EXECUTIVE FUNCTIONING AND RESTING-STATE FUNCTIONAL CONNECTIVITY IN ALCOHOL USE DISORDER

by

SHANNON M. MCNALLY

(Under the Direction of Lawrence H. Sweet)

ABSTRACT

Alcohol use disorder (AUD) is a chronic, relapsing brain disease in which individuals compulsively seek alcohol. Extant literature has increasingly recognized the importance of executive functions in AUD, though few studies have attempted to identify resting state functional connectivity substrates for executive dysfunction in AUD. The current study used a case-control design to investigate differences in latent executive function and within and between network connectivity in the executive control (ECN) and default mode (DMN) networks for individuals with AUD (63) and a control group (60). The study also aimed to determine whether within and between network connectivity was mechanistically important in the association between AUD and executive function. It was hypothesized that the AUD group would exhibit worse EF performance, weaker within and between network connectivity, and that functional connectivity would mediate the association between AUD and worse executive function performance. In contrast of hypotheses, EF did not significantly differ between groups, within and between ECN and DMN connectivity were not significantly associated with latent EF, and there were no significant indirect effects via within or between ECN and DMN connectivity. We did find, however, that the ECN was significantly associated with AUD status. There were also

two noteworthy incidental findings. First, processing speed was significantly associated with AUD status, with the AUD group demonstrating slower processing speed performance. Second, follow-up analyses demonstrated sex differences in within and between ECN and DMN connectivity. Overall, it seems that though the ECN is related to AUD, functional connectivity alone cannot account for variability and complexity of cognitive outcomes associated with AUD. This highlights the need for continued research that attempts to clarify factors that influence outcomes associated with AUD.

INDEX WORDS: Executive Functioning, Functional Connectivity, Alcohol Use Disorder, Default Mode, Executive Control

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SHANNON M. MCNALLY

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by

Shannon M. McNally

Major Professor:	Lawrence H. Sweet
Committee:	Lloyd Stephen Miller
	Gregory P. Strauss

Electronic Version Approved:

Ron Walcott
Vice Provost for Graduate Education and Dean of the Graduate School
The University of Georgia
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INTRODUCTION

Alcohol Use Disorder (AUD) is characterized as a chronic, relapsing brain disease in which individuals compulsively seek alcohol, experience a loss of control over intake, and are subject to negative emotional states in the absence of alcohol. AUD constitutes a serious public health concern, increasing risk for disease, illness, and mortality for over 28 million adults in the United States (SAMHSA, 2021). Alcohol accounts for 140,000 deaths each year in the US alone and 3 million deaths worldwide, making it the third leading preventable cause (CDC; World Health Organization, 2018). Moreover, AUD has massive medical, psychosocial, and economic consequences, costing the US an estimated $249 billion annually (Sacks et al., 2015; World Health Organization, 2018).

Despite these staggering consequences, approximately 1 out of 8 adults meet criteria for AUD (Grant et al., 2015). Even more disconcerting is that the US has seen significant upward trajectories in high-risk drinking (30%) and AUD (49.4%) over a 10-year period (Grant et al., 2017). Excessive alcohol use, described by the National Institute on Alcohol Abuse and Alcoholism (NIAAA) as high-risk drinking, equates to equal to or greater than 15 weekly drinks for men and equal or greater than 8 weekly drinks for women (Sacks et al., 2015). Alcohol misuse has been associated with increased risk of both immediate harms including violence (e.g., assault, suicide) and motor vehicle accidents, as well as more distal, indirect consequences (Duke et al., 2018; Mayshak et al., 2022; Taylor & Rehm, 2013; Wiener et al., 2018). Chronic alcohol misuse has been found to negatively impact overall health, and has been linked to cancer,

cardiovascular disease, cerebrovascular disease, and liver disease (Shield et al., 2014). Alcohol misuse has also been associated with depression, anxiety, unemployment, and problems with social relationships (Brière et al., 2014; Compton et al., 2014).

Prevention and treatment for AUDs has not kept pace with the increasing rates of alcohol use. Though many individuals with AUD recover without formal intervention, data from a meta-analysis showed that less than 50% of people with AUD achieve remission after a period of several years (Grant et al., 2015; Fleury et al., 2016). Given the significant consequences of AUD, improvements in identification of biological markers and characterization of outcomes is critical. Insights gained by understanding neural substrates of executive functioning, a key factor in the maintenance of AUD, has the potential to inform early risk identification, promote treatments that target altered brain processes, and improve diagnostic, prognostic and outcome assessments.

Models of Alcohol Use Disorder

According to the brain disease model of addiction (BDMA) model, three recurring stages constitute the addiction cycle: binge and intoxication, withdrawal and negative affect, and preoccupation and anticipation, or craving (Volkow et al., 2016). Existing neurobiological and psychological theories for etiology of addiction have increasingly emphasized the role of cognition in its onset, maintenance, and treatment of addictions (Koob & Volkow, 2010; Kwako et al., 2016; Wiers et al., 2013). In efforts to clarify mechanisms for this cycle, dual-process theories of addiction have predominated in the substance and alcohol misuse literature (e.g., Bechara, 2005; Bickel et al., 2015; Koob & Volkow, 2010; Wiers et al., 2013). Central to these theories is that the interaction between two complementary neurocognitive systems (i.e., two processes), impulsive processes and control processes, subserve the addiction cycle. These

models define impulsive systems as those that involve reflexive, automatic, and spontaneous processes while control systems involve reflective, slower, deliberate processes (Lindgren et al., 2019).

The impaired response inhibition and salience attribution (iRISA) model is one such dual-process model that proposes that two cognitive functions, response inhibition (i.e., impulsive processes) and salience attribution (i.e., control processes), and their neural substrates are critical to this cycle of addiction (Goldstein & Volkow 2002, 2011). This model predicts that there is greater recruitment of motivational and salience brain networks in response to alcohol-related cues but decreased engagement when alcohol-related cues are absent. Goldstein & Volkow (2011, 2016) emphasize the involvement of the prefrontal cortex as it typically directs attention towards salient cues, inhibits limbic reward regions, and subserves higher-order motivational processes revising early theories that focused on midbrain (e.g., ventral tegmentum and substantia nigra) and basal ganglia (e.g., ventral striatum) dopamine pathways due to their role in reward, conditioning, and habit formation (Di Chiara & Imperato, 1988; Wise, 1996; Everitt et al., 2001).

Appreciation of the dynamics between impulsive and control systems in dual process models of alcohol use and addiction has become increasingly important, as there is evidence suggesting that the interaction between these systems change over the cycle of addiction (Lindgren et al., 2019; Stacy & Wiers, 2010). Thus, neurobiological models of addiction mirror this increasing focus on the dynamics between impulsive and control systems, highlighting the interplay between prefrontal cortical regions and midbrain regions in drug-seeking behavior and maintenance (Bechara, 2005; Goldstein & Volkow, 2011; Koob & Volkow, 2010).

Taken together, dual process models hypothesize that impulsive systems prevail when the control system is dysfunctional, but are appropriately inhibited when control system are intact (Stacy & Wiers, 2010). As the addiction cycle progresses, the impulsive system is thought to strengthen as the control system weakens, resulting in perpetuation of alcohol misuse and associated negative consequences. Thus, dysfunction of the control systems secondary to chronic alcohol misuse contributes to reduced capacity to self-regulate and inhibit, resulting in continued impairment in decision making related to alcohol use, further perpetuating the cycle (Koob & Volkow, 2010; Lindgren et al., 2019).

Executive Functioning and Alcohol Use Disorder

Executive functions (EF) are a group of complex, multicomponent, top-down processes of cognitive function that work in tandem to facilitate selection of behaviors in accordance with one's goals (Diamond, 2013; Hofmann et al., 2012). Intact EF is dependent on the interactions between fundamental cognitive skills (e.g., attention, visuospatial perception, processing speed) and higher-order cognitive functions (e.g., concept formation, cognitive flexibility, inhibition). Integrative frameworks of EF posit that core components of EF, inhibitory control, working memory, and cognitive flexibility, are distinguishable yet interrelated, and are critical in goal-directed behavior, self-regulation, future planning, prioritization and sequencing of actions, and navigation of novel situations (Miyake et al., 2000; Garon et al., 2008; Banich, 2009; Miyake and Friedman, 2012; Diamond, 2013).

Individual differences in EF have been linked to health outcomes and overall functioning, such as interpersonal problems (e.g., Sprague et al., 2011; De Panfilis et al., 2013), academic and occupational performance (e.g., Miller et al., 2012; Valiente et al., 2013), physical health (e.g., Falkowski et al., 2014), mental health (e.g., Willcutt et al., 2005; Bora et al., 2009; Snyder,

2013), and substance use (e.g., Ersche et al., 2012). The core EF subdomains of inhibitory control, working memory, and cognitive flexibility (Diamond, 2013) are commonly implicated in AUD. Associations between EF and AUD are thought to be bidirectional in that executive dysfunction increases the likelihood that individuals will misuse alcohol and that alcohol misuse in turn affects brain circuitry for executive functions (Tapert et al., 2004; Peeters et al., 2014).

Inhibitory Control. Inhibitory control, also commonly referred to as response inhibition or inhibition, refers to the ability to purposefully withhold, change, or delay an automatic behavioral response (Logan et al., 1984). Regulation of one's attention, thoughts, and behavioral and emotional responses facilitates appropriate decision-making and responses. Objective measures of inhibitory control have been developed, and assess by presenting conditions where the participant must inhibit an automatic, reflexive response (e.g., reading a word, following a cued and/or more salient stimulus) in lieu of a more effortful response consistent with the task demand (e.g., attending to incongruent stimuli such as ink color conflicting with the printed color word or incongruent directional arrows). Objective measures of inhibitory control include the stop-signal or go/no-go task (Diamond, 2013), the Stroop task (MacLeod, 1992; Banich & Depue, 2015), and Flanker Tasks (Eriksen & Eriksen, 1974).

Studies have consistently observed deficits in inhibitory control among individuals with heavy alcohol misuse and AUD (e.g., Smith et al., 2014). Even among individuals not dependent on alcohol, inhibitory control has been shown to be worse in individuals who drink more heavily (Christiansen et al., 2012; Houston et al. 2014; Smith et al. 2014). Further, inhibitory control has been found to be predictive of progression from heavy drinking to dependence (Rubio et al. 2008) and relapse (Rupp et al., 2006), as well as adolescent alcohol initiation and increased use (Fernie et al., 2013; Nigg et al., 2006). Inhibitory control has been proposed as a mechanism by

which alcohol dependence perpetuates through its influence on cue reactivity. Specifically, researchers have found elevated craving responses to alcohol-related cues in heavy drinkers with reduced inhibitory control (Papachristou et al. 2013). With respect to the addiction cycle, atypical inhibitory control is thought to impair the ability to regulate behavior in response to salient, alcohol-related cues, resulting in increased likelihood that individuals will continue to consume alcohol (de Wit 2009; Jones et al. 2013).

Working Memory. Baddeley (2003) described working memory (WM) as a "limited capacity system, which temporarily maintains and stores information, and supports human thought processes by providing an interface between perception, long-term memory and action." Core processes of working memory, according to most models, encompass maintenance and manipulation of information via short-term memory in order to accomplish a goal, as well as utilization of top-down cognitive control to overcome interference during tasks (Hofmann et al., 2012). Further, WM models describe a central executive system, verbal WM storage system, and visuospatial WM storage system (Baddeley, 2003). Working memory capacity is typically assessed by tasks that require individuals to attend to a string of stimuli (e.g., numbers, symbols, spatial order/location) and respond identically and manipulate the response in some way (e.g., backwards, serially). For example, Spatial Span assesses visuospatial working memory by requiring participants to attend to the order in which the examiner taps spatially distributed blocks, with series of increasing length, and the participant must repeat the sequence in the same and backward order. Digit Span assesses auditory attention and working memory by requiring individuals to repeat a string of numbers presented orally in forward (i.e., exactly as it was read to them), backward, and in order from smallest to largest number.

