myelin-related compensatory mechanisms. As noted below, a priority for the future is to examine changes in ICM over time in people with AUD, while examining other systemic and central markers of inflammation (e.g., de Timary, Stärkel, Delzenne, & Leclercq, 2017; García-Baos, Alegre-Zurano, Cantacorps, Martín-Sánchez, & Valverde, 2021).

Other priorities for future research include studying a larger sample of participants with a full range of alcohol involvement (e.g., across the continuum from social drinking through mild to severe AUD). As a proof-of-concept study, it was intentional to compare moderate/severe AUD with social drinkers, but a dimensional study will help to further characterize ICM variation in relation to AUD severity. Another important next step is to observe changes in ICM longitudinally which would not only address the question of when ICM-related differences emerge, but also what are the factors that relate to these differences such as timing of initiation of excessive drinking. Due to our cross-sectional design, we are unable to answer many compelling questions, such as whether ICM differences result from excessive alcohol use over time or whether ICM differences are present prior to onset of AUD (i.e., consequence or cause). Another important priority is to examine what happens to ICM when people reduce or stop alcohol consumption following treatment and whether individual differences in ICM at entry to treatment predict subsequent treatment outcomes (e.g., Cardenas et al., 2011; Durazzo et al., 2011).

Other limitations of our current study apart from the cross-sectional design include differences between the AUD and control participants; there were some differences between groups that should lead to some caution while interpreting the results. While some differences were deliberately due to the design (e.g., AUDIT score), there were significant differences in education, income, and proportion of participants who reported tobacco or cannabis use. Of these

variables, only current smoking was associated with ICM and sensitivity analyses revealed that several differences remained even after controlling for smoking status.

In conclusion, this is the first study to our knowledge to examine ICM-related MRI signal in people diagnosed with AUD. The distribution of ICM across the cortex was largely similar between the AUD and control groups, although a more precise analysis revealed several areas of greater ICM signal in the AUD participants. These initial findings offer proof-of-concept for studying ICM in addiction samples and provide a foundation for future studies to unpack the clinical and neurocognitive significance of the differences observed, neurobiological mechanisms (e.g., compensatory or neuroinflammatory changes), and potential for normalization of ICM following treatment.

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Table 1. Sample Characteristics

Variable	**AUD (N = 30)**	**CON (N = 33)**	***p***
Age	39.63 (9.65)	36.93 (10.46)	.29
Sex	33% Female	58% Female	.06
Race	86% White	84% White	.67
Education	14.43 (2.62)	17.45 (2.58)	<.001
Income (Median)	$30-45,000	$60-75,000	<.001
DSM-5 AUD Severity	3% Moderate 97% Severe	N/A	
AUDIT	31.36 (5.50)	3.84 (1.75)	<.001
Drinks/Week	16.06 (24.35)	3.06 (1.98)	.003
Weekly Cannabis	23%	6%	.007
Current Smoker	50%	6%	<.001
FTND Total (smokers)	4.53 (2.67)	2.33 (2.08)	.20
Handedness	80% Right	84% Right	.90

Note: AUD = alcohol use disorder; CON = control; DSM-5 = Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; AUDIT = Alcohol Use Disorders Identification Test; FTND = Fagerstrom Test for Nicotine Dependence

Table 2. Region of Interest Analysis and Associations with Alcohol Severity

		Left Hemisphere				***Right Hemisphere***				***AUDIT Total***	
										Left	***Right***
#	**Region**	***F***	***P***	**ηp²**	**d**	***F***	***P***	**ηp²**	**d**	**r**	**r**
1	Anterior Insula	2.50	0.119	0.039	0.40	3.83	0.055	0.059	0.49	.223	.224
2	Mid-Posterior Insula	2.32	0.133	0.037	0.38	3.99	0.049	0.061	0.50	.222	.225
3	Precuneus	4.66	0.035	0.071	0.54	2.65	0.108	0.042	0.41	.260*	.204
4	Primary Motor (M1)	1.15	0.288	0.019	0.27	5.59	0.021	0.084	0.59	.159	.329**
5	IFG	2.56	0.115	0.040	0.40	1.36	0.249	0.022	0.29	.203	.156
6	DLPFC (BA8)	3.65	0.061	0.057	0.48	8.88	0.004	0.127	0.75	.238	.341**
7	DLPFC (BA9)	2.98	0.090	0.047	0.43	3.36	0.072	0.052	0.46	.220	.207
8	DLPFC (BA46)	3.16	0.080	0.049	0.45	4.25	0.044	0.065	0.52	.234	.225
9	Medial PFC (BA10)	0.74	0.394	0.012	0.21	0.80	0.373	0.013	0.22	.114	.150
10	Medial PFC (BA8)	3.23	0.077	0.050	0.45	1.57	0.216	0.025	0.31	.201	.190
11	Medial PFC (BA9)	2.20	0.143	0.035	0.37	1.22	0.274	0.020	0.28	.186	.151
12	VMPFC	4.27	0.043	0.065	0.52	2.60	0.112	0.041	0.40	.235	.219
13	PCC (BA23)	0.71	0.403	0.012	0.21	0.26	0.610	0.004	0.13	.102	.066
14	PCC (BA31)	4.02	0.049	0.062	0.50	5.28	0.025	0.080	0.58	.241	.290*
15	Middle Cingulate	4.27	0.043	0.065	0.52	3.09	0.084	0.048	0.44	.251*	.226
16	ACC	3.40	0.070	0.053	0.46	2.63	0.110	0.041	0.41	.229	.210
17	STG	1.28	0.262	0.021	0.28	3.25	0.077	0.051	0.45	.156	.235
18	MTG	0.55	0.461	0.009	0.19	3.22	0.078	0.050	0.45	.129	.226
19	ITG	0.36	0.552	0.006	0.15	0.95	0.334	0.015	0.24	.092	.119
20	Temporal Pole	2.74	0.103	0.043	0.41	6.01	0.017	0.090	0.61	.244	.285*

Note: *p<.05; **p<.01; IFG = inferior frontal gyrus; DLPFC = dorsolateral prefrontal cortex; PFC = prefrontal cortex; BA = Brodmann area; VMPFC = ventromedial prefrontal cortex; PCC = posterior cingulate cortex; ACC = anterior cingulate cortex; STG = superior temporal gyrus; MTG = middle temporal gyrus; ITG = inferior temporal gyrus; AUDIT = Alcohol Use Disorders Identification Test

Figure 1. Anatomical locations of *a priori* regions of interest generated from the multimodial parcellation atlas. A total of 20 ROIs were examined in each hemisphere. Region numbers correspond to numeric labels in Table 2, and full list of MMP regions comprising each ROI are provided in Supplementary Table 1.

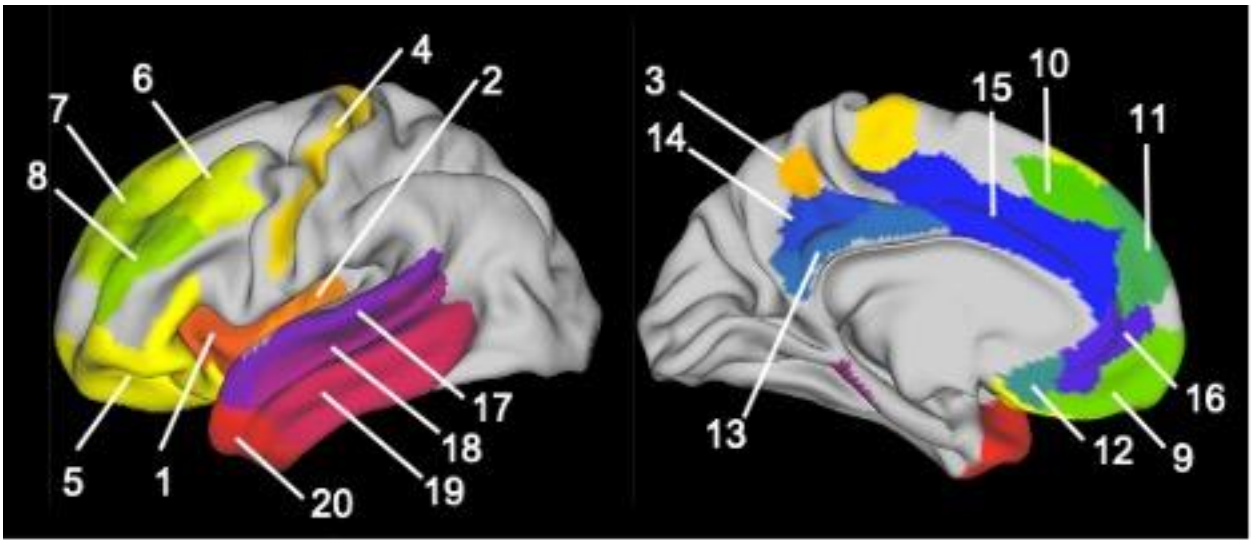


Figure 2. Group average ICM maps for AUD (top) and control (middle) participants. Bottom panel depicts vertex-wise effect size maps (Cohen's d) reflecting differences between AUD and controls. In each panel data are projected onto the middle-depth cortical surface, shown in lateral, medial and superior views for left and right hemispheres separately.

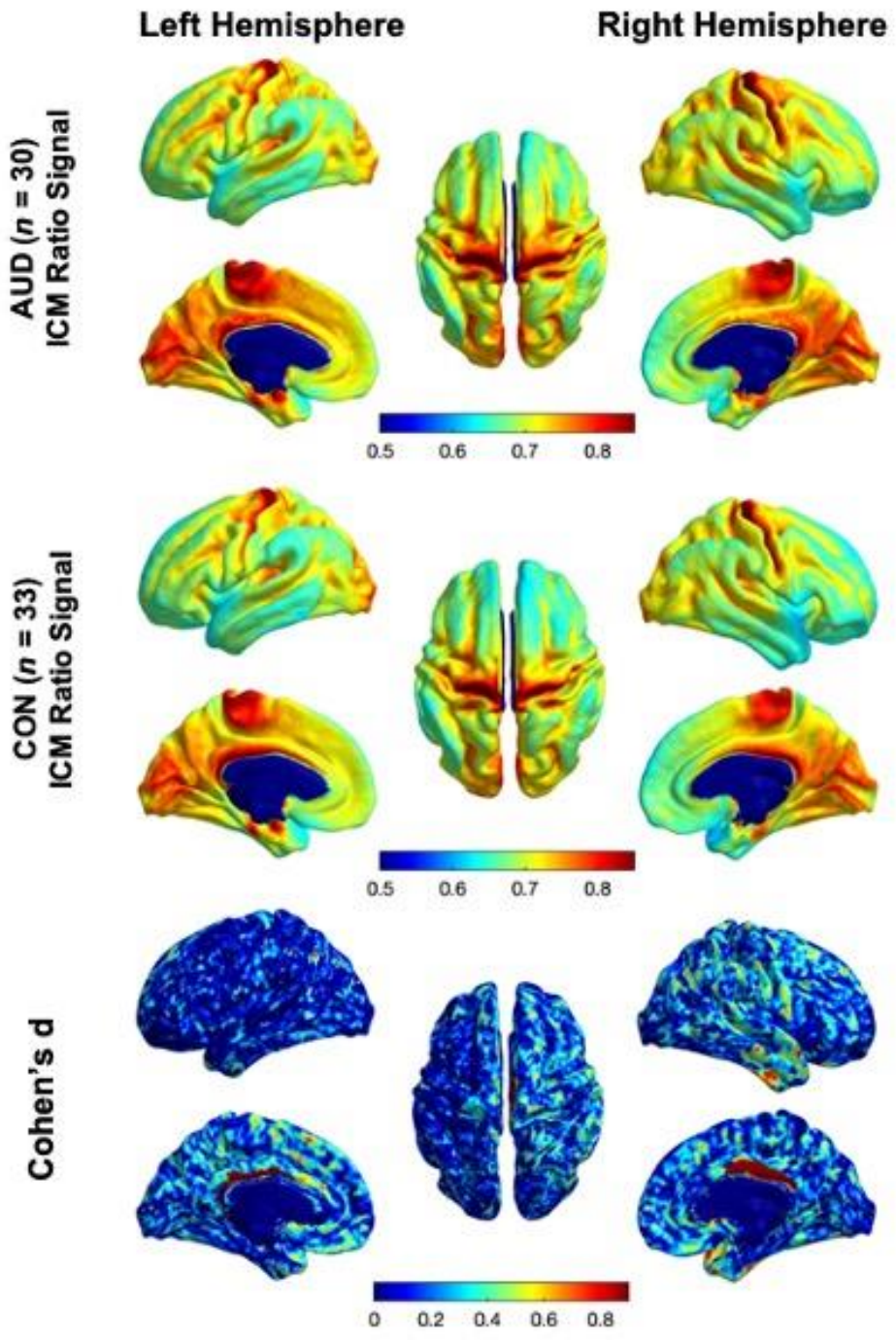
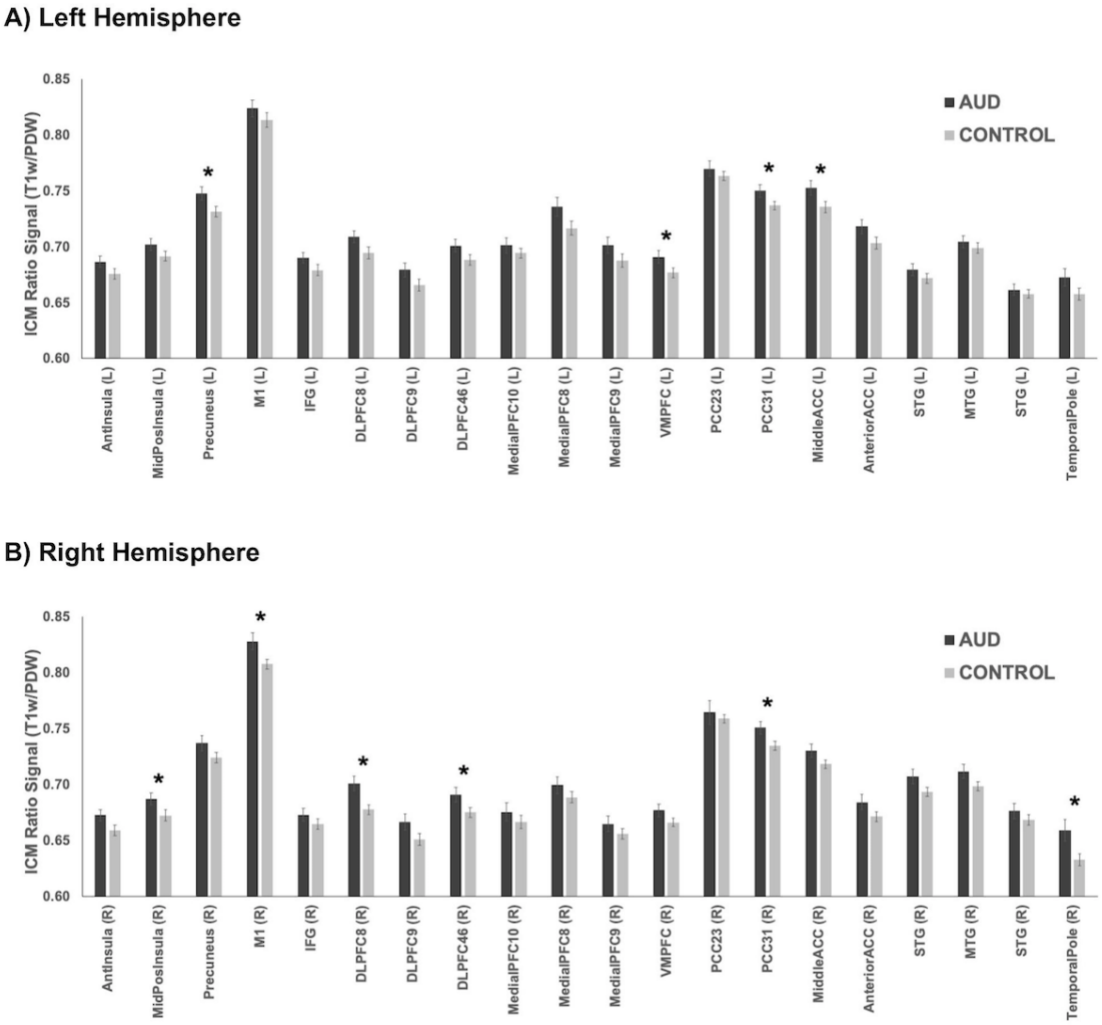


Figure 3. Extracted ICM-related ratio signal values for each *a priori* ROI for left hemisphere (Panel A) and right hemisphere (Panel B). AUD group shown in black; control group shown in gray. Bars reflect mean + 1 standard error. *p<.05. Region abbreviations provided in Table 2.



3.7 Supplementary Materials

Supplementary Methods

MRI Scanning Protocol

For our anatomical reference, we acquired a 3D T1-weighted anatomical image of the whole head using a 3D inversion-recovery gradient-echo sequence (GE 3D BRAVO; Inversion time (TI)=450ms, TE=3.2ms, TR=58.4ms, flip angle=12°, field of view (FOV)=25.6×25.6×25.6cm). This image was used as a reference for all registration steps. We also acquired two T1-weighted images with high intracortical contrast (one per hemisphere) using an inversion-recovery gradient-echo sequence (GE 3D BRAVO; TI=1000ms; TR=8.4ms; TE=3.2ms; flip angle=12°; FOV=24×10×24cm; Matrix=240×100×240cm; time between end of acquisition block and next 180° pulse (TD)=1100ms; centric phase encoding) that was used in the creation of the ICM maps. Each hemisphere was imaged separately, and the resulting images were stitched together to form a complete anatomical image. Lastly, we collected a 3D proton density-weighted image of the whole head (GE 3D FSPGR; TR=7.9ms, TE=3.1ms, flip angle=4°, FOV=24×17×24cm) to normalize intensity inhomogeneities and remove T2*-weighting in the high intracortical contrast T1-weighted image.

Image Preprocessing and ICM Calculations

Raw DICOM image files were assembled into NIFTI datasets using MRIcroGL's *dcm2nii*. To account for head motion between scans, all images were registered to the T_1-weighted image with high intracortical contrast using a 6-parameter linear affine registration using FLIRT. All images (T_1, T_1 with high intracortical contrast, proton density-weighted) were then registered to the MNI 152 T_1 1mm brain atlas. The resulting image was filtered using a 5x5x5 mm 3D median filter. A strongly T_1-weighted ratio image was created by dividing the T_1-

weighted high intracortical contrast image by the filtered proton-density-weighted image. This removed radiofrequency receive field (B_1-) inhomogeneities, some radiofrequency transmit field (B_1+) inhomogeneities, and T_2*-weighting arising from the gradient echo readout in the inversion-recovery image. The ratio image still contained some B_1+ inhomogeneity from the magnetization preparation portion of the inversion-recovery pulse sequence. Freesurfer segmentation was performed using *recon-all*, with manual corrections for gray matter / pial boundary errors. The remaining processing steps closely followed the Human Connectome Project's minimal processing pipeline using custom scripts for myelin mapping adapted from the HCP scripts (Glasser et al., 2013) (https://github.com/Washington-University/HCPpipelines). These scripts use the output of Freesurfer's *recon-all* to generate myelin maps from the image data. Surface data was then brought into MATLAB using gifti toolbox and ICM surface visualizations were created using the SurfStat toolbox.

Supplementary Table 1. Regions of Interest from Multimodal Parcellation Atlas

#	Region	MMP #s
1	Insula (anterior)	109,111,112
2	Insula (middle/posterior)	106,167,168
3	Precuneus	27
4	Primary motor cortex (M1)	8
5	Inferior frontal gyrus / orbitofrontal cortex	66,75,76,77,90, 91,92,93,94,166
6	DLPFC (BA8)	67,68,70,73
7	DLPFC (BA9)	71,87
8	DLPFC (BA46)	83,84,85,86
9	Medial frontal gyrus (BA10)	65,88
10	Medial frontal gyrus (BA8)	63
11	Medial frontal gyrus (BA9)	69
12	Ventromedial PFC	164
13	Posterior cingulate (BA23)	32,33,34
14	Posterior cingulate (BA31)	35,161,162
15	Anterior / Middle cingulate	41,57,58,59,60, 62,179,180
16	Anterior cingulate	61,64,165
17	Superior temporal	123,125,172,28
18	Middle temporal	126,128,129,130,139,176
19	Inferior temporal	132,133,134,137,177
20	Temporal pole	131,172

Chapter 4: Resting State Functional Connectivity in Alcohol Users and Co-Users of Other Substances

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4.1 Abstract

Introduction: Polysubstance use is the use of more than one psychoactive substance either simultaneously or independently and has been reported in roughly 49% of individuals who seek treatment for substance use. Numerous studies have found that polysubstance use is associated with poor cognitive performance as well as abnormalities in brain structure and function. The issue, however, is that many polysubstance use studies have failed to examine illicit drugs or have not included individuals who use more than three substances in their samples. The aim of the current study was to use resting-state functional connectivity (rs-FC) techniques to examine patterns of functional connectivity in participants who report using multiple substances compared to participants who report using a single substance (alcohol).