Working memory has been consistently shown to be impaired in AUD (e.g., Chanraud et al., 2007; Lawrence et al., 2009; Martelli et al., 2017). Though cognitive impairments in AUD often present as behavioral impulsivity (i.e., tendency to engage in inappropriate behavior without consideration of negative consequences; Dick et al., 2010; de Wit, 2009), researchers have recognized the role of WM in impulsive choices and poor decision-making (Hinson et al., 2003; Khurana et al., 2013). Further, WM training is thought to improve overall EF and impulse control and appears to be a mechanism in AUD (Bickel et al., 2014; Verdejo-Garcia, 2016).

Cognitive Flexibility. Cognitive flexibility (set shifting, mental flexibility) refers to the ability to shift flexibility between thoughts, task sets, stimulus attributes, strategies, or behaviors in accordance with the changing rules, priorities, or demands of a situation (Hofmann et al., 2012; Diamond, 2013; Zelazo, 2015). It encompasses perceptual, cognitive, and behavioral responses where individuals are able to inhibit or discontinue a previous response set while generating an alternative. Cognitive flexibility builds upon inhibitory control and working memory, emerging later in development (Davidson et al., 2006; Garon et al., 2008). Efficient cognitive flexibility facilitates organization of multiple tasks and application of novel, adaptive behavior necessary for successful engagement in various situations. Difficulty engaging in flexible thinking often results in perseverative responses, or difficulty inhibiting a prepotent response and making continued errors (i.e., perseverations) despite unsuccessful results (Zelazo et al., 2003). A variety of tasks involving task-switching and set-shifting have been developed to measure cognitive flexibility. The Wisconsin Card Sorting Task (WCST; Milner 1964; Stuss et al., 2000) is one of the oldest, well-described tests of prefrontal cortex function. During the WCST, participants are asked to sort cards according to one of several sorting criteria (e.g., color, form, number). Based on feedback, participants deduce the correct sorting strategy, which

then changes throughout the test. Subsequently, participants must flexibly adapt their sorting strategy in order to effectively complete sorts. The Dimensional Change Card Sort Test (DCCS) adapted a simple version of task switching (Zelazo et al., 1996; 2003), where participants are asked to change their sorting strategy from one dimension to another. Despite the relative simplicity of the task, preference to the initial sorting strategy is evident in slowed reaction times when required to sort according to another dimension (e.g., Diamond & Kirkham, 2005).

Compared to inhibitory control and WM, relatively fewer studies have investigated cognitive flexibility in AUD. Still, there is some evidence that alcohol misuse is associated with worse cognitive flexibility. For example, one study found cognitive flexibility to be impaired in a sample of non-patient men and women with high levels of alcohol consumption (Houston et al., 2014).

Processing Speed. Processing speed refers to the ability to rapidly perform tasks that may be simple or complex. Though it is not traditionally included in models of higher-order cognitive functions such as executive function, it has been consistently shown to be associated with higher order tasks (Lichtenberger & Kaufman, 2012). Its association with cognitive functions such as EF is thought to be due to its role as a key cognitive function on which higher-order functions depend (Kail & Salthouse, 1994). There is evidence that improvements in EF functions such as working memory can be attributable, in part, to improvements in processing speed (Kail, 1991). Similarly, declines in cognitive functions during aging have been linked to declines in processing speed (Salthouse, 2005; Daugherty, Shair, Kavcic, & Giordani, 2020). Processing speed is typically assessed using coding tasks and sequencing tasks, such as the Trail Making Test. Importantly, speed is emphasized during tasks instructions and performance can be evaluated on completion time or number of correct items within a set time.

Though not as widely studied as EF in AUD, extant literature has found processing speed to be slower in individuals with history of heavy drinking, including slower reaction times and slower performance on the Digit Symbol subtest of the Wechsler Adult Intelligence Scale (Kopera et al., 2012; Pfefferbaum et al., 2009; Ratti et al., 2002). Another study found that individuals with history of alcohol use disorder tend to sacrifice speed for accuracy, leading to poor efficiency (Sullivan et al., 2002).

Neuroimaging and Alcohol Use Disorder

Both structural and functional neuroimaging methods have been utilized to investigate substrates of key mechanisms in binge/intoxication, preoccupation/anticipation and withdrawal/negative affect stages of addiction. Functional brain imaging in particular has lent itself as a robust method to detect functional neural changes, potentially before structural changes have occurred. Thus, neural patterns identified through functional brain imaging may serve as markers for early AUD-related changes in the brain and, subsequently, cognition.

Principles of Functional MRI and the BOLD Response. Functional MRI (fMRI) attempts to estimate fluctuations in neural activity in the brain in an effort to provide a proximal measurement for brain function. Since neurons do not have internal sources of energy, they are provided with energy by adjacent capillaries. This process is called the hemodynamic response. It is based on the notion that activated neurons signal and metabolize oxygen at higher rates (Stamatakis et al., 2017). Through this process, regions surrounding activated neurons experience increases in cerebral blood flow. Measurement of T2* relaxation is sensitive to local concentrations of paramagnetic deoxyhemoglobin in the brain (Ogawa, Lee, Kay & Tank, 1990). The basis for such estimation is referred to as the blood oxygen level-dependent (BOLD) signal (Bandettini et al., 1992; Frahm et al., 1992; Ogawa et al., 1990; Thulborn et al., 1982). It is

commonly thought that BOLD signal equates to a measurement of neuronal oxygen consumption; however, it rather represents a decrease in paramagnetic deoxyhemoglobin and subsequent over-oxygenation of the region that occurs when metabolic rate increases (Attwell & Iadecola, 2002). In other words, the BOLD signal is not a measure of neuronal activity, per se, but rather detection of changes in relative levels of oxyhemoglobin and deoxyhemoglobin secondary to the hemodynamic response. This response, supported by the vascular system, occurs on a one to two second delay following activation and peaks at four to five seconds, which results in an oversupply of oxygenated blood (i.e., excess oxyhemoglobin) compared to deoxyhemoglobin (Stamatakis et al., 2017). Thus, though spatial resolution for fMRI is suitable, it is not well suited for temporal resolution.

Resting State Functional MRI. In contrast to task-based functional MRI, rs-fMRI does not require participants or patients to perform a specific task while in the scanner. rs-fMRI captures spontaneous BOLD signal alterations that occur in the brain at "rest", which are thought to reflect intrinsic functional connectivity. Specifically, rs-fMRI focuses on slow-wave (<.01Hz) spontaneous fluctuations thought to reflect "baseline" brain function and this organization at rest has been shown to reflect functioning when activated. Indeed, studies have shown atypical connectivity to reflect inefficient and disorganized processing (Chanraud et al., 2011; Greicius, 2008). Tambini and colleagues (2010) showed that an individual's resting-state functional connectivity map can predict brain activation patterns during a task. Temporal correlations among spontaneous BOLD signals were first reported in bilateral motor cortices (Biswal et al., 1995). Since then, resting state functional MRI (rs-fMRI) has become a widely-used and meaningful tool in efforts to investigate functionally connected networks throughout the brain (Smith et al., 2013). Evolving rs-fMRI methods have been instrumental in advancing scientific

and clinical understanding of brain development, health, disease, and aging (Fair et al., 2008; Supekar et al., 2009; Bettus et al., 2010; Fox & Greicius, 2010; Qin et al., 2012; Lin et al., 2018).

Functional connectivity analyses have identified differences in neural network synchrony at rest, supporting the notion that regions of the brain work together even in the absence of a task (Biswal et al., 1995; Greicius et al., 2003; Fox et al., 2005; Raichle 2011). Evidence from functional connectivity analyses of resting state fMRI (rs-fMRI) data have revealed intrinsic networks in the brain, and have further demonstrated that these networks are valid and reliable substrates for cognition (Hampson et al., 2002; Beckmann et al., 2005; Seeley et al., 2007). Further, resting state functional connectivity has been shown to reflect structural connectivity, supporting its usefulness in investigating how key connected regions are communicating (Greicius et al., 2009; van den Heuvel & Sporns, 2011).

Although original task-based fMRI methods were influential in linking brain regions and networks to functions, rs-fMRI has several advantages that support its utility and practicality in studying diverse populations. First, there is no need for fMRI compatible stimulus presentation and response collection devices, as rs-fMRI does not rely on tasks to elicit neural function. Second, multiple networks are observable from a single rs-fMRI session without needing to administer multiple tasks or undergo multiple conditions. Additionally, fMRI provides a wealth of information collected in a relatively straight forward manner making it an efficient tool for patient populations who may have difficulty with task instructions.

Multiple ways to conceptualize and analyze rs-fMRI data have been developed, each with its unique advantages. Approaches to analyzing rs-fMRI data can broadly be divided into two categories: functional segregation and functional integration (Liu et al., 1999; Tononi et al., 1994). In functional segregation methods, local function of specific brain regions is investigated.

These methods assess functional activity and are typically used in brain mapping. Functional integration methods conceptualize the brain as an integrated network, taking interest in functional relationships, or connectivity, between seed and target brain regions. Within functional integration methods, model-free methods (e.g., principal and independent component analyses) do not rely on a priori regions of interest. Rather, these methods use multivariate decomposition to separate the BOLD signal into several temporally correlated functional networks (Kiviniemi et al., 2003; van de Ven et al., 2004). Model-based methods rely on a priori regions of interest (i.e., seeds) to estimate correlations between intra- and inter-network regions.

Seed-based functional connectivity analysis, also referred to as ROI-based functional connectivity, is a model-based method that aims to determine whether fluctuations in given target regions are associated across time with fluctuations in an a priori seed region of interest. Coupling among brain regions, which indicate associated involvement in shared underlying functional processes, can be represented through several metrics including cross-correlation coefficients, partial correlations, and multiple regressions (Bastos & Schoffelen, 2016). For example, strength of BOLD fluctuations associations among a given region's time series and target regions may be derived through correlations (e.g., Fox & Raichle, 2007) or general linear models that account for artifacts such as head motion and respiration, among other factors.

Intrinsic Networks. The executive control network (ECN) has been shown to subserve integration of sensory and cognitive information, regulation of cognition and behavior, and engage in working memory processes through prefrontal lobe activity. Resting-state fMRI studies have also found intrinsic connectivity among ECN regions (e.g., Beckmann et al., 2005; Vincent et al., 2008). The dorsolateral prefrontal (DLPFC) and posterior parietal (PPC) cortices are most commonly described ECN regions (Niendam et al., 2012; Damoiseaux et al., 2006;

Petersen et al., 2019; Fede et al., 2019). The ECN subserves weighing and selection of behavioral responses, and plays a critical role in representing and maintaining goals during motivated behavior (Badre, 2008; Miller & Cohen, 2001). This includes inhibition of motor and cognitive responses, cognitive flexibility, and maintenance and manipulation of information (Aron et al., 2014; Robbins et al., 2012).

The default mode network (DMN) subserves self-directed or self-referential cognitive processes important for higher order cognitive regulatory functions, including self-awareness and reflection (Murray et al., 2012; Northoff et al., 2006). Greicius and colleagues (2003) delineated the DMN by placing regions of interest seeds in the ventral medial prefrontal cortex (VMPFC), dorsal medial prefrontal cortex (DMPFC) and posterior cingulate cortex (PCC), identifying a coherent network. The PCC along with the medial precuneus were among the first to be described in the DMN. These regions have been found to be important for recollection of previously learned items (Vincent et al., 2006). The DMPFC has been associated with self-referential judgments (Gusnard et al., 2001). It is unsurprising that the VMPFC has been found to be critical for social behavior, mood control, and motivation given its anatomical neurocircuitry. Through the orbitofrontal cortex in the VMPFC, information is relayed to midbrain structures (e.g., amygdala, hypothalamus, periaqueductal gray matter; Zhang & Volkow, 2019). Inefficient engagement in non-self-directed cognitively demanding tasks has been linked to aberrant DMN activity (Sutherland et al., 2012).