Methods: Participants were drawn from a larger neuroimaging study examining structural and functional brain correlates of alcohol misuse. From there, participants were placed into one of three groups based on their frequency of alcohol, tobacco, cannabis, and illicit drug use. We quantified participants' substance use based on their responses on the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), the Alcohol Use Disorder Identification Test (AUDIT), and the Fagerström Test for Nicotine Dependence (FTND) questionnaire. The final sample consisted of 82 participants (27 mono users who reported using alcohol, 24 dual users who reported using alcohol and one other substance, and 29 tri+ users who reported using alcohol and at least two other substances),

Results: Within the salience network there was a significant difference between the three groups in a cluster located in the right occipital cortex. Within the temporal network there were two significant clusters that differed between the three groups—one in the right orbitofrontal cortex and one in the left orbitofrontal cortex. Tri+ users were found to have the lowest amount of activity in these three regions and dual users were found to have the highest amount of activity within these regions. Exploratory analyses within the dual use group revealed higher activity within those who used alcohol+cannabis compared to those who used alcohol+tobacco.

Discussion: Findings from the current study indicate that the use of three or more substances may significantly impact rs-FC within the salience and the temporal network. Exploratory analyses indicating that those who use alcohol+cannabis have significantly higher rs-FC than those who use alcohol+tobacco is perplexing although not uncommon. Future research should examine larger samples of polysubstance users to ensure adequate sample size for comparisons across specific substance combinations. In particular, future studies are needed to better understand the increase in rs-FC for individuals who use alcohol+cannabis.

4.2 Introduction

Polysubstance use refers to the use of more than one psychoactive substance over a period of time, either simultaneously or independently (Connor, Gullo, White, & Kelly, 2014). This pattern of substance use is highly common (e.g., Bhalla, Stefanovics, & Rosenheck, 2017; Morley, Ferris, Winstock, & Lynskey, 2017). In fact, a comprehensive review by Connor et al. (2014) reported that between 18-34% of adolescents and young adults use multiple substances, and retrospective studies have found that early polysubstance use is associated with drug use later in life, most notably, non-medical prescription drug use. In another study examining the prevalence of polysubstance use among 406 adults receiving inpatient psychiatric treatment for mental health and substance use problems, 16% were considered to be polysubstance users (Timko, Ilgen, Haverfield, Shelley, & Breland, 2017). Finally, a study published in 2007 by Kedia et al. examined the intake records of 69,981 admissions to publicly funded substance use treatment centers and found that 51% of individuals reported mono substance use and that 49% of individuals reported polysubstance use (29% used two substances, 15% used three substances, and 5% reported using four to nine substances; Kedia, Sell, & Relyea, 2007). The article by Kedia not only demonstrates the prevalence of polysubstance use, but also confirms that alcohol is the most prevalent substance used alone (Kedia et al., 2007). In fact, mono alcohol use (39.9%) was almost twice as prevalent as the next leading mono used substances, cocaine (22.2%) and cannabis (20.1%) (Kedia et al., 2007). These prevalence rates are complemented by research consistently showing that polysubstance users are at a higher risk of comorbid psychopathology, health problems, and deficits in cognitive functioning (Connor et al., 2014).

Although the majority of people with a SUD use multiple substances, much of the research studying SUDs includes participants who only use one substance, or the published

reports tend to focus on one substance as the participants' "primary" substance of choice (Bhalla et al., 2017; Morley et al., 2017). Doing so ignores a variety of contributing factors and potential confounds and reduces the ecological validity of the samples. This is particularly relevant in studies examining neural correlates of addictive disorders. In this case, the effect of substance use on the brain has been consistently shown to result in negative structural and functional consequences (Gould, 2010; Nelson et al., 2017; Unterrainer et al., 2019; Wilcox et al., 2019). However, the issue of examining substances in isolation, or not fully exploring substances beyond the primary substance, has again, potentially confounded some of this literature and made it less generalizable. In order to more comprehensively characterize the negative impact of substance use on the structure and function of the brain, research needs to specifically examine people who use multiple substances and compare patterns observed in these individuals with people who only use a single substance and non-users.

Research has shown that polysubstance use can have detrimental and, in some cases, additive effects on neurocognitive performance, brain structure, and brain function. In the case of neurocognitive performance, Moody and colleagues (Moody et al., 2016) examined the effects of polysubstance use on delay discounting in a sample of community controls, heavy smokers, and people with alcohol and/or cocaine use disorders All substance-using groups discounted delayed rewards more steeply (i.e., were more impulsive) compared to the control group, but more importantly, the dual-substance users who smoked cigarettes in addition to another substance were more impulsive than mono-substance users. However, there was also a ceiling effect in which no significant differences were found between tri-substance users and dual-substance users. Pennington and colleagues (Pennington et al., 2015) examined neurocognitive performance in polysubstance users, alcohol-only users, and controls and found poorer

processing speed, cognitive efficiency, working memory, and inhibitory control performance in polysubstance group compared to the other two groups. Lastly, a functional MRI study by Raj et al. (Raj et al., 2010) examined semantic memory encoding and recognition in a group of polysubstance users. While polysubstance use was not associated with task performance deficits, polysubstance use was associated with decreased activation in various frontal, occipital, and temporal regions (Raj et al., 2010).

Polysubstance use is also associated with deficits in brain structure and metabolic function. Studies have found that individuals who report polysubstance use exhibit decreased gray matter volume in the ventromedial prefrontal cortex (A. M. Kaag et al., 2018), significantly smaller volume and surface area of the orbitofrontal cortex when compared to controls (Pennington et al., 2015), and significant thinning of the anterior cingulate cortex (Pennington et al., 2015). White matter is also negatively impacted, with studies reporting decreased global white matter integrity and demyelination of the prefrontal cortex (Anne Marije Kaag et al., 2017). In the case of brain metabolism, Abe et al. (Abé et al., 2013) examined polysubstance users, alcohol only users, and control participants and found that the polysubstance users consistently had metabolic abnormalities in the temporal gray matter, the cerebellar vermis, and the lenticular nuclei. Although studying brain metabolites can provide important clues about brain function, this approach does not provide information about functional connectivity.

The preceding studies have offered evidence of differences in brain structure and function between polysubstance users and controls, however these studies do not provide information about functional connectivity in the brain. A common method of assessing patterns of connectivity is exploring resting state functional connectivity (rs-FC) derived from functional MRI scans. Resting-state functional connectivity is an important variable to explore for several

reasons, the first being that it provides an avenue to examine ongoing, spontaneous brain activity. It has been argued that the brain consumes upwards of 20% of one's total energy (Clarke & Sokoloff, 1999) but that task-related changes in brain activity may only account for up to 5% (Raichle & Mintun, 2006). Therefore, focusing on task-related activation only captures a small portion of total brain activity (Fox & Greicius, 2010). On the other hand, examining the intrinsic and spontaneous activity of the brain provides a greater amount of data that can be compared between groups (Fox & Greicius, 2010). Second, it has been suggested that rs-FC offers better signal-to-noise ratio than does task-based fMRI (Fox & Greicius, 2010) with some studies reporting up to 80% of a task-based fMRI BOLD signal needing to be discarded as a result of noise (Fox, Snyder, Zacks, & Raichle, 2006). Third, task-based fMRI is inextricably tied to the specific behavioral paradigms used and task parameters vary widely across studies, further complicating ability to directly compare results. Finally, rs-FC largely does not depend on a participant's cognitive or physical ability and allows for more diverse populations to be analyzed.

Although rs-FC has emerged as a useful technique for exploring functional connectivity, rs-FC in polysubstance users is largely unexplored. Vegera et al. (Vegara et al., 2017) used rs-FC to explore functional connectivity in participants who reported hazardous alcohol use and/or cigarette smoking in comparison to a control group with no history of alcohol or substance use disorders. The sample included 51 controls, 28 drinkers, 73 smokers, and 36 smokers-and-drinkers. Numerous resting state networks (subcortical, cerebellum, auditory, sensorimotor, visual, salience, default mode network, executive control network, and precuneus) were found to be hypo-active in the smoking, drinking, and smoking-and-drinking groups, relative to controls. In addition, four of these resting state networks were significantly related to alcohol and tobacco

use severity, as measured by the AUDIT and FTND scales (Vegara et al., 2017; Vergara, Weiland, Hutchison, & Calhoun, 2018). A subsequent study by this group (Vergara et al., 2018) extended these findings to include participants who used combinations of alcohol, tobacco, and cannabis. Resting state fMRI data from 534 participants assigned to groups based on reported use of alcohol, tobacco, or cannabis (as well as the various combinations of those substances) were compared to a control group. A unique contribution of the Vergara et al. (2018) study was the inclusion of tri-substance group who reported alcohol+tobacco+cannabis use. The drinker group exhibited decreased connectivity in sensory and motor networks, whereas the tobacco use group exhibited increased connectivity between dorsal striatum and sensorimotor regions. Combination of cannabis and tobacco were found to have contrasting effects compared to single use of these substances, however alcohol and cannabis were found to have an additive effect. Together, the two studies by Vergara et al. provide initial evidence of significant differences in functional connectivity measured via rs-fMRI in participants who report using one or more substances. The results also suggest that the specific combinations of substances may have important implications for the direction of the observed results. Two important limitations of these studies, however, include the absence of participants who report using illicit drugs, other than cannabis, and the absence of participants who report using more than three substances (Kedia et al., 2007).

The aim of the current study was to use rs-FC techniques to further characterize patterns of functional connectivity in participants who report using multiple substances compared to participants who report using a single substance (alcohol). Given that data were drawn from a larger study primarily focused on neural correlates of alcohol misuse, the present design is best described as a comparison of a mono (alcohol-only) group compared to two polysubstance

groups (a dual user group reporting alcohol and one other substance, and a tri+ user group reporting alcohol and at least two other substances). The additional substances included tobacco, cannabis, and various illicit drugs (e.g., cocaine, methamphetamine, heroin, sedatives, among others). Thus, the current study design is generally similar to the two studies by Vergera et al. (2017, 2018) with the addition of participants who report using illicit substances other than cannabis. We sought to examine five large-scale brain networks that have been found to be significantly affected by either polysubstance use specifically (Abé et al., 2013; Vegara et al., 2017), or substance use broadly (Geng et al., 2017; Zilverstand, Huang, Alia-Klein, & Goldstein, 2018), including the default mode network (DMN), the salience network, the executive control network(s), the cerebellar network, and a temporal network. Previous studies have sometimes revealed counterintuitive patterns or effects in different directions for different polysubstance use groups. Thus, it is unclear whether this heterogeneity is due to a lack of consistency in the definition of polysubstance use, or due to the opposing effects that different substances may exert on the brain, such as the contrasting effects of tobacco and cannabis in the Vergara et al., (2018) study. For that reason, hypotheses for the current study were intentionally largely exploratory. We hypothesized that as the degree of polysubstance use increased (i.e., from mono to dual to tri-substance or greater use), rs-FC within the networks of interest would decrease. We also sought to examine differences between specific substance profiles within dual and tri-substance groups and continuous associations between rs-FC and measures of addiction severity.

4.3 Methods

4.3.1 Participants

Participants were drawn from a larger neuroimaging study examining structural and functional brain correlates of alcohol use disorder. Participants were recruited from the general Hamilton, ON community, as well as from four addiction treatment centres in the region. General inclusion criteria for the study required that all participants be between the ages of 25-55, have no MRI contraindications (i.e., implanted metal, copper IUD), have no history of severe head or brain trauma with loss of consciousness, neurological disorder, or severe psychiatric disorder (schizophrenia, bipolar disorder, post-traumatic stress disorder).

As a starting point, all participants recruited for the larger study were at minimum social drinkers who consumed alcohol at least weekly, with a subset of the larger study recruited based on meeting DSM-5 criteria for alcohol use disorder. The final sample of 82 participants in the current study were placed into one of three groups based on their frequency of substance use. We quantified participants' substance use based on their responses on the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST), the Alcohol Use Disorder Identification Test (AUDIT), and the Fagerström Test for Nicotine Dependence (FTND) questionnaire. Although the studies by Vergara et al. (2017, 2018) used hazardous use cutoff scores on the AUDIT and FTND or a cannabis cutoff based on 60-day retrospective interview, using the same cutoff strategy in the current study yielded group Ns that were too small for analysis (i.e., the largest group $N = 17$, but the majority of others were $N < 10$). Therefore, the decision to use frequency of use as a grouping variable was considered more appropriate and was in line with previously published studies focusing on polysubstance use (Abé et al., 2013; A. M. Kaag et al., 2018; Anne Marije Kaag et al., 2017; Moody et al., 2016; Pennington et al., 2015; Raj et al., 2010). In order

to adhere to similar guidelines as those used in previously published papers, we sought to use a monthly or greater cut off for both the AUDIT and the ASSIST. For the FTND, anyone who smoked at least one cigarette a day was included in one of the three groups, as was done by Moody et al. (2016).

Those who used alcohol at least monthly but did not report using any other substances were placed in the mono user (i.e., alcohol-only) group (N = 27). Those who used alcohol and one other substance at least monthly were placed into our dual-user group (N = 24), and those who used alcohol and two or more other substances at least monthly were placed into our tri+ user group (N = 29). Since all participants in the parent study were at minimum social drinkers, there were no participants who were classified as non-users. For a list of all substances examined, as well as group demographics, please see Table 1. The tri+ group, in particular, was heterogenous in the number of substances used. The majority (69.0%) of participants in this group reported currently using three or four substances, while smaller percentages reported using five (20.7%), six (6.9%), or seven (3.4%) substances.

4.3.2 Procedures

The Hamilton Integrated Research Ethics Board (HiREB) approved the study (Project #1747) and participants provided informed consent prior to starting the study. Individuals who were willing to participate in the study were first screened either in person or over the phone to determine their eligibility. Individuals who met all eligibility criteria were then scheduled for the first of two sessions. The in-person screening session took place at either our laboratory (at St. Joseph's Healthcare Hamilton) or at the participants respective treatment centres if the participant was unable to leave.

During the screening session, participants completed a battery of self-report questionnaires, neurocognitive tests, and a clinical interview for alcohol and substance use. Upon completion of the first session, participants received a $25 gift card to local stores and coffee shops. Those who were eligible and willing to participate in the second session were then scheduled for an MRI at the Imaging Research Centre at St. Joseph's Healthcare Hamilton. All participants completed the necessary safety questionnaires and brief interview with the MRI technologist prior to beginning the MRI scan. The MRI scan lasted roughly 40 minutes, after which participants were debriefed, received a $25 gift card, and the session concluded.

4.3.3 Measures

For the current study, we examined participants' responses on various measures relating to substance use, frequency of use, and demographics. These measures were administered either on the computer, one-on-one with a researcher, or individually using paper and pencil. Descriptions of the measures used in the current study can be found below.

Demographics. A study-specific demographic questionnaire asked participants to provide information on their age, sex assigned at birth, gender identity, ethnicity, years of education, smoking status, marital status, income, height, weight, and handedness.

Alcohol Use. The Alcohol Use Disorders Identification Test (AUDIT; Saunders, Aasland, Babor, de la Fuente, & Grant, 1993) consists of 10 items and is used to assess alcohol consumption, drinking behaviours, and alcohol-related problems. For the current study, we examined participants' responses to item #1 ("How often do you have a drink containing alcohol?"). Participants who reported monthly or greater use of alcohol were considered for inclusion into

one of the three substance using groups. Total AUDIT scores are also reported for descriptive purposes in Table 1, with a cutoff of 8 or greater indicating hazardous use.

Drug Use. The NIDA Modified Alcohol, Smoking and Substance Involvement Screening Test (ASSIST; National Institute on Drug Abuse, 2012) is a self-report screen for levels of problematic substance use in adults. The version used in the current study consisted of ten substances (e.g., cannabis, hallucinogens, amphetamines, opioids, etc.; see Table 1 for full list of substances) and asked participants to rate their use of these substances in the past three months, or the last three months of their use period (for participants who were in recovery). Response options ranged from Never to Multiple Times Daily. Two responses for the "Other" category—Methadone and Xyrem—were re-coded as prescription opioid and prescription sleep aid categories, respectively. For the current study, participants who reported monthly or greater use of any of the listed substances were considered for inclusion into one of the three substance using groups. Severity of drug use (excluding cannabis) was assessed via the Drug Use Disorders Identification Test (DUDIT; Berman, Bergman, Palmstierna, & Schlyter, 2005), and severity of cannabis use was assessed via the Cannabis Use Disorders Identification Test-Revised (CUDIT; Adamson et al., 2010). Cutoff scores of 8+ and 12+ were used to indicate hazardous use for the DUDIT and CUDIT, respectively.

***Tobacco Use*.** The Fagerström Test for Nicotine Dependence (FTND; Heatherton, Kozlowski, Frecker, & Fagerstrom, 1991) is a measure used to assess one's addiction to nicotine. The measure contains six items that evaluate the quantity of cigarette consumption, the compulsion to use, and dependence. For the current study we examined item #4 "How many cigarettes per day

do you smoke?" Participants who smoked at least one cigarette per day were placed into one of the three substance using groups; this cut off has been used in previous literature on polysubstance use (Moody et al., 2016). For descriptive purposes, the total FTND score is also reported, with a cutoff of 4+ indicating hazardous tobacco use.

Alcohol and Substance Use Disorder Diagnoses. All participants completed the alcohol use disorder module of the Structured Clinical Interview for DSM-5 (SCID-5; American Psychiatric Association, 2015). Additionally, participants completed the substance use module of the SCID-5 if they reported any substance use. The SCID-5 interviews were used to provide a diagnosis of a current (i.e., in the last 12 months) alcohol or substance use disorder for the purpose of research (not clinically).

4.3.4 MRI Image Acquisition

MRI images were acquired on a 3T General Electric Discovery scanner using a 32-channel receive-only radio frequency coil for the head and a transmit radio frequency body coil. For our anatomical reference, we acquired a 3D T1-weighted anatomical image of the whole head using a 3D inversion-recovery gradient-echo sequence (GE 3D BRAVO; Inversion time (TI) = 450 ms, TE = 3.2 ms, TR = 58.4 ms, flip angle = 12°, field of view (FOV) = 25.6×25.6×25.6 cm). This image was used for registration and processing. Two 5 minute, 24 second resting state (total resting state time: 10:48) series were collected with a short break in between for participants to relax. During the resting state scan series, participants were instructed to "lay perfectly still with their eyes open, and not try not to think about anything"; participants were allowed to blink. Resting state functional imaging was completed using a T2*-interleaved

echo-planar imaging sequence with TR = 3000 ms, TE = 35 ms, flip angle = 90°, 3.5 mm thick, 36 axial slices, matrix 64 × 64 resolution over 24 mm FOV.

4.3.5 Data Processing and Data Analysis

Structural and functional MRI data were preprocessed using the Statistical Parametric Mapping Software SPM12 (http:// www.fil.ion.ucl.ac.uk/spm) and CONN Functional Connectivity Toolbox Version 19.b (www.nitrc.org/projects/conn). MRI data was first obtained in DICOM file format and were subsequently converted to NIFTI file format using SPM. NIFTI files were then uploaded to CONN for further preprocessing. We used the default preprocessing pipeline for volume-based analyses. Structural scans were centered to (0, 0, 0) coordinates (translation), segmented into grey matter, white matter, and cerebrospinal fluid, and normalized to Montreal Neurological Institute (MNI) space.

Functional scans were realigned and unwarped (subject motion estimation and correction), and centered to (0, 0, 0) coordinates (translation). For motion detection and outlier identification, we used CONN's conservative subject-motion setting. ART-based identification of outliers was used; subject motion greater than 0.5mm was detected and discarded. Functional data were then segmented into grey matter, white matter, and cerebrospinal fluid, normalized to MNI space, and spatially smoothed to increase the signal to noise ratio with a 4-mm FWHM Gaussian filter.