In addition to functioning as cohesive networks individually, functional balance between networks has been studied in efforts to elucidate complex behaviors. Early efforts in describing network interactions found evidence that supported the existence of anticorrelations between the DMN and a “task-positive network” at rest (Fox et al., 2005; Fair et al., 2007; Seeley et al.,

2007). Importantly, the anticorrelations between the task-positive and task-negative networks mirrored patterns elicited through attention-demanding tasks, where task-active network activity increased as the DMN activity decreased.

Functional Connectivity and EF. Functional imaging has been pivotal in clarifying networks of brain regions that subserve the complexities of EF. EF involves the coordination of activities reliant on cortical and subcortical brain structures, which makes them vulnerable to a wide range of disorders. Task-based studies have provided corroborating evidence regarding involvement of frontal regions in EF tasks including, cognitive flexibility, working memory and inhibition (e.g., Curtis & D'Esposito, 2003; Blasi et al., 2006; Sweet et al., 2008; Niendam et al., 2012; Jansen et al., 2015). The engagement of such cognitive processes is then supported by parietal connections (i.e., PPC) which facilitate effortful performance (Nelson et al., 2000). These functional findings have been supported by structural connectivity research (Shen et al., 2019). Specifically, the authors described a "structural core" for the ECN that converged with functional network connectivity, and found that the bilateral prefrontal cortices were central to the network and most strongly associated with EF performance. They also found fronto-parietal connections that mirrored the ECN and strongly correlated with EF performance.

The DMN has been a target of functional research, as its relatively higher activity level during resting conditions makes it a logical neural marker candidate in resting-state studies. Moreover, there is evidence that the DMN is active during goal-directed tasks with a self-related cognition/internally directed component (Buckner & Carroll, 2007; Andrews-Hanna et al., 2010). Its role in cognitive functions has been attributed to its strong, dynamic interactions with other large-scale networks, including the ECN (Raichle 2015; Spreng et al., 2012). Specifically, its interactions with the ECN have been shown to be important in attentional control and impulsivity

(Fox et al., 2005; Shannon et al., 2011). Beyond its connections with large-scale networks, DMN activity itself has been linked to tasks that require large cognitive shifts (Kim et al., 2012; Crittenden et al., 2015). These authors proposed that the DMN is important in releasing attentional focus from one cognitive set in order to allow focus to switch to a new cognitive set. This requires inhibition of a response to a previous rule and maintenance of what the previous rule was so that a shift to a new rule can be made. Taken together, efficient connectivity within and between the ECN and DMN networks is critical for flexible, fluid engagement of executive processes.

Functional Connectivity in AUD. Robust bodies of literature for networks such as the ECN and DMN have generated corroborating evidence in support of their central involvement in AUD (Zilverstrand, 2018). Aberrant connections between ECN and DMN networks that subserve key executive functions are thought to contribute to craving and relapse (Zhang & Volkow, 2019). There is significant work delineating neural differences for task-based fMRI in AUD, and one meta-analysis demonstrated greater engagement of DMN and ECN in response to alcohol-related cues (Myrick et al., 2004).

Short- and long-term alcohol use effects on rs-fMRI between and within network connectivity has been relatively understudied and results have been mixed. Additionally, earlier endeavors to investigate resting state functional connectivity in alcohol users and AUD reasonably focused their efforts on the reward network in order to clarify acute effects of alcohol misuse. Camchong and colleagues (2013) found that in individuals who were long-term abstinent, there was decreased synchrony within limbic reward regions. With elaboration of more recent models and expansion of attention to the complexity of cognitive processes and behaviors that maintain patterns of alcohol misuse, researchers have turned their attention to other networks

that, when aberrantly connected, allow impulsive and reward-driven systems to prevail. The ECN and DMN resting state within network connectivity patterns have been found to be particularly informative in differentiating among those with and without AUD (Zhu et al., 2018). Chanraud and colleagues (2011) found a reduction in functional connectivity within the DMN in a small sample of individuals who were alcohol-dependent (DSM-IV). Müller-Oehring and colleagues (2015) found the DMN and ECN have not only weaker within-network connectivity, but a more expanded out-side network connectivity pattern in abstinent alcoholic men. In contrast, some research has found there to be increased within network functional connectivity in the DMN and left ECN in individuals with AUD compared to controls, but they did not find a significant difference in between-network connectivity for the DMN and left ECN (Zhu et al., 2017).

Neuroimaging, Executive Functioning, and Alcohol Use Disorder

Predominant models of addiction have increasingly expanded their focus from emphasizing the role of midbrain dopamine regions to appreciating the role of the prefrontal cortex (Goldstein & Volkow, 2011). The prefrontal cortex mediates a range of processes involved in emotion, cognition and behavior, which elucidates the wide array of behavioral disruption observed in AUDs. Thus, when the prefrontal cortex becomes preferential to alcohol-related cues and reward, it does not effectively engage to support tasks that are reliant on frontal executive systems. This decreased sensitivity to non-alcohol related cues has been conceptualized as an allostatic adaptation (Volkow et al., 2004). Similar to tolerance, it has been asserted that compensatory brain changes occur in response to frequent and high intake of alcohol, which subsequently dampens motivational processes in response to other cues and tasks. Dysfunction in the prefrontal cortex also affects response inhibition. Impaired response inhibition and sensitivity

of the prefrontal cortex to alcohol-related cues increase risk of maintenance and relapse of alcohol misuse.

The iRISA dual process model further posits that key frontal-supported systems (i.e., executive function) compromised by ECN and DMN dysfunction further reduce individuals' abilities to engage in decision-making that accounts for short- and long-term consequences in the context of acute cues, past outcomes, and diverse goals. Dysfunction in key nodes of the ECN, including the DLPFC and PPC, affect one's ability to support higher-order cognition and put forth effortful performance. Dysfunction of midline core of the DMN, which includes the PCC/precuneus and MPFC, affects individual's ability to engage in efficient self-referential cognition and impedes their ability to disengage from a previous cognitive set and shift to another (Kim et al., 2012; Crittenden et al., 2015). Thus, this frontal dysregulation coupled with atypical midbrain functioning then impede efficient executive functioning, and subsequently impair decision-making related to alcohol and related risky behaviors. Executive functions are critical to the efficiency and effectiveness of the control system processes, as cognitive flexibility, working memory, inhibitory control, and information processing are the foundations upon which individuals effectively engage in complex decision-making (Diamond, 2013). EFs have been posited to be important in controlling substance use in neurobiological and cognitive models of addiction (e.g., Bechara, 2005; Koob & Volkow, 2010). Cognitive flexibility allows individuals to switch between thinking sets, and allows for flexibility in problem solving (e.g., considering coping strategies in place of self-medicating via alcohol). Working memory plays an important role in integrating information about the consequences of substance use and contingencies surrounding alcohol decision-making (Hofmann et al., 2008). Inhibitory control facilitates the ability to inhibit an automatic learned response (e.g., consuming alcohol),

providing more time for that individual to engage in higher-order, flexible thinking. Processing speed supports efficient engagement of these higher order functions.

In a small sample of participants with AUD, Galandra and colleagues (2019) utilized a comprehensive neuropsychological battery to investigate associations with between and within network connectivity among many networks including executive control (bilateral, right and left fronto-parietal), attentional (anterior, posterior, dorsal) salience, default mode, language, sensorimotor, visual, limbic, basal ganglia-thalamus, and cerebellar networks. The researchers used a principal component analysis to define neurocognitive domains, including high- and lower-level executive functions. Given the high overlap of skills involved in executive functioning, this yielded a range of skills that loaded onto high-level EF (e.g., verbal reasoning, copy drawing) that might have confounded findings related to core executive functions implicated in AUD. Still, their findings between low-level EFs and the ECN were important in linking between and within network connectivity patterns underlying cognitive dysfunction in AUD.

Another small study investigated connectivity and cognitive performance among abstinent men and women who had met DSM-IV criteria for alcohol dependence and abuse compared to controls (Müller-Oehring et al., 2015). This study utilized the Wechsler Memory Scale (Wechsler, 1987) subtests of verbal (digit span) and visual (block span) working memory, as well as the Trail Making Test (Reitan & Wolfson, 1985) for perceptual motor processing speed and flexibility (Trails A, B). In addition to weaker within-network and expanded outside-network connectivity in the DMN and ECN as described above, they also found worse cognitive performance to be associated with this pattern of aberrant connectivity. Thus, this study provided evidence in support of aberrant within and atypical expanded network connectivity in relation

cognitive functions in abstinent individuals with AUD, but did not investigate all key components of EF or evaluate indirect effects.

Rationale, Aims, and Hypotheses

The effects of heavy drinking have been characterized for severe alcohol misuse in inpatient settings as well as those with lower drinking levels who do not meet criteria for AUD (Stavro et al., 2013). The effects for those who meet criteria for AUD, but not to the degree that warrants in-patient treatment, have been relatively understudied (Meredith et al., 2020). Additionally, existing studies often include polysubstance users, making it difficult to interpret the effects of alcohol alone (e.g., Fernández-Serrano et al., 2010).

Another set of limitations of existing studies in alcohol misuse is related to neurocognitive factors. Often, single tests are used to draw inferences about a component of EF (e.g., Houston et al., 2014). Conversely, studies analyze tests individually, and draw inferences about a given subdomain of EF based on performance on that single measure. While valuable, the way in which heavy alcohol use affects regions in the ECN and DMN makes interpretation of single domains of EF difficult as these are seldom affected in isolation. Studies that have combined EF have either done so through averaging or deriving data-driven components. Given its complexity, a latent variable based on theory that represents core components of EF may be valuable. Finally, studies have typically used classic neuropsychological tests given their validity and reliability. The NIH Toolbox is a standardized neurocognitive battery developed by the NIH's Blueprint for Neuroscience Research initiative (Hodes et al., 2013). Given its ease of administration, computer-based platform, and relative brevity, the NIH Toolbox has been an increasingly useful tool for clinicians and researchers (Weintraub et al., 2013). The NIH Toolbox is not synonymous with a comprehensive neuropsychological evaluation, but its format lends itself to being a useful

screening tool. This is especially important for outpatient AUD populations, as overt cognitive dysfunction is not typically a primary presenting problem and time for a full battery is not always prioritized or feasible. While the toolbox has been employed in a number of clinical and healthy populations, its utility in AUD has been understudied.

Finally, most studies to date have focused on linking intrinsic connectivity to outcomes in efforts to predict alcohol use severity (Weiland et al., 2014) and relapse vulnerability (Kohno et al., 2017). Additionally, studies investigating network connectivity have emphasized ECN and salience or reward networks (e.g., Camchong et al., 2013). Given that EF may serve as a mechanism by which alcohol-related decision making occurs, thereby promoting craving and relapse, it is important that we understand how AUD affects neural substrates for EF as this perpetuates the addiction cycle. Specifically, dynamics within and between the ECN and DMN appear to be critical is supporting engagement and efficiency of EFs.

The proposed study aims to address these gaps in the literature by investigating resting state functional connectivity within and between the ECN and DMN, and whether these dynamics mediate the association between AUD and latent, theory-derived EF. In addition to clarifying the indirect role of functional networks, this study will expand upon efforts (Meredith et al., 2020) to establish utility of the NIH Toolbox for AUD patients.

The first aim of the proposed study is to determine whether there are differences in latent EF in individuals who meet criteria for AUD compared to controls. Due to existing theories that there is unity and diversity in EF (e.g., Snyder et al., 2015), a follow-up analysis to determine whether there are differences in specific aspects of EF will be conducted. It is hypothesized that EF performance will be worse in individuals with AUD compared to controls.