Independent Components Analysis (ICA) was completed using a combination of Group ICA of fMRI toolbox (GIFT; http:// mialab.mrn.org/software/gift/index.html) for SPM 12 (http:// www.fil.ion.ucl.ac.uk/spm) and CONN software (www.nitrc.org/projects/conn). Following the preprocessing of functional scans using CONN, scans were then uploaded to GIFT which was used to estimate the number of independent components present in the data set. Components

were estimated from all datasets of the fMRI data using the minimum description length (MDL) criteria to estimate the components and to determine 39 independent components (IC's). To run the IC analyses, we used CONN Functional Connectivity Toolbox Version 19.b (www.nitrc.org/projects/conn). We selected the group-ICA analysis type and we specified 39 factors. The CONN ICA measure follows Calhoun's group-ICA methodology (Calhound, Adali, Pearlson, & Pekar, 2001). This offers possible subject-level dimensionality reduction, concatenation across subjects, group-level Singular Value Decomposition for dimensionality reduction, and a fastICA algorithm for group-level independent component definition (see Calhoun et al. 2001 for method details). Our networks of interest were identified and confirmed through the use of CONN software that matches BOLD signal to several network templates and deduces the most likely network that is represented by the BOLD activation. Networks were also anatomically verified by Ph.D. level scientists. Network consensus ratings were also performed between co-authors.

As mentioned above, we examined Rs-FC in 5 large-scale brain networks, including the DMN, the salience network, the executive control network(s), the cerebellar network, and a temporal network. We included realignment, quality control, and scrubbing as first level covariates before extracting fischer transformed functional connectivity values for each subject, from each significant cluster, and importing the values into SPSS (version 27, https://www.ibm.com/analytics/spss-statistics-software) in order to conduct statistical analyses. A voxel height threshold of $p < 0.001$ and cluster threshold of 0.05-FDR corrected was used to identify significant clusters that were correlated with specific regions. Statistical analyses were first performed using an ANCOVA, covarying for income and education. We then explored significant clusters using *post hoc* testing between individual polysubstance use groups.

4.4 Results

4.4.1 Sample Characteristics

Between each of the three groups, we examined differences with regard to age, income, education, handedness, race, and sex assigned at birth; please see Table 1. Income ($p = .001$) and education ($p < .001$) differed significantly between the three groups and were included as covariates in the primary analyses.

The dual and tri+ groups reported significantly higher scores on the AUDIT compared to the mono (alcohol) group, however they did not significantly differ from each other. All three groups significantly differed on DUDIT, CUDIT, and FTND total scores. Thus, the dual and tri+ groups were characterized by greater drug, cannabis, and tobacco severity, but importantly not significantly greater alcohol severity. These patterns are confirmed by percentage of participants reporting hazardous scores on these scales.

4.4.2 Primary Analyses - ICA Connectivity

Of the 5 networks of interest, two demonstrated significant group differences, the salience network and the temporal network. In the current paper, the salience network has been defined as activation in regions such as the anterior insula and dorsal anterior cingulate cortex. In the current paper, the temporal network has been defined as activation in regions such as the inferior frontal gyrus, the superior temporal gyrus, and the temporal poles. Results within these networks are presented below.

Salience Network. Within the salience network (depicted in Figure 1a) we found a significant difference between the three groups in a cluster located in the right occipital cortex (x = 28, y = -90, z = 10), $F(2,77) = 15.94$, $p < .001$, $\eta^2_p = 0.292$, see Figure 2a). Post hoc analyses examining individual group differences revealed that the tri+ users had significantly less

functional connectivity than both the mono and dual groups within this cluster; there was no statistically significant difference between the mono and dual users. Interestingly, dual users demonstrated the greatest functional connectivity within this cluster among the three groups (although not significantly more than the mono users). See Table 2 for full results.

Temporal Network. Within the temporal network (Figure 1b) we found two significant clusters that differed between the three groups—one in the right orbitofrontal cortex (14, 42, -16) $F(2,77) = 19.43$, $p < .001$, $\eta^2_p = 0.335$, (Figure 2b) and one in the left orbitofrontal cortex (-18, 40, -18) $F(2,77) = 15.77$, $p < .001$, $\eta^2_p = 0.290$ (Figure 2b). Post hoc analyses examining individual group differences revealed similar findings as those in the salience network; the tri+ users had significantly less connectivity in the clusters than both the mono and dual using groups, however there was no statistically significant difference between the mono and dual users. Moreover, the same finding regarding the dual users having the highest functional connectivity was found within these orbitofrontal clusters. See Table 2 for full results.

4.4.3 Exploratory Analyses by Specific Substance Types

We conducted exploratory pairwise comparisons to further clarify the patterns of activation between the dual and mono groups. We were unable to examine pairwise comparisons within the tri+ user group due to low numbers of participants and the degree of heterogeneity. We first began by examining the difference between the dual users who were alcohol and cannabis users (50%, n = 13), and those who were alcohol and tobacco users (50%, n = 13). We found that within all three significant clusters, the individuals who used alcohol and cannabis had greater mean connectivity relative to the individuals who used alcohol and tobacco. Although the differences were not statistically significant (ps = .16-.52) potentially due to small number of

participants in each subgroup, the effect sizes were medium in magnitude (d = 0.26-0.56). See Table 3 for full results.

We then compared activation in the two dual groups to the alcohol-only group to examine the effect of adding either cannabis or tobacco on top of alcohol. All comparisons between our alcohol-only users and our dual alcohol+cannabis users in the three clusters remained significant, with the dual alcohol+cannabis group exhibiting greater functional connectivity. However, when we compared our alcohol-only users to our alcohol+tobacco users, only two clusters remained significantly higher in the dual alcohol+tobacco group (left and right orbitofrontal cortex). The cluster in the right occipital cortex was no longer significant (p = .460). Full results in Table 4.

4.4.4 Correlations with Substance Use Variables

Spearman correlations were used to examine correlations between the clinical substance use scales (AUDIT, FTND, DUDIT, CUDIT), participants' total number of substances, and the rs-FC networks that were significant. The salience network was found to be negatively correlated with the total number of substances used (ρ = -0.4, $p < 0.01$) and the DUDIT total score (ρ = -0.4, $p < 0.01$). As well, one of the temporal networks (with the right orbitofrontal cortex cluster) was found to be negatively correlated with the total number of substances used (ρ = -0.3, $p < 0.01$) as well as the total DUDIT score (ρ = -0.3, $p < 0.01$). See Figure 3.

4.5 Discussion

The primary aim of this study was to examine rs-FC in a variety of large-scale brain networks among participants who report using alcohol alone or in combination with one or more other substances. Although previous studies have examined polysubstance users with regard to neurocognition (Moody et al., 2016; Pennington et al., 2015), task-based fMRI (Raj et al., 2010),

and structural brain correlates (Abé et al., 2013; A. M. Kaag et al., 2018; Pennington et al., 2015), only two studies to date have systematically explored rs-FC in relation to the number of substances used (Vegara et al., 2017; Vergara et al., 2018). Moreover, only one of those studies explored rs-FC in participants who currently use more than two substances, which leaves combinations involving cannabis and other drugs largely unexamined.

Although we did not have specific hypotheses about each of the individual networks, we predicted that connectivity would decrease as the number of substances increased. Our results were somewhat consistent with this hypothesis, in that polysubstance users who reported using three or more substances exhibited lower functional connectivity in comparison to those who are were alcohol only/mono or dual substance users. This was again demonstrated in our correlation analyses whereby a significant negative relationship was observed between the number of substances used and the salience network, as well as the number of substances used and the temporal network (right OFC cluster).

With regard to the rs-FC results, we found two networks (salience and temporal) and three clusters (right occipital cortex, left and right orbitofrontal cortices) that demonstrated significant results between the three groups. In all of these cases, the tri+ group exhibited the least connectivity, which was in line with our hypothesis. A surprising finding, however, was that the additive negative effect of using multiple substances on functional connectivity did not hold for the dual users group. Instead, the dual group exhibited the highest amount of connectivity relative to the mono and tri+ user group.

There are multiple potential explanations for why the tri+ user group exhibited the lowest connectivity. First, this group exhibited substantially greater severity of substance use other than alcohol, including a higher percentage of participants who smoked cigarettes, as well as higher

cannabis and other drug severity. Of note, the dual and tri+ groups were not significantly different in terms of alcohol use severity, suggesting that the decreased functional connectivity in the tri+ group may be best explained by greater substance use disorder severity. Second, we postulate that the tri+ group may demonstrate the lowest connectivity because the tri+ group was an extremely heterogenous group in terms of their substance use. While a majority of this group reported using three or four substances, a sizable percentage used five to seven substances, which is not uncommon in the case of polysubstance use (Kedia et al., 2007). A study by Vergara et al. (2018) examined tri substance users using dynamic functional network connectivity and found that each substance, or their combination, had a separate and identifiable effect on the brain. Alcohol was found to have an overarching effect of reduced in dynamic functional network connectivity, and the combination of cannabis+tobacco did not appear to demonstrate an additive effect when compared to either substance, cannabis or tobacco, individually (Vergara et al., 2018). Our sample of Tri+ users unfortunately was not sufficiently powered to examine each substance individually. It would be interesting to explore whether a single substance in a group of Tri+ users is driving the overall patterns observed, or if the results are a consequence of combining multiple substances. Future studies should seek to expand on this work by recruiting larger samples of polysubstance users to address this question.

Our findings of significant differences in the salience and temporal networks are consistent with previous research implicating these networks in substance use disorders (Hanlon, Dowdle, Naselaris, Canterberry, & Cortese, 2014; Mackey et al., 2018; Zilverstand et al., 2018). In the first case, the salience network is responsible for detecting and filtering incoming salient stimuli, and also contributes to various cognitive functions such as communication and self-awareness through the integration of other networks and senses (Menon,

2015). In the case of substance use, a study by Zilverstand et al (2018) reviewed 105 addiction related neuroimaging studies and found six large-scale brain networks (including the salience network) were consistently impaired during drug cue exposure, decision making tasks, inhibitory control tasks, and social-emotional processing. Moreover, when they examined resting-state activity, five of these same six networks (including the salience network) were found to have altered connectivity (Zilverstand et al., 2018). An interesting finding from our study was the significant relationship between the salience network and the cluster found in the occipital cortex. A meta-analysis by Hanlon et al (2014) reviewed 55 functional neuroimaging drug cue-reactivity studies and found that 86% of the studies that examined drug cues versus neutral cues, showed significant drug-elicited activity in the visual cortex (Hanlon et al., 2014). Hanlon et al., (2014) postulated that over time, as individuals with addictive disorders repetitively use a rewarding substance, salience for the substance may transfer to various substance-related cues (Hanlon et al., 2014). This can create an attentional bias which has been demonstrated across drug classes and has been implicated as a possible biomarker or treatment target of addiction (Hanlon et al., 2014).