Second, the study will determine if there are differences in between and within network connectivity in the ECN and DMN for AUD and controls. Given extant literature (e.g., Müller-Oehring et al., 2015), we expect that there will be weaker within and between network connectivity in the AUD group compared to control group.

The third aim of the proposed study is to examine associations between RSFC and EF. As has been found in previous studies (e.g., Jansen et al., 2015; Kim et al., 2012; Crittenden et al., 2015), we expect that stronger within and between network connectivity will be associated with better EF performance.

Finally, we aim to determine whether within and between network RSFC for the ECN and DMN are mechanistically important in the association between AUD status and EF through mediation modeling. Given that separate bodies of literature have linked alcohol-related factors to both resting-state networks and EF, and that resting-state networks have been linked to EF, it is expected that there will be a significant indirect effect for the associations among AUD, aberrant RSFC, and worse EF performance.

CHAPTER 2

METHOD

Participants

Data for the current study was part of an observational case-controlled design comparing individuals with AUD and healthy drinking controls. Participants (123 total) included 55 men and 68 women, ages 21-56, with AUD (n=63) and matched control participants (n=60). To be eligible for the study, AUD participants were required to meet both DSM-5 criteria for AUD (American Psychiatric Association, 2013) and high-risk drinking as defined by NIAAA (i.e., males >14 drinks per week and females >7 per week) in the 28 days preceding study enrollment. Control participants were determined to be eligible if they did not have current or past DSM-5 AUD diagnosis and met criteria to be defined as low-risk drinkers per NIAAA (i.e., males <14 per week, females <7 per week). All participants were required to be right-handed and fluent English speakers. The control group was matched to the AUD group on (a) sex, (b) age (±5 years), (c) income, (d) smoking status (smoker/non-smoker), (e) verbal IQ (±5 points on Shipley 2; Kaya et al., 2012), and (f) number of depressive and anxiety symptoms. Participants were excluded from the study based on the following criteria: (a) inability to provide informed consent, (b) history of DSM-5 substance abuse disorder other than alcohol or tobacco (see Study Eligibility Measures), (c) greater than weekly use of recreational drugs other than alcohol or tobacco products including vaping, (d) history of schizophrenia-spectrum/psychotic disorders or bipolar disorder by interview, (e) MRI research contraindications (e.g., metallic implants, pregnancy, injury involving metal, claustrophobia), and (f) history of significant brain injury

(e.g., TBI, stroke) or neurological disorders, (g) lower than ninth grade education to ensure adequate literacy, (h) currently receiving/seeking treatment and/or has recently (within the past 90 days) received treatment for alcohol or other substance-related problems. The study was performed in accordance with the approval and recommendations of the Hamilton Integrated Research Ethics Board and subjects provide written informed consent in accordance with the Declaration of Helsinki.

Procedures

Recruitment occurred in the context of an ongoing NIH-funded (R01AA025911) research collaboration between the University of Georgia in Athens GA, USA and McMaster University in Hamilton ON, Canada. Participants were recruited in Hamilton using community advertisements (e.g., flyers, emails, public announcements, and print and online advertising).

First, written consent was obtained from prospective participants. Prospective participants were then screened by telephone or through an online assessment through REDCap to determine initial study eligibility. Individuals who were found to not meet study criteria or decided not to continue but exceed the NIAAA drinking guidelines were given *Rethinking Drinking*, a guide to healthy drinking and self-change strategies. Participants were then scheduled for two in-person assessments at the Peter Boris Center for Addictions Research in Hamilton, which were held within one week of each other. The first in-person assessment consisted of a 3-hour session that included an interview and computer-based assessments. This included confirmation of age via government issued identification, DSM-5 AUD diagnosis using a structured clinical interview, and drinking level via the Diagnostic Assessment for Research and Treatment (DART) Form-90 (Westerberg et al., 1999; Tonigan et al., 1997). Computer assessments were administered using Inquisit™ and REDCap software. All participants then attended a second 3-hour visit that

comprised of a 60-minute MRI scan and the remaining behavioral and cognitive assessments. Participants provided a breath sample using an Alcohol Sensor Breathalyzer at the beginning of each study visit to confirm sobriety. Participants were compensated $15/hour for their time via gift cards for vendors that do not sell alcohol. Public transportation and parking vouchers were provided as needed.

Measures

Study Eligibility Measures. The Diagnostic Assessment for Research and Treatment (DART) is a semi-structured interview developed to determine AUD and substance use disorder status. Form-90 is a reliable and valid interview that utilizes a day-by-day calendar method to reconstruct alcohol and illicit drug use for the past 90 days (Westerberg et al., 1999; Tonigan et al., 1997). In this study, it was used to measure drinking 28 days prior to enrollment (i.e., drinks/week, % drinking days, and % heavy drinking days). The World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test (WHO-ASSIST) is a self-report measure of illicit substance use other than alcohol and tobacco. It was developed to detect and manage substance use in primary and general medical care settings. The WHO-ASSIST has undergone three phases of testing to ensure feasibility, reliability, validity, flexibility, and cross-cultural relevance (WHO ASSIST Working Group, 2002; Humeniuk et al., 2008). An Intoximeters breathalyzer was used to measure breathe alcohol. Individuals who presented to their evaluation intoxicated were rescheduled.

Control Measures. The verbal subscale of the Shipley Institute of Living Scale-2 (SILS-2) was used to estimate verbal IQ. The SILS-2 is a revised and standardized brief, robust measure of intelligence with demonstrated reliability and validity (Kaya et al., 2012). The

Fagerstrom Test for Nicotine Dependence (FTND) is a standard assessment to document smoker status and nicotine dependence (Heatherton et al., 1991; Pomerleau et al., 1989).

Inhibitory Control. The NIH Toolbox Flanker Inhibitory Control and Attention Test (Flanker Task) is a reliable and valid measure of inhibitory control adapted for inclusion in the NIH Toolbox (Eriksen & Eriksen 1974; Rueda et al., 2004; Zelazo et al., 2014). During this three-minute task, participants were instructed to focus on a specific stimulus within each item and respond appropriately. Items may have congruent or incongruent flanking distractor-stimuli (i.e., arrows oriented in the same or different direction as the middle, target stimuli), which require the participant to inhibit distraction. A single age-adjusted score based on a 2-vector scoring method that includes both response accuracy and reaction time was calculated for each participant, with higher scores indicating better performance (Weintraub et al., 2013).

Working Memory. The List Sorting task from the NIH Toolbox is a measure of working memory, developed to assess the storage and manipulation of information over short periods of time (Baddeley, 1992). During this task, participants were visually and aurally presented with a series of objects (e.g., food or animals), which they were to remember, mentally re-order, and respond according to the task condition rules (Tulsky et al., 2014). There were two conditions: a one-list and a two-list. In the one-list condition, participants were given a series of objects, either food or animals, to which they responded with order of size from smallest to largest. In the two-list condition, participants were presented with both food and animals. They were asked to respond by first listing food from smallest to largest, then animals in order from smallest to largest. This task has demonstrated convergent validity with other working memory measures, shows expected changes over the age span, and exhibits strong test-retest ability (Tulsky et al.,

2014). A single age-adjusted score based on the total number of items correct across trials was calculated (Weintraub et al., 2013).

Cognitive Flexibility. The NIH Toolbox Dimensional Change Card Sort task is a measure of cognitive flexibility that was originally developed by Zelazo and colleagues (Frye et al., 1995) and subsequently adapted for the NIH Toolbox (Zelazo et al., 2014). During this four-minute task, participants were shown two target pictures that vary along two dimensions, either shape or color. They were then given a cue that instructed them the dimension in which the cards should be sorted. In one block, participants sort by color, in another, form, and then they complete a block in which the sorting rule switches, testing the participant's ability to flexibly switch between cognitive sets and effectively adapt their responses. A single age-adjusted performance score was derived from both accuracy and reaction time, with higher scores indicating better performance (Weintraub et al., 2013). The Dimensional Change Card Sort task demonstrated sensitivity to age-related cognitive changes in adults, excellent test-retest reliability, and good convergent and discriminant validity (Zelazo et al., 2015).

Processing Speed. The NIH Toolbox Pattern Comparison Processing Speed Test is a measure of processing speed that was designed to be brief versatile in use across the lifespan (Carlozzi et al., 2014; Carlozzi et al., 2013). This task requires participants to identify whether two visual patterns are the same or not. Responses are indicated by pressing a "yes" or "no" button. For the full test, patterns that are not identical can vary on one of three dimensions: color differences, adding/taking something away, or one versus many of an object (ages 3-15 only). The items were designed so that number of errors committed are minimized. During development, items with less than 75% accuracy were not included in the final version. The

score for this task reflects the number of correct items out of 130 items total that were correctly indicated in a 90 second time limit.

Latent EF. Studies frequently overgeneralize a single measure of EF to represent overall EF, or consider individual components of EF to be singularly representative of a given construct. Due to its complexity, EF is difficult to measure and study (e.g., Jurado & Rosselli, 2007). Evidence has increasingly suggested that EF shows both unity and diversity in that EF components correlate with one another, but there is uniqueness among each component (Teuber, 1972; Snyder, 2015). Further, there is support that processing speed is a critical cognitive function that supports efficient EF (Kail & Salthouse, 1994). Researchers have demonstrated that tasks designed to measure EF inherently include variance attributable to factors other than EF (e.g., language), and suggest that the systematic variance and measurement error make it difficult to draw conclusions about EF (Miyake et al., 2000; Snyder et al., 2015). It has been suggested that latent variable approaches used to extract shared variance across tasks avoid contamination from error variance (Snyder et al., 2015). Thus, a latent variable comprised of EF measures for inhibitory control, working memory, cognitive flexibility, and processing speed via confirmatory factor analysis (CFA) was used in analysis as these are most likely to best capture the underlying processes that manifest as performance deficits in cognitive tasks related to AUD.

Resting State FMRI

Data Acquisition. Imaging data was collected on a research-dedicated 3T whole-body, short-bore GE Discovery 750 MRI system at St. Joseph's Healthcare Hamilton Image Research Center using a 32-channel head coil. Whole-brain anatomical structural images was acquired using high-resolution T1-weighted fast spoiled gradient echo scan (D BRAVO sequence, straight axial plain, TR = 8.2ms, TE = 3.2ms, TI = 450, 12-degree flip angle, 192 contiguous 1mm slices,

voxel size = 1mm isotropic, field of view = 25.6cm, matrix = 256x256, bandwidth = 31.2kHz, 244Hz/pixel). Resting state gradient echo, echo planar fMRI images was acquired according to the following parameters: TR = 2000ms, TE = 30ms, flip angle = 90 degrees, field of view = 22.4cm, matrix = 64x64, 40 3.5mm axial slices, voxel size = 3.5mm isotropic, bandwidth = 250kHz (7812 Hz/pixel, acceleration factor = 2). Nine minutes of resting state functional connectivity (RSFC) activity with 270 continuous volumes were collected. After being positioned in the scanner, all participants were instructed to passively observe a fixation cross (+). Participants were then interviewed after the scanning session to ensure that they did not fall asleep during the scan.

Image Processing. The entire resting-state series was used for analysis, resulting in nine minutes of data (270 volumes), which is consistent with supported recommendations of 5-10 minutes for resting-state data (Shehzad et al., 2009; Van Dijk et al., 2012). Data was preprocessed with Analysis of Functional Neuroimages software (AFNI; Cox; 1996). Specifically, the "afni_proc.py" program in AFNI was utilized to generate a script to pre-process the rsFMRI data. "Afni_proc.py" is a Python program that accepts a series of options as input that outputs the processing steps in a script used to analyze datasets from one subject. The generated script is a Unix tcsh script file that then directs all of the AFNI programs to process the data as specified. Use of "afni_proc.py" has several advantages over using idiosyncratic, "in-house" developed pipelines. First, the pipeline has been extensively evaluated and has demonstrated utility in several populations. The use of a flexible and compact program that then synthesizes and coordinates all of AFNI's programming minimizes errors inherent in developing a novel script. Output includes data analysis as well as diagnostic tools and intermediate output datasets to facilitate quality control and troubleshooting.

To prepare functional data for subsequent resting state functional connectivity analysis, the following preprocessing blocks were executed by the script: despiking, slice time correction, alignment to anatomical data, registration to standard space, volume registration, blurring, masking, scaling to percent signal change, and general linear modeling (GLM) analysis to remove all known effects on the residual BOLD signal time course. Specifically, data was despiked to truncate outlier intensity spikes for each voxel's time series. Functional data was aligned to the T1-weighted anatomical data collected during the same scanning session. Non-linear transformation was performed to align data to standardized Talairach space. Next, data was registered to the individual's volume with the least deviation from the mean of their series to reduce the need for large registration transformations. Data was spatially smoothed using a 5mm FWHM Gaussian filter. Masking includes exclusion of the ventricles and areas outside of the brain. Six standard motion parameters and their temporal derivatives were extracted and included as regressors in the voxelwise GLM procedure used to remove any of their effects on observed BOLD signal. To ensure that only steady state MRI signal was represented in analyses, the initial three volumes of each imaging run were removed. Volumes with excessive inter-TR motion (0.2 mm along any axis) were censored, and participants with greater than 25% censored volumes were excluded (n=15). Three additional subjects were removed due to quality control (i.e., suboptimal alignment of echo planar volumes to anatomical images despite multiple attempts). Since the current study only utilized participants who completed neuroimaging and passed these quality control steps, analyses were performed to examine potential differences between excluded participants and the final study sample.

Functional Connectivity Processing. Seed and target regions of interest (ROI) for the executive control network (ECN) were defined according to extant literature that has consistently

found evidence in support of bilateral dorsolateral prefrontal cortex (DLPFC) and bilateral posterior parietal cortex (PPC) involvement (e.g., Weiland et al., 2014; Fede et al., 2019; Zhu et al., 2017), resulting in 4 ROIs for the ECN, to be used as seed and target regions (Figure 1). Definition of the ROIs for the default mode network (DMN) were similarly informed by extant literature (Figure 2; e.g., Andrews-Hanna et al., 2010; Zhang & Volkow, 2019). Precuneus/posterior cingulate (PCu), medial prefrontal cortex (mPFC), and bilateral lateral parietal cortex (LPC) served as seeds and targets for the DMN, resulting in 4 ROIs.

Given that *a priori* selected ROIs for ECN and DMN networks were consistent with nodes defined in the CONN Toolbox, an open-source software for functional connectivity analysis of fMRI data (Whitfield-Gabrieli and Nieto-Castanon, 2012), CONN toolbox coordinates were used for analysis. To create *a priori* seed regions with uniform cluster sizes, 5mm spheres were drawn around center of mass for each set of coordinates. Regions were cross-compared with the Glasser HCP anatomical atlas in AFNI (Glasser et al., 2016).

To test functional connectivity hypotheses, a single estimate of overall network connectivity for the ECN and for the DMN was created. However, associations among pairs of nodes within each network were also explored for possible group and mediation effects. To this end, ROIs served as both target and seed regions in all possible pair-wise combinations within and between networks (Figure 3).

To accomplish this, the residual GLM beta-weights were averaged within each seed ROI (i.e., across voxels) at each time point (i.e., each echo planar brain volume) to generate a mean wave form for each ROI over time. These average waveforms were then used as an independent variable in two sets of four (i.e., one for each of four ROIs in each of two networks) voxel-wise correlation analyses to predict the observed BOLD signal (i.e., GLM beta-weights) in each voxel

of the brain. Fischer's r to z transformations were performed to convert Pearson correlations (r values) to Z-scores in every voxel of the eight resulting brain maps per individual.

Next, within-ECN, within-DMN, and between-ECN-DMN Z-scores were generated for each participant. For each network (i.e., ECN and DMN), Z-values were averaged across all four target regions of all four within-network seed-target brain maps of each person. These averages represent an estimate of overall within-network connectivity for the ECN and DMN per participant. Specifically, the ECN seed ROI analyses resulted in an average z-value that represents the mean reciprocal synchrony of all four target ECN ROIs (i.e., within-network synchrony). DMN (i.e., PCu, MPFC, and LPC) seed ROI analyses resulted in an average z-value that represents the mean reciprocal synchrony of all four target DMN ROIs (i.e., within-network synchrony). Between-network mean z-scores were voxelwise averages for each participant across the eight target ROIs of all eight inter-network seed-target correlation analyses (i.e., four ECS to DMN and four DMN to ECN). These three Z-scores were used as continuous measures of network connectivity in group level analyses and structural equation models.

Data Analysis

To perform structural equation model (SEM) analysis, MPlus version 8.2 (Muthén & Muthén) was used. Data was checked for normality (i.e., normal distribution), linearity of relationship among variables, homoscedasticity (i.e., equal distribution of residuals), and multicollinearity (i.e., whether predictors are highly correlated with one another). Outlier variables (n=0) were examined for data that was more than 3.29 standard deviations from the mean (Tabachnick & Fidell, 2007). Since product coefficients derived in mediation model estimations seldom meet the normality assumptions, a core assumption in traditional maximum-likelihood estimation methods (Preacher & Hayes, 2008; Shrout & Bolger, 2002), nonnormality

of data was accounted for via bootstrapping techniques (Preacher & Hayes, 2008). Missing data points were estimated via full information maximum likelihood methods. Missing data were quantified and assumed to be missing at random (i.e., missing variables would be related to observed variables but unrelated to the missing values themselves; Schafer & Graham, 2002). To assess model fit, fit indices from each category including absolute (i.e., chi-square test of model fit; standardized root mean square residual, SRMR; root mean square error of approximation, RMSEA), relative fit (Tucker-Lewis Index, TLI), and noncentrality-based indices (the comparative fit index, CFI) were reviewed prior to interpretation of results. Generally, fit indices are interpreted as follows for RMSEA and SRMR: poor fit >.1; mediocre fit .08-.1; acceptable fit .05-.08; close fit .01-.05; exact fit .00. Fit indices for CFI and TLI broadly are interpreted as follows: poor fit <.85; mediocre fit .85-.9; acceptable fit .9-95; close fit .95-.99; exact fit 1 (Brown, 2006). Fit indices were considered based on their appropriateness for the given sample size of this study. For example, chi-square is artificially inflated for large sample sizes but is appropriate for sample sizes of approximately 75-200 (Schermelleh-Engel et al., 2003). Chi square can also be affected when there are large correlations within the model. TLI, SRMR, and RMSEA are relatively independent of sample size (Chen, 2007; Ding et al., 1995; Gerbing & Anderson, 1992). CFI specifically performs better for studies with small sample sizes (Chen, 2007; Hu & Bentler, 1998). Kenny and colleagues (2014) have argued against using RMSEA for models with lower degrees of freedom and sample size as RMSEA can be artificially large.

To confirm factor structure for executive function, confirmatory factor analysis (CFA) was performed with the NIH Toolbox Flanker Inhibitory Control and Attention Test, List Sorting task, Dimensional Change Card Sort task, and Pattern Comparison Processing Speed Test. CFA aims to reproduce observed relationships among a group of variables within a latent variable. It

is an a priori approach, where its factors are selected based on empirical evidence and theory (Brown, 2015). Next, the associations between AUD status and EF and AUD status and RSFC, and RSFC and EF were evaluated. A parallel mediation model where ECN, DMN, and ECN-DMN between network connectivity are entered as simultaneous mediators between AUD and EF was examined. Both direct effects and indirect effects were estimated. Standardized effects and 95% confidence intervals will be examined, and all statistical tests were conducted using a two-tailed $p<.05$ threshold.

Specifically, the estimated SEM model addressed the following hypotheses:

1. To determine whether latent EF is worse in a sample of individuals AUD compared to controls.
2. To determine whether RSFC within the ECN and DMN networks are different in AUD compared to controls. Similarly, to determine whether between-network connectivity between the ECN and DMN is different in AUD compared to controls.
3. To determine whether RSFC within and between the ECN and DMN are associated with latent EF.
4. To determine whether within and between network RSFC for ECN and DMN mediate the association between AUD status and EF.

Power Analysis

The data for the current study was collected as a part of an ongoing study. As such, power analyses were conducted to ensure that the proposed model was appropriate for projected sample size (120). Monte Carlo procedures in MPlus were used to conduct power analyses (Muthén and Muthén, 2002). The Monte Carlo approach to power analysis repeatedly samples the proposed serial mediation model under a given population model with specific parameter

values. Monte Carlo procedures are robust in handling measurement models, nonnormality, and estimating power when there is missing data (Davey & Salva, 2009). The specific parameter values were determined by expected population estimates derived from existing literature (i.e., the theoretical true relationships between variables). This approach to power analysis in SEM yields estimates of power to detect the effects of interest within the model. Effect size parameters used to estimate statistical power for associations among alcohol-related variables, ECN and DMN functional connectivity, and EF were expected to be in the small to medium range (i.e., 0.2 to 0.4) based on available literature (e.g., Galandra et al., 2019; Chanraud et al., 2011; Müller-Oehring et al., 2015), with indirect effects estimated to be in the small range (i.e., .05 to .2). 10,000 successful replications with 120 observations were conducted to determine if the proposed model could detect the upper range of these effect sizes (i.e., .4 for direct effects and .2 for indirect effects) as well as smaller effects (i.e., 0.2 for direct effects and 0.05 for indirect effects). The RMSEA indicated close fit for the model with lower estimate of effect sizes (0.23), suggesting that the model as a whole is appropriate (MacCallum, Browne, & Sugawara, 1996). The power was greater than .80 for all direct and indirect paths of interest in the proposed parallel mediation model. Similarly, power for a separate model for between network ECN-DMN connectivity was greater than .80 for all paths of interest.