In addition to the salience network, we also found significant differences between the groups in the temporal network. There are eight cognitive domains that have been associated with the temporal lobe and its systems, such as speech, hearing, memory, visuospatial processing, emotional processing, and semantic processing (Patel, Biso, & Fowler, 2020). A study by Geng et al., (Geng et al., 2017) examined whole brain resting state connectivity in a sample of cocaine users and found less connectivity between the temporal poles and regions of the default mode network (Geng et al., 2017). This finding is particularly interesting given that our study found a significant relationship between the temporal network and two clusters in the

orbitofrontal cortex (sometimes considered to be part of the default mode network given its relationship to the ventromedial prefrontal cortex; Phillips, MacPherson, & Della Sala, 2002). The orbitofrontal cortex, a region involved in emotion, reward, learning, decision making, and promoting motivated behaviors (Sung il Kim, 2013; Mooreman, 2018), plays an important role in the neurobiology of addiction as outlined in an extensive review by Mooreman (2018). Specifically, drug and alcohol use have significant impacts on the OFC with regard to circuitry, structure, and activity (Mooreman, 2018). Because of these drug related disruptions to the OFC, substance users, even up to ten years later, often display inflexible behaviours, impaired decision making, and stronger drug-associated signalling (Mooreman, 2018).

Our secondary aim for the current study was to delve deeper into the group-level differences by examining our specific substance use profiles within the groups. In the case of the dual use group, we found that individuals who used alcohol and cannabis had greater mean connectivity relative to the individuals who used alcohol and tobacco. We also found that the alcohol+cannabis group exhibited greater functional connectivity in all three of the significant clusters from the primary analyses than our alcohol only users. These findings were somewhat similar to those in the Vergara et al. (2018) study, in which the drinking+canabis group demonstrated a greater degree of mean occupancy rates in two dynamic functional connectivity states than the drinking+smoking group. However, due to the relatively small sub-group sizes in these exploratory analyses, the present comparisons among dual use subgroups should be interpreted with caution. It is difficult to offer an explanation as to why using cannabis in addition to alcohol may be related to an increase in connectivity, however this was an exploratory analysis and should be examined in more detail, with a larger sample, before definitive conclusions are drawn. Moreover, cross sectional studies such as this do not allow us

to examine the reverse possibility that those who have greater connectivity, may be more likely to use cannabis.

This study's findings should be considered in the context of its limitations. First, the study design was cross sectional and does not allow for causality or temporal associations between rs-FC and substance use to be examined. The study also did not have a control group of non-users. A criterion of the larger MRI study from which the current data were drawn was that participants must use at least one psychoactive substance, resulting in a sample of participants who were at minimum mono users. This hindered our ability to examine differences between *any* substance use and *no* substance use. Another limitation was the inability to examine the tri+ group in more detail with regard to their substance use due to a relatively small sample size (n = 29) that constrained power for substance-specific analyses. Finally, the substance use measures in the parent study did not assess if participants in the dual and tri+ groups used their substances simultaneously or concurrently. Unfortunately, we are unable to explore the differences in rs-FC based on simultaneous or concurrent use (e.g., Vegara et al., 2017).

Overall, the current study contributes to an important, yet understudied, area of research and has raised a number of empirical questions that remain to be examined. These results suggest that that polysubstance use, specifically tri+ use, appears to be related to lower functional connectivity, and that there may be something peculiar about the combination of cannabis and alcohol with respect to functional connectivity. Most importantly, this study supports that importance of conducting neuroimaging research in samples of polysubstance users. A majority of people who use substances and struggle with substance use disorder report using more than one substance (Bhalla et al., 2017; Morley et al., 2017). Choosing to study substances

independent of one another or opting to omit participants because of simultaneous substance use ignores the complexity of real-word substance use patterns.

4.6 References

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Table 1. Group Characteristics

	Mono Use Group (N=27)	**Dual Use Group (N=26)**	**Tri + Use Group (N=29)**	**P Value**
Age	37.3 (SD 11.1)	40.5 (SD 9.6)	35.9 (SD 10.3)	*P = .252*
Gender	55% Female	46% Female	38% Female	*P = .254*
Income	$60,000-74,999	$45,000-59,999	$30,000-44,999	*P = .001*
Education	17.5 years (SD 3.4)	15.1 years (SD 2.9)	13.2 years (SD 2.4)	*P = <.001*
Race	81% White	92% White	76% White	*P = .623*
Handedness	89% Right	80% Right	82% Right	*P = .409*
AUD+	26%	62%	59%	*P = .015*
AUD DSM-5 Severity	7% Mild; 0% Moderate; 19% Severe	12% Mild; 4% Moderate; 46% Severe	3% Mild; 0% Moderate; 55% Severe	
AUD SCID Total	4.00 (SD = 6.87)	11.69 (SD = 8.48)	11.48 (SD = 9.23)	*P < .001*
SUD+	0%	23%	83%	*P < .001*
SUD DSM-5 Severity	0% Mild; 0% Moderate; 0% Severe	12% Mild; 0% Moderate; 7% Severe	0% Mild; 12% Moderate; 66% Severe	
SUD SCID	0.00 (SD = 0.00)	3.35 (SD = 5.38)	14.97 (SD = 7.82)	*P < .001*
AUDIT Total	10.29 (SD 9.32)	21.62 (SD 11.99)	17.49 (SD 13.45)	*P = .003*
AUDIT 8+	48%	77%	62%	
DUDIT Total	0.59 (SD 1.53)	7.77 (SD 8.93)	27.45 (SD 12.31)	*P < .001*
DUDIT 8+	0%	38%	97%	
CUDIT Total	0.48 (SD 0.93)	5.87 (SD 9.09)	12.38 (SD 10.25)	*P < .001*
CUDIT 12+	0%	22%	44%	
FTND Total	0.00 (SD 0.00)	4.96 (SD 6.40)	13.78 (SD 13.37)	*P < .001*
FTND 4+	0%	40%	76%	
≥ Monthly Substance Use				
Alcohol	100%	100%	96%	
Tobacco		50%	89%	
Cannabis		50%	79%	
Cocaine			65%	
Methamphetamine			20%	
Heroin			17%	
Sedative			43%	
Prescription Opioid			24%	
Prescription Sleep Aid			21%	
LSD			17%	
Prescription Stimulant			0%	
Inhalant			0%	

Table 2. Group Differences Within Each Significant Cluster

Network (region)	**Mono Users *Mean (SE)***	**Dual Users *Mean (SE)***	**Tri+ Users *Mean (SE)***	***F***	***Sig***	**Pairwise Comparisons**
Salience (right occipital cortex)	0.153 (.397)	1.084 (.365)	-1.828 (.374)	15.93	.000	Mono v. Dual (p = .273)
						Mono v. Tri+ (p = .004)
						Dual v. Tri+ (p = <.001)
Temporal (right orbitofrontal cortex)	-0.833 (.488)	1.723 (.449)	-2.095 (.460)	19.43	.000	Mono v. Dual (p = .001)
						Mono v. Tri+ (p = .296)
						Dual v. Tri+ (p = <.001)
Temporal (left orbitofrontal cortex)	-0.664 (567)	1.771 (.521)	-2.308 (.535)	15.76	.000	Mono v. Dual (p = .007)
						Mono v. Tri+ (p = .164)
						Dual v. Tri+ (p = <.001)

***Controlling for income and education*

Table 3. Examining Mean Cluster Values Within the Dual Use Group Based on Substance Use Profile

Network (region)	**Alcohol + Cannabis (N = 13)**	**Alcohol + Tobacco (N = 13)**	
	Mean (SE)	*Mean (SE)*	*Sig.*
Salience (right occipital cortex)	1.563 (.496)	0.583 (.460)	0.161
Temporal (right orbitofrontal cortex)	2.042 (.631)	1.448 (.638)	0.515
Temporal (left orbitofrontal cortex)	2.379 (.794)	1.278 (.784)	0.334

Table 4. Comparing Alcohol Only Users to Those Who Use Alcohol Plus One Other Substance

Network (region)	**Alcohol v. Alcohol + Cannabis**			**Alcohol v. Alcohol + Tobacco**		
	F	*Mean Square*	*Sig.*	*F*	*Mean Square*	*Sig.*
Salience (right occipital cortex)	6.119	16.890	.018	0.556	1.456	.460
Temporal (right orbitofrontal cortex)	13.543	79.613	.001	8.678	51.315	.005
Temporal (left orbitofrontal cortex)	12.896	104.730	.001	6.037	48.644	.019

Figure 1a-b. Coronal and Axial Views of the Salience and Temporal Networks Examined in the Current Study