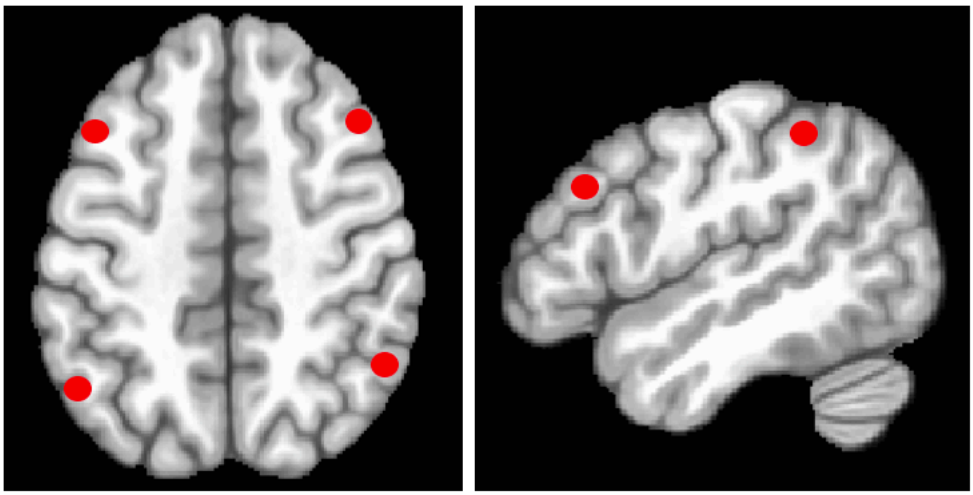
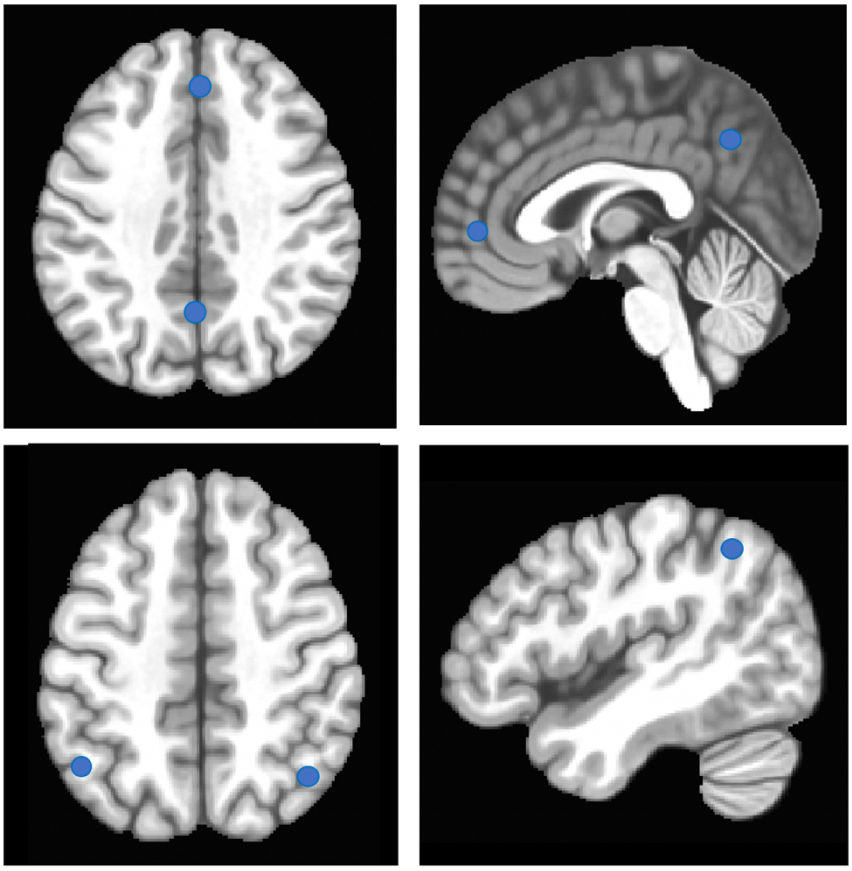


Figure 1. Seeds for Executive Control Network. Axial and sagittal views for left and right dorsolateral prefrontal cortices and lateral parietal lobes



Axial and sagittal views of medial prefrontal cortex and precuneus.

Axial and sagittal views of left and right posterior parietal cortices.

Figure 2. Seeds for the Default Mode Network

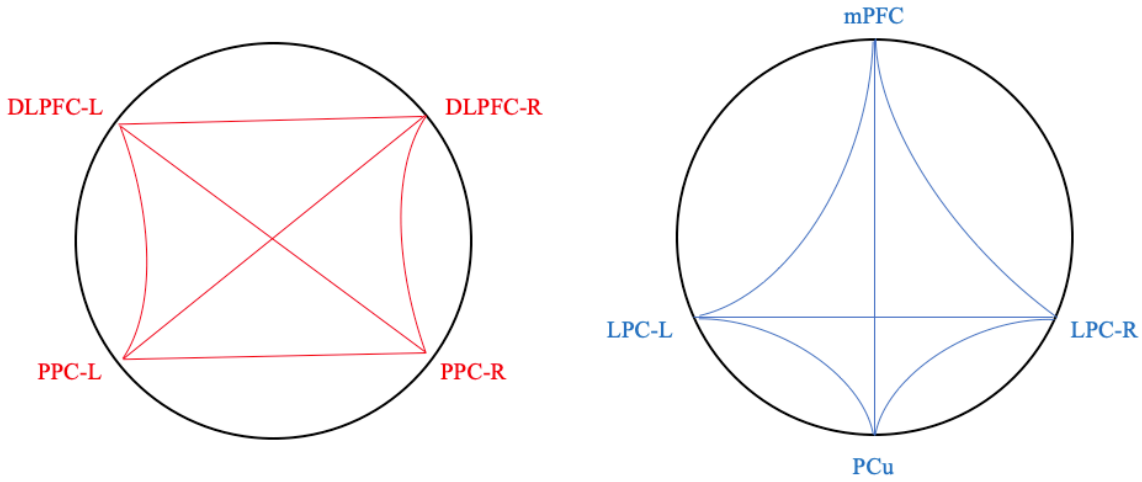


Figure 3. Example schematic of seed to target functional within network connectivity for ECN (red, left) and DMN (blue, right)
Note. PCu = precuneus; mPFC = medial prefrontal cortex; LPC= lateral parietal cortex, left; DLPFC = dorsolateral prefrontal cortex; PPC = posterior parietal cortex

CHAPTER 3

RESULTS

Descriptive Statistics and Preliminary Analyses

Study sample demographic and descriptive characteristics are presented by AUD status in Table 1. There were significant differences between AUD and control groups in education and estimated verbal IQ. AUD participants also drank significantly more alcohol and exhibited more AUD symptoms, as expected by study design. Since Flanker was moderately positively skewed, a square root transformation was performed. Pattern Comparison was reflected, squared, and re-reflected given moderate negative skew. Other variables used for analysis showed acceptable skewness (between -1 and 1) and kurtosis (between -2 and 2). There were no significant outliers that met criteria for removal (Tabachnick & Fidell, 2007). Bivariate zero-order correlations between alcohol variables, network resting state functional connectivity, and cognitive performance are presented in Table 2. There were no significant differences in demographic, alcohol, or cognitive variables between individuals who had completed were excluded during fMRI quality control (e.g., excessive movement, suboptimal alignment) and those who were not.

Latent Executive Function

The latent executive function factor was comprised of NIH Toolbox List Sort for working memory, Card Sort for cognitive flexibility, Flanker test for inhibitory control, and Pattern Comparison for processing speed (Figure 4). Model fit was in the acceptable to close range ($\chi^2(2)=3.158$, p=.206, CFI=.990, RMSEA=.069, SRMR=.026). Since indicators were not cross-loaded, factor loadings may be interpreted as correlations between the indicator and factor.

Factor loadings for Card Sort, Flanker, and Pattern Comparison were greater than .40 and significant at a two-tailed significance of p<.001 (Brown, 2015). Factor loading for List Sort was .203, p=.039. Though parsimonious models are often favored, it is similarly important that models reflect evidence-based theory of constructs (Brown, 2015). Given that literature regarding executive functions and alcohol use similarly support the inclusion of working memory (i.e., List Sort), it was retained in the model.

AUD and EF

The association between AUD status and latent EF was assessed to evaluate the first study hypothesis, that latent EF performance would be worse in AUD group (Table 3). Given that estimated intelligence, as measured by the Shipley Verbal IQ score, was significantly different between groups and significantly correlated with EF measures, it was included in the analysis. Model fit ranged from the acceptable to poor range ($\chi^2(8)=18.160$, p=.020, CFI=.929, RMSEA=.104, SRMR=.058). Parameter estimates are interpreted with caution. AUD was not significantly associated with latent EF (β = -.147, p=.150), though verbal intelligence was significantly positively associated (Shipley; β = .306, p=.002).

Planned follow up analyses to examine associations with specific measures of EF were performed, controlling for estimated verbal intelligence (Table 3). AUD was significantly negatively associated with processing speed (Pattern Comparison; β = -.227, p=.013). There were no significant associations between AUD and working memory (List Sort; β = .033, p=.724), inhibitory control (Flanker; β = -.003, p=.971), or cognitive flexibility (Card Sort; β = -.120, p=.203). Estimated verbal intelligence (Shipley) was significantly positively associated with working memory (List Sort; β = .300, p=.001), inhibitory control (Flanker; β = .329,

p<.001), and cognitive flexibility (Card Sort; β = .220, p=.017), but not with processing speed (Pattern Comparison; β = .144, p=.121).

Given significant association between AUD and processing speed, a series of separate follow up exploratory mediation analyses were performed to examine whether processing speed might mediate the association between AUD and EF (Table 4, Figure 5). Though processing speed was not a significant mediator of working memory (List Sort; β = -.058, p=.067), it significantly mediated the association between AUD and inhibitory control (Flanker; β = -.144, p=.003) and cognitive flexibility (Card Sort; β = -.174, p=.002).

AUD and RSFC

Associations between AUD status and resting state functional connectivity within the DMN and ECN and between the DMN and ECN were evaluated (Table 5). The Shipley Verbal IQ was similarly included in the analysis as it was significantly different between groups and there is evidence of cognitive reserve factors such as IQ associated with connectivity (Stern et al., 2021). The SEM model was just-identified as this analysis did not evaluate a model per se, but rather associations among these variables. Subsequently, model fit indices are not reported. AUD status was significantly negatively associated with ECN connectivity (β = -.256, p=.005), even when controlling for association between AUD and verbal IQ (β = .075, p=.429). There were no significant associations between AUD and DMN (β = .012, p=.904) or ECN – DMN between network connectivity (β = .048, p=.617). Similarly, verbal IQ was not associated with within ECN connectivity (β = .075, p=.429), within DMN connectivity (β = .096, p=.327) or ECN – DMN between network connectivity (β = .066, p=.498). Sex, however, was significantly associated with within ECN connectivity (β = .201, p=.021), DMN connectivity (β = -.225, p=.011), and between ECN-DMN network connectivity (β = .181, p=.047).

Given that AUD was significantly associated with ECN, associations between AUD and node-to-node connectivity within the ECN were further explored through partial correlations (Table 6, Figure 6). When controlling for sex and verbal IQ, AUD was significantly associated with connectivity between the left DLPFC and right posterior parietal cortex (β = -.209, p=.025), right DLPFC and left posterior parietal cortex (r = -.184, p=.050), right DLPFC and right posterior parietal cortex (r = -.200, p=.032), left posterior parietal cortex and left DLPFC (r = -.182, p=.050), and right posterior parietal cortex and left DLPFC (r = -.198, p=.034). Connections between the left DLPFC and right DLPFC (r = -.138, p=.141), left DLPFC and right posterior parietal (r = -.162, p=.084), right DLPFC and left DLPFC (r = -.150, p=.108), left posterior parietal and right DLPFC (r = -.117, p=.212), left and right posterior parietal (r = -.044, p=.642), right posterior parietal and right DLPFC (r = -.162, p=.084), and right and left posterior parietal cortices (r = -.058, p=.535) were not significant.

RSFC and EF

Analyses were also performed to examine associations for within and between ECN and DMN connectivity and both latent EF and individual cognitive measures (Table 7). The model evaluating RSFC and latent EF showed acceptable to close fit ($\chi^2(22)=20.468$, p=.108, CFI=.950, RMSEA=.057, SRMR=.065). Controlling for verbal IQ and sex, EF was not significantly associated with ECN (β = .316, p=.055), DMN (β = -.026, p=.877) or between ECN-DMN (β = -.135, p=.394) connectivity. Model fit for individual cognitive measures was just identified. Though zero-order correlations showed significant associations between the ECN and Flanker test (r= .182, p= .045), this was not observed when verbal IQ was accounted for in the SEM model (β = .111, p=.216). There were also no significant associations between ECN and working memory (List Sort; β = .138, p=.124), cognitive flexibility (Card Sort; β = .004, p=.961), or

processing speed (Pattern Comparison; β = .131, p=.150). There were no significant associations between DMN and working memory (List Sort; β = -.086, p=.331), inhibitory control (Flanker; β = -.002, p=.984), cognitive flexibility (Card Sort; β = .142, p=.110), or processing speed (Pattern Comparison; β = .148, p=.094). Similarly, there were no significant associations between ECN-DMN between network connectivity and working memory (List Sort; β = -.108, p=.232), inhibitory control (Flanker; β = .011, p=.907), cognitive flexibility (Card Sort; β = .014, p=.874), or processing speed (Pattern Comparison; β = -.054, p=.555). Verbal IQ (Shipley), however, was significantly associated with working memory (List Sort; β = .279, p=.001), inhibitory control (Flanker; β = .313, p<.001), cognitive flexibility (Card Sort; β = .246, p=.005), and processing speed (Pattern Comparison; β = .190, p=.031).

Mediation Analysis

Hypotheses that ECN, DMN, and between network connectivity would mediate the association between AUD and EF were tested using a SEM parallel mediation model (Table 8, Figure 7). Model fit was in the close to acceptable range ($\chi^2(22)=30.468$, p=.108, CFI=.950, RMSEA=.057, SRMR=.065). Results of direct effects were consistent with previously described path models, where AUD remained significantly associated with ECN within network connectivity (β = -.266, p=.001) but not with DMN within network connectivity (β = -.039, p=.663) or ECN – DMN between network connectivity (β = .039, p=.667). Contrary to hypotheses, there were no significant associations among ECN and EF (β = .314, p=.066), DMN and EF (β = -.029, p=.868), or ECN – DMN between network connectivity and EF (β = -.134, p=.395). Consistent with path models, sex was significantly associated with within ECN connectivity (β = .206, p=.015), DMN connectivity (β = -.197, p=.026), and between ECN-DMN network connectivity (β = .186, p=.037). There was no significant mediating effect between

AUD status and EF via the ECN (β = -.082, p=.118), the DMN (β = .002, p=.810) or ECN-DMN between network connectivity (β = -.005, p=.700)

A follow-up moderation analyses was conducted to explore whether sex moderated the association between AUD and between and within ECN and DMN connectivity. The moderation analysis did not yield a significant result (Table 9).

Table 1. Participant Characteristics

	Total Sample N=123	AUD M (SD) N=63	CTRL M(SD) N=60	t	df	p	Effect Size (Cohen's d)
Age	32.2 (9.8)	32.8 (10.4)	31.4 (9.2)	.81	121	.422	.13
Female N (%)	68 (55.3%)	35 (55.6%)	33 (55%)	-.06	121	.951	-.01
Education	15.4 (2.8)	14.8 (2.7)	16.1 (2.6)	-2.86	121	.005**	-.52
Household Income		5.4 (2.7)	5.5 (2.5)				
Clinical Characteristics							
Symptom Count		6.5 (2.5)	0 (0)	20.94	62	<.001**	3.69
Drinks per week	15.2 (15.8)	25.0 (16.6)	4.6 (2.8)	9.67	65.84	<.001**	1.70
Male		34.5 (16.8)	6.1 (3.3)				
Female		17.5 (12.0)	3.3 (1.5)				
AUD Severity				27.58	61	<.001**	4.91
0 N (%)	60 (48.8%)	0	60				
1 N (%)	7 (5.7%)	7 (11.1%)	0				
2 N (%)	22 (17.9%)	22 (24.9%)	0				
3 N (%)	33 (26.8%)	33 (52.4%)	0				
Smoker (%)	38 (30.9%)	25 (39.7%)	13 (21.7%)				
Shipley IQ	105.4 (13.5)	100.9 (13.9)	110.4 (11.1)	-4.10	114.31	<.001**	-.75
List Sort	101.2 (12.5)	100.4 (12.8)	101.9 (12.2)	-.67	120	.507	-.12
Flanker Test	90.1(14.5)	88.1 (13.4)	92.2 (15.3)	-1.59	120	.115	-.29
Card Sort	99.4 (18.5)	96.3 (17.3)	102.7 (19.2)	-1.94	120	.055	-.35
Processing Speed	107.6 (23.0)	101.6 (23.8)	114.1 (20.4)	-3.11	120	.002**	-.56
DMN Connectivity	.46 (.14)	.45 (.13)	.47 (.15)	-.60	121	.552	-.11
ECN Connectivity	.30 (.11)	.27 (.09)	.33 (.12)	-2.92	108.12	.004**	-.53
ECN-DMN Connectivity	.09 (.09)	.09 (.08)	.09 (.11)	.088	121	.930	.02

Note. Shipley IQ, List Sort, Flanker, Card Sort, and Processing Speed scores are age-corrected standard scores (M=100, SD=15)

Table 2. Zero order correlations

	AUD status	AUD severity	AUD symptoms	Drinks per week	Verbal IQ	List Sort	Flanker Test	Card Sort	PS	ECN-DMN	ECN
Severity	-.927**										
Symptoms	-.881**	.968**									
Drinks	-.650**	.676**	.667**								
Verbal IQ	.352**	-.361**	-.383**	-.283**							
List Sort	.061	-.047	-.053	-.152	.288**						
Flanker	.144	-.169	-.174	-.062	.329**	.143					
Card Sort	.174	-.209*	-.229*	-.047	.262**	.118	.589**				
PS	.273**	-.281**	-.277**	-.163	.215*	.242**	.501**	.611**			
ECN-DMN	-.008	-.002	-.011	.047	.045	-.050	.080	-.003	-.035		
ECN	.258**	-.261**	-.239**	-.140	.160	.168	.182*	.047	.154	.255**	
DMN	.054	-.132	-.126	-.116	.097	-.049	.033	.147	.128	-.130	0.005

Note. AUD= alcohol use disorder; symptoms= number of AUD symptoms; drinks= number of standard drinks per week; verbal IQ= Shipley IQ standard score; List Sort= NIH Toolbox List Sorting task; Flanker= NIH Toolbox Flanker Inhibitory Control and Attention Test; Card Sort= NIH Toolbox Dimensional Change Card Sort task; PS= NIH Toolbox Pattern Comparison Processing Speed Test; ECN-DMN= between network connectivity; ECN= executive control network; DMN= default mode network.
** p<.01; *p<.05

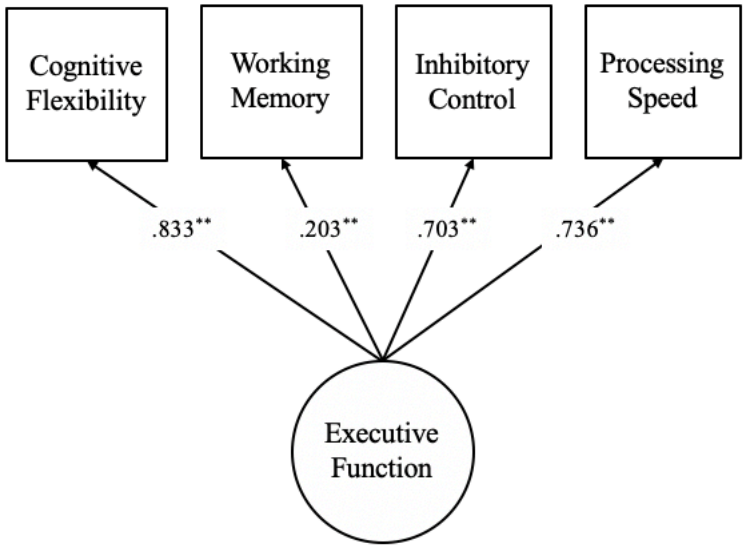


Figure 4. Measurement model for executive function

Table 3. Associations between AUD and latent EF and follow-up analysis with individual EF measures

				95% C.I.	
	B(S.E.)	β	*p*	*Lower*	*Upper*
AUD → EF	-4.554 (3.200)	-.147	.150	-.347	.053
Shipley → EF	.352 (.119)	.306	.002**	.111	.500
AUD → List Sort	.840 (2.378)	.033	.724	-.152	.218
AUD → Flanker	-.005 (.141)	-.003	.971	-.186	.179
AUD → Card Sort	-4.464 (3.531)	-.120	.203	-.304	.065
AUD → PS	-.921 (.381)	-.227	.013*	-.407	-.047
Shipley → List Sort	.281 (.088)	.300	.001**	.122	.477
Shipley → Flanker	.018 (.005)	.329	<.001**	.156	.503
Shipley → Card Sort	.305 (.131)	.220	.017*	.039	.401
Shipley → PS	.022 (.014)	.144	.121	-.038	.327

Note. AUD= alcohol use disorder status; EF= latent executive function; Shipley= Shipley Verbal IQ standard score; List Sort= NIH Toolbox List Sorting task; Flanker= NIH Toolbox Flanker Inhibitory Control and Attention Test; Card Sort= NIH Toolbox Dimensional Change Card Sort task; PS= NIH Toolbox Pattern Comparison Processing Speed Test.
** p<.01; *p<.05

Table 4. Follow-up separate mediation analyses with PS as a mediator

				95% C.I.	
	B(S.E.)	β	*p*	*Lower*	*Upper*
AUD → PS	-13.475 (4.118)	-.290	.001**	-.456	-.124
AUD → List Sort	2.066 (2.398)	.083	.388	-.105	.270
PS → List Sort	.108 (.049)	.201	.027*	.022	.379
Shipley → List Sort	.256 (.087)	.276	.003**	.097	.455
AUD → PS → List Sort	-1.453 (.801)	-.058	.067	-.120	.004
AUD → PS	-13.474 (4.118)	-.290	.001**	-.456	-.124
AUD → Flanker	3.298 (2.420)	.115	.173	-.050	.281
PS → Flanker	.306 (.050)	.498	<.001**	.355	.641
Shipley → Flanker	.283 (.088)	.266	.001**	.105	.428
AUD → PS → Flanker	-4.125 (.1.429)	-.144	.003**	-.240	-.049
AUD → PS	-13.473 (4.118)	-.290	.001**	-.456	-.124
AUD → Card Sort	.970 (2.933)	.026	.741	-.129	.182
PS → Card Sort	.478 (.060)	.602	<.001**	.478	.725
Shipley → Card Sort	.198 (.107)	.144	.066	-.009	.297
AUD → PS → Card Sort	-4.125 (.1.429)	-.174	.002**	-.283	-.066

Note. AUD= alcohol use disorder status; Shipley= Shipley Verbal IQ standard score; List Sort= NIH Toolbox List Sorting task; Flanker= NIH Toolbox Flanker Inhibitory Control and Attention Test; Card Sort= NIH Toolbox Dimensional Change Card Sort task; PS= NIH Toolbox Pattern Comparison Processing Speed Test.
** p<.01; *p<.05

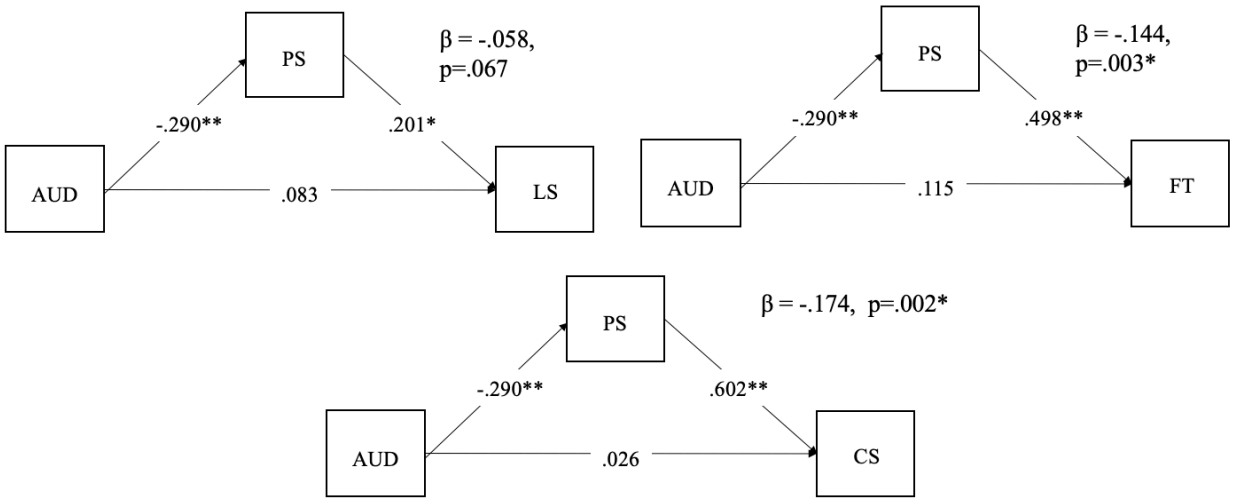


Figure 5. Standardized estimates for follow-up mediation analyses with processing speed as a mediator between AUD and EF measures.