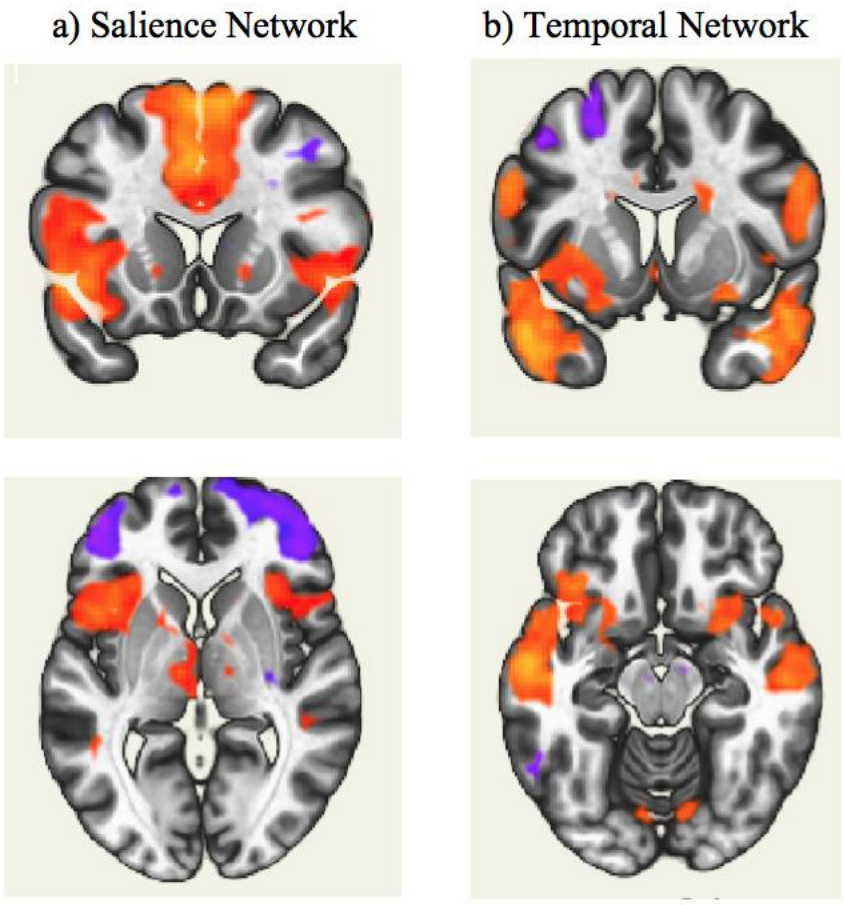
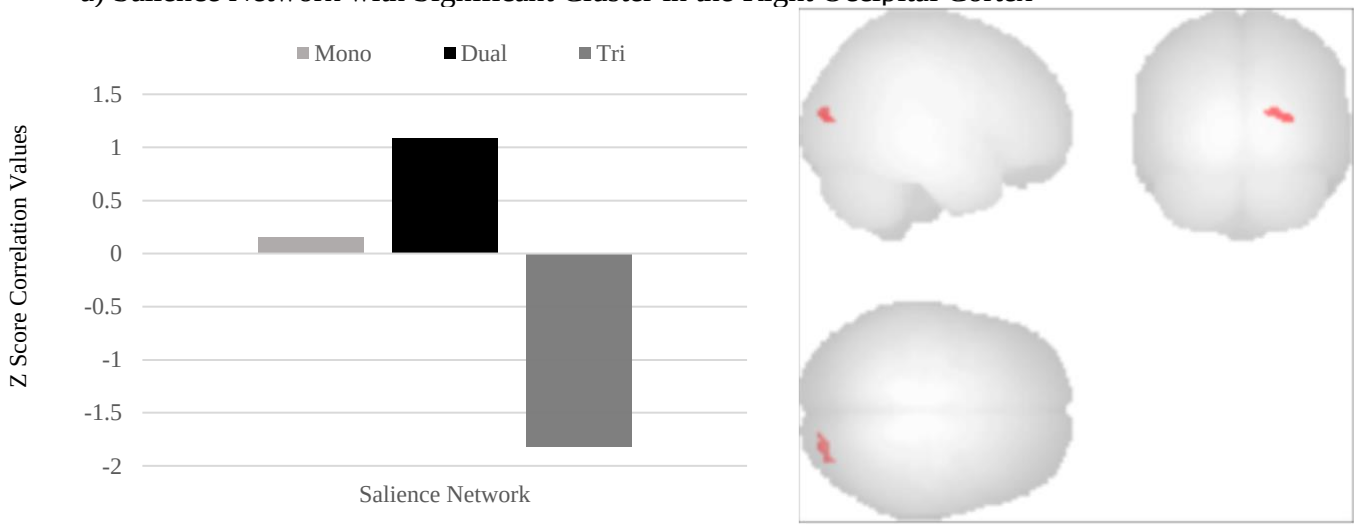


Figure 2a-b.
Left: Bar Graphs Displaying Significant Cluster Means Between Groups.
Right: Visual Representation of the Significant Clusters

a) Salience Network with Significant Cluster in the Right Occipital Cortex



b) Temporal Network with Significant Clusters in the Left and Right Orbitofrontal Cortices

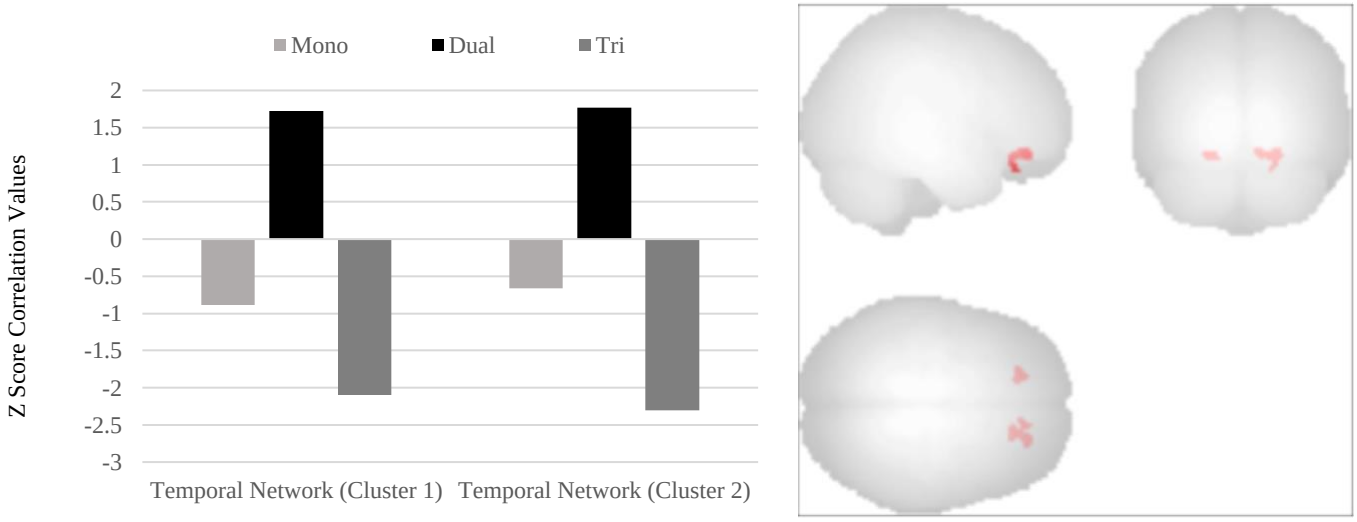
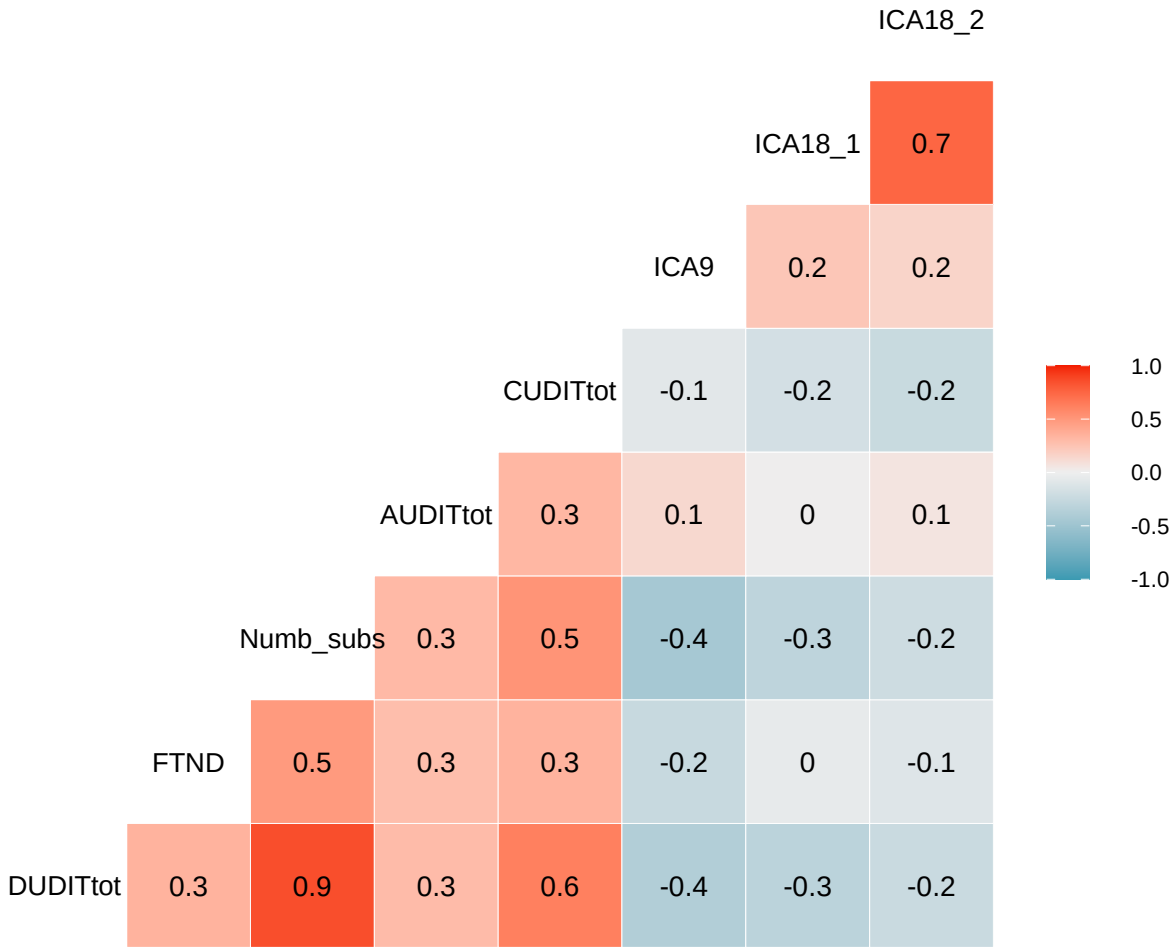


Figure 3. Heat Map of Correlations Between Significant Clusters and Substance Use Variables



*ICA9 = salience network, ICA18_1 = temporal cluster 1, ICA18_2 = temporal cluster 2, Numb_subs = participants' total number of substances, FTND = The Fagerström Test for Nicotine Dependence, AUDITtot = AUDIT total score, DUDITtot = DUDIT total score, CUDITtot = CUDIT total score

*Correlations > ± 0.3 are significant at p<.001

Chapter 5: General Discussion

5.1 Summary of Findings

We know from the literature on substance use disorders (SUD), that there appear to be various abnormalities regarding brain structure and brain function within this population. There is a host of well-supported scientific evidence to suggest that those with SUD often experience reductions in grey and white mater volumes, reduced cortical thickness overall as well as in specific brain regions, and decreased brain activation in various large-scale networks and specific regions (Bühler & Mann, 2011; Mackey et al., 2018; Wilcox et al., 2019); however, there remain a number of gaps in the literature, as well as a number of opportunities for novel research to be introduced.

The primary goal of this thesis was to examine structural and functional correlates of substance use disorder. This goal was accomplished through three studies that examined different substance using populations, different neuroimaging and analysis methodologies, and different aspects of brain structure and function.

In our first study (Chapter 2), we examined a comprehensive list of twenty-four brain regions to determine which regions were associated with drinking quantity and heavy drinking. Moreover, we sought to carry out this research in a large, sex-balanced sample. We hypothesized that cortical thickness in a variety of brain regions would be negatively associated with alcohol use. This hypothesis was confirmed when results demonstrated that 14 of our 24 regions of interest (ROI's) were associated with the frequency of heavy alcohol use, and when 18 of our 24 ROI's were associated with alcohol quantity; most notably the DLPFC was found to be uniquely

associated with both of these drinking variables. In each of these findings, higher degrees of alcohol misuse were associated with lower cortical thickness. As for the investigation into sex differences, we found a significant region and sex interaction in 10 of the 24 ROI's which was specific to male participants.

In our second study (Chapter 3), we sought to continue our investigation into alcohol use and cortical structure by exploring a heavily myelinated region of the cortex through use of a novel MRI pulse sequence. Although white matter and cortical thickness have been examined in the field of SUD's previously, this particular tissue, namely ICM, had not yet been examined. We hypothesized that individuals with chronic alcohol use would demonstrate less ICM signal than our participants who were healthy social drinkers. Although our findings were not in line with our hypotheses, we speculate that perhaps the increase in ICM signal that was present for the alcohol users was a result of neuroinflammation from chronic alcohol use.

Finally, for the third study, we expanded our population from alcohol users to people who use multiple substances, and from structural to functional neuroimaging. We recognized through our previous studies that alcohol is often accompanied by the use of additional substances, especially in individuals who have more severe substance use disorders, and therefore sought to examine a sample of polysubstance users (PSU). Further, when we began exploring the existing literature surrounding PSU, we found very limited research surrounding resting-state functional connectivity (rs-FC) in this population. We were not only eager to explore this understudied topic of rs-FC in PSU, but were also interested in seeing whether similar brain regions, that had been noted in our *structural* imaging studies, would be found in a functional analysis. Therefore, in Chapter 4 we examined mono (alcohol-alone), dual (alcohol + one other substance), and tri+ (alcohol + two or more other substance) users and found that the rs-FC within two large-scale

brain networks appeared to be significantly different between the three groups. Results demonstrated that the activation between the salience network and the right occipital cortex, as well as the activation between the temporal network and the left and right orbitofrontal cortices, demonstrated the least amount of activation in the tri+ user group, and the greatest amount of activation in the dual user group. Upon further analysis, we found that within the dual users, those who used alcohol and cannabis had greater mean connectivity within the three significant clusters relative to the individuals who used alcohol and tobacco, however when we attempted to explore these findings further within the tri+ group, we were limited by small sample sizes.

This thesis and the studies within it, aimed to investigate neural correlates of substance use disorder. The studies included in this thesis have reduced ambiguity from previously published studies, have addressed gaps in the literature, and have brought novel technology and novel findings to the field.

5.2 Significance and Implications

This thesis added three studies to the research field, each with their own significant findings and clinical implications.

Chapter 2 demonstrated that thinner cortex in various brain regions was associated with greater alcohol consumption and more frequent heavy drinking. This study also demonstrated the unique association that the left DLPFC had with alcohol use compared to other brain regions and demonstrate sex differences in associations of cortical thickness with alcohol use particularly for males. As well, this study indicated that the associations between cortical morphometry and alcohol use appeared in a relatively young and typical sample of drinkers, demonstrating that

morphometric brain abnormalities are not limited to middle aged or chronic users and highlights the need for early interventions and longitudinal research.

Chapter 3 found that while ICM did not appear to be globally disrupted or drastically different between those with AUD and control participants, there was higher ICM-related signal within some specific ROI's such as the DLPFC, VMPFC, PCC, ACC, posterior insula, and the precuneus. This study also found that these specific ROI's were found to be correlated with higher AUDIT scores (i.e., more problematic alcohol use). Although the findings of this study were contrary to our hypothesis, this allowed us to hypothesize that less ICM-related signal may be the result of a larger dilemma such as neuroinflammation due to prolonged and chronic alcohol use, once again highlighting the need for longitudinal research.

Chapter 4 showed that rs-FC between the salience network and the occipital cortex, as well as between the temporal network and the orbitofrontal cortices, was lowest for individuals who reported using three or more substances. We also found that individuals who reported using two substances, either alcohol and cannabis or alcohol and nicotine, had the greatest amount of rs-FC within these networks and regions. This study highlights the importance of examining polysubstance use and the potential interaction and combination effects that may arise in the brain when different substances are taken.

Within each chapter, the significant findings and important findings were discussed in depth and in detail and have been briefly summarized above, however the commonalities that were found within each of the studies and that span this thesis, such as frequently implicated brain regions, warrant further discussion.

As has been shown in previous large-scale reviews and meta-analyses, the frontal regions of the brain are by far the most commonly implicated in substance use disorders (Bühler &

Mann, 2011; Mackey et al., 2018; Wilcox et al., 2019), and this notion has been echoed within this thesis. The dorsolateral prefrontal cortex (DLPFC) arose as a notable region within all three of the studies included in this thesis. Moreover, the studies in this thesis also found that frontal regions such as the orbitofrontal cortex (OFC), the ventromedial prefrontal cortex (vmPFC), and the inferior frontal gyrus (IFG) were associated with substance use. Given that the frontal lobes are responsible for executive control, abstract functioning, motivation, emotion regulation, and motor functions to some extent (Firat, 2019), these findings highlight the importance of exploring the frontal lobes as a neural marker of SUD and targeting the frontal lobes in SUD treatments.

5.3 Future Directions

As can be seen within the discussion sections of each of the study chapters in this thesis, there remain a number of items that warrant further research and investigation such as delving deeper into the effects that combined use of multiple substances can have on the brain and exploring inflammation throughout the body and brain in response to alcohol use. Additionally, an overarching point that was echoed throughout each of the studies, and perhaps the most beneficial direction for future research to travel, is the use of longitudinal study designs.

Longitudinal studies may elucidate many of the unanswerable questions noted throughout this thesis and would greatly advance the field of SUD research. Within Chapter 2, we were unable to determine whether the reduction of cortical thickness within various brain regions was a direct result of prolonged exposure to alcohol (i.e., a consequence), a predisposing factor that was present before initiation of alcohol use (i.e., a cause), or very likely both to some extent. Similarly, within Chapter 3, participants were assessed at a single time point which forces a

number of questions surrounding cause, effect, inflammation, and time course, to remain unanswered. However, had these two studies had MRI data from multiple time points, we may have been able to provide some more conclusive answers regarding the effect of alcohol on cortical thickness or ICM within our samples.

In the case of Chapter 4, the benefits of a longitudinal study are twofold. First, it would have allowed for the polysubstance use groups to be examined at multiple time points and ideally would indicate whether there are any rs-FC changes to be observed in response to different substance using profiles. Second, it has been said that an individual's brain activity can change significantly depending on the day, the time of day, how much sleep the individual has had, and many other variables (Elliot et al., 2020; Farahani et al., 2019; Orban, Kong, Li, Chee, & Yeo, 2020). Therefore, not only would a longitudinal study allow for a timeline to be examined but would also allow for multiple time points to be combined in order to generate a more reliable and generalizable overall finding for each PSU individual or group.

Although longitudinal studies can be costly, time intensive, and can result in an overwhelming amount of data, they are also one of the only study designs that can allow scientists to examine how variables may be related to one another with regard to time and development.

5.4 Limitations

This thesis, and the studies within it, have several limitations that warrant acknowledgment. Study specific limitations have been addressed in the discussion section of every chapter however, broader limitations that transcend the thesis are as follows.

As mentioned within the above section, *Future Directions*, the studies included in this thesis were cross sectional in nature and therefore are unable to provide us with any evidence to examine whether or not abnormal structural and functional findings within the brain are variables that may lead to substance use, or whether these variables may be a result of substance use.

Additionally, this thesis utilized neuroimaging methods such as MRI and fMRI in order to examine the associations between substance use and the brain. These findings should be interpreted with caution given that neuroimaging methods are simply a proxy measure of brain activity and structure, and that any amount of movement within the scanner can greatly affect the results that are produced (Gilmore, Buser, & Hanson, 2019). Additionally, structural and functional MRI data is often subjected to a variety of preprocessing steps that work to produce a high-resolution image that can be examined; however, brain tissues and regions are often measured in millimetres, and therefore may be greatly affected by preprocessing steps such as denoising, smoothing, and motion correction (Despotović, Goossens, & Philips, 2015).

Finally, the studies within this thesis imposed relatively strict restrictions on which individuals could be included, and furthermore, which groups the individuals would be placed into. Individuals were included in the studies if they self-reported consuming at least one alcoholic beverage in the past week, and were excluded if they reported severe neurodevelopmental, neuropsychiatric, or neurologic disorders. Moreover, in Chapter 3 and 4, participants were placed into various participants groups based on their substance use within the past year, regardless of what their longer SUD history may have been (i.e., recently began using, a binge user, recently entered a treatment facility, a short but recent relapse, chronic lifelong user, etc.). The criteria utilized throughout this thesis are common among research in the field of

SUD, however they also limit the generalizability of the results and they force SUD to be regarded as a static and dichotomous variable rather than an organic and biological disease.

5.5 Conclusions

In conclusion this thesis has added to the understanding of brain correlates of alcohol use, has explored ICM as a novel tissue through an innovative MRI pulse sequence, and has added to an understudied area of SUD literature. This work has showcased that indeed structural and functional abnormalities do exist in the brains of substance users, most notably for those who use alcohol or more than three different substances. These findings highlight the need for longitudinal research in order to help delineate whether these abnormalities are present before substance use or are a result of substance use.

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