Note. AUD = Alcohol Use Disorder status; PS = NIH Toolbox Pattern Comparison Processing Speed Test; LS= NIH Toolbox List Sorting task; FT = NIH Toolbox Flanker Inhibitory Control and Attention Test; CS = NIH Toolbox Dimensional Change Card Sort task.

*p<.05, **p<.001

Table 5. Associations between AUD and RSFC

				95% C.I.	
	B(S.E.)	β	*p*	*Lower*	*Upper*
AUD → DMN	.003 (.027)	.012	.904	-.176	.199
AUD → ECN	-.055 (.020)	-.256	.005**	-.432	-.079
AUD → ECN – DMN	.009 (.018)	.048	.617	-.141	.238
Sex → DMN	-.063 (.025)	-.225	.011*	-.400	-.051
Sex → ECN	.044 (.019)	.201	.021*	.030	.371
Sex → ECN – DMN	.035 (.018)	.181	.047*	.003	.359
Shipley → DMN	.002 (.001)	.096	.327	-.045	.335
Shipley → ECN	.000 (.001)	.075	.429	-.155	.216
Shipley → ECN – DMN	.000 (.786)	.066	.498	-.167	.220

Note. AUD= alcohol use disorder status; Shipley= Shipley Verbal IQ standard score; ECN= executive control network; DMN= default mode network; ECN-DMN= between network connectivity.
** p<.01; *p<.05

Table 6. Partial correlations between AUD, ECN node-to-node connectivity and EF measures controlling for sex and IQ

	lpfc. rpfc	lpfc. lppc	lpfc. rppc	rpfc. lpfc	rpfc. lppc	rpfc. rppc	lppc. lpfc	lppc. rpfc	lppc. rppc	rppc. lpfc	rppc. rpfc	rppc. lppc
CS	.131	-.065	.168	.122	.014	-.032	-.097	-.006	-.039	.176	.010	.042
LS	-.043	.172	.063	.008	.125	.066	.217*	.171	.113	.066	.023	.019
FT	.120	-.084	.112	.092	.06	-.045	.028	.168	.197*	.137	.014	.201*
PS	.115	.080	.135	.124	.073	-.033	.137	.102	.089	.170	.010	.118
AUD	-.138	-.162	-.209*	-.150	-.184*	-.200*	-.182*	-.117	-.044	-.198*	-.162	-.058

Note. CS = NIH Toolbox Dimensional Change Card Sort task; LS= NIH Toolbox List Sorting task; FT = NIH Toolbox Flanker Inhibitory Control and Attention Test; PS = NIH Toolbox Pattern Comparison Processing Speed Test; AUD = Alcohol Use Disorder status; lpfc= left dorsal prefrontal cortex; rpfc= right dorsal prefrontal cortex; lppc= left posterior parietal cortex; rppc= right posterior parietal cortex.
** p<.01; *p<.05

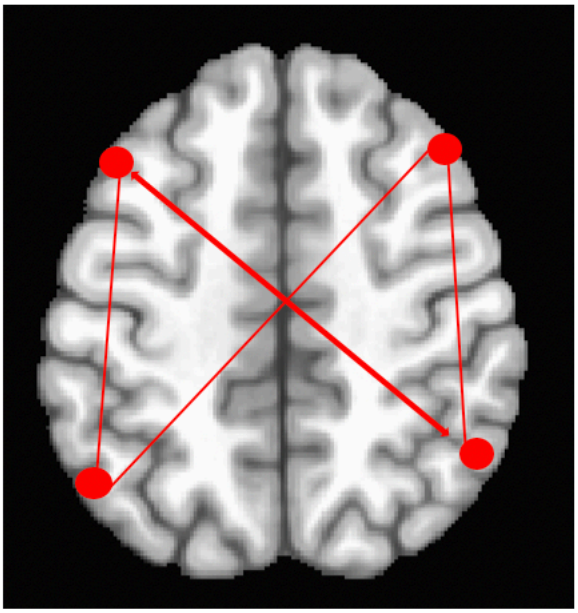


Figure 6. Seed to target associations within the ECN significantly associated with AUD status

Table 7. Associations among RSFC networks and individual EF measures

				95% C.I.	
	B(S.E.)	β	*p*	*Lower*	*Upper*
ECN → EF	15.412 (8.431)	.316	.055	-.007	.640
DMN → EF	-.995 (6.448)	-.026	.877	-.357	.305
ECN – DMM → EF	-7.466 (9.123)	-.135	.394	-.446	.176
Shipley → EF	.259 (.079)	.659	.001**	.287	1.031
Sex → ECN	.046 (.020)	.210	.017*	.037	.382
Sex → DMN	-.055 (.025)	-.197	.026*	-.370	-.023
Sex → ECN – DMN	.035 (.017)	.185	.037*	.011	.359
ECN → List Sort	16.063 (10.538)	.138	.124	-.038	.315
ECN → Flanker	.772 (.628)	.111	.216	-.065	.287
ECN → Card Sort	.764 (15.822)	.004	.961	-.176	.185
ECN → PS	2.450 (1.716)	.131	.150	-.048	.310
DMN → List Sort	-7.769 (8.018)	-.086	.331	-.259	.087
DMN → Flanker	-.009 (.478)	-.002	.984	-.174	.171
DMN → Card Sort	19.055 (12.038)	.142	.110	-.032	.316
DMN → PS	2.163 (1.306)	.148	.094	-.025	.322
ECN – DMN → List Sort	-14.289 (12.014)	-.108	.232	-.284	.069
ECN – DMN → Flanker	.084 (.716)	.011	.907	-.166	.187
ECN – DMN → Card Sort	2.855 (18.037)	.014	.874	-.165	.194
ECN – DMN → PS	-1.154 (1.956)	-.054	.555	-.233	.125
Shipley → List Sort	.262 (.083)	.279	.001**	.112	.447
Shipley → Flanker	.018 (.005)	.313	<.001**	.148	.477
Shipley → Card Sort	.341 (.125)	.246	.005**	.075	.417
Shipley → PS	.029 (.014)	.190	.031*	.017	.362

Note: ECN= executive control network; DMN= default mode network; ECN-DMN= between network connectivity; Shipley= Shipley Verbal IQ standard score; List Sort= NIH Toolbox List Sorting task; Flanker= NIH Toolbox Flanker Inhibitory Control and Attention Test; Card Sort= NIH Toolbox Dimensional Change Card Sort task; PS= NIH Toolbox Pattern Comparison Processing Speed Test.
** p<.01; *p<.05

Table 8. Parallel mediation model

				95% C.I.	
	B(S.E.)	β	*p*	*Lower*	*Upper*
AUD → DMN	-.011 (.025)	-.039	.663	-.216	.137
AUD → ECN	-.058 (.019)	-.266	.001**	-.430	-.102
AUD → ECN-DMN	.007 (.017)	.039	.667	-.138	.216
AUD → EF	.128 (2.125)	.012	.952	-.389	.390
Sex → DMN	-.055 (.025)	-.197	.026*	-.317	-.024
Sex → ECN	.045 (.019)	.206	.015*	.040	.373
Sex → ECN-DMN	.036 (.017)	.186	.037*	.011	.360
DMN → EF	-1.129 (6.837)	-.029	.868	-.377	.280
ECN → EF	15.608 (9.038)	.314	.066	-.027	.642
ECN-DMN → EF	-7.562 (9.285)	-.134	.395	-.443	.174
Shipley → EF	.262 (.090)	.652	.002**	.218	1.067
AUD → DMN→ EF	.012 (.080)	.002	.810	-.013	.016
AUD → ECN → EF	-.901 (.599)	-.082	.118	-.187	.020
AUD → ECN-DMN→ EF	-.056 (.148)	-.005	.700	-.032	.021

Note: AUD= alcohol use disorder status; ECN= executive control network; DMN= default mode network; ECN-DMN= between network connectivity; EF= latent executive function; Shipley= Shipley Verbal IQ standard score.
** p<.01; *p<.05

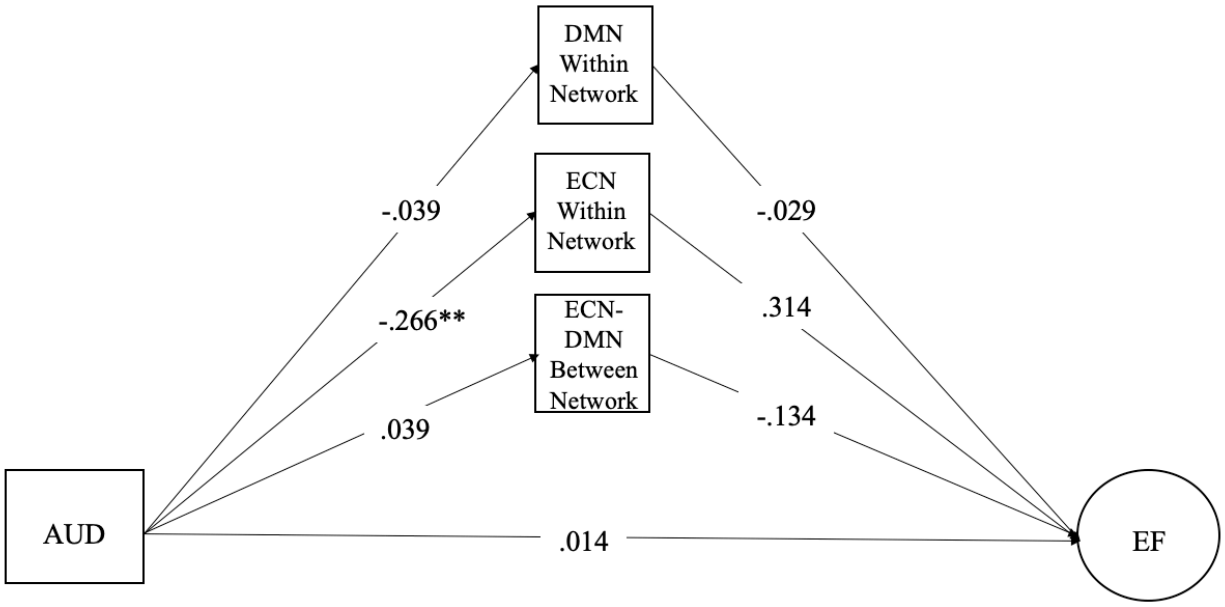


Figure 7. Standardized estimates for parallel mediation model.
Note. AUD = Alcohol Use Disorder status; EF = executive function
*p<.05, **p<.001

Table 9. Exploratory AUD moderation analysis

				95% C.I.	
	B(S.E.)	β	*p*	*Lower*	*Upper*
AUD → ECN	-.052 (.025)	-.239	.035*	-.461	-.017
AUD → DMN	-.015 (.033)	-.053	.656	-.286	.180
AUD → ECN-DMN	-.011 (.023)	-.058	.625	-.292	.176
Sex → ECN	.044 (.027)	.202	.097	-.036	.439
Sex → DMN	-.049 (.035)	-.177	.160	-.423	.070
Sex → ECN-DMN	.015 (.024)	.078	.537	-.170	.327
AUD*Sex→ ECN	-.009 (.037)	-.035	.810	-.318	.248
AUD* Sex → DMN	-.001 (.050)	-.004	.979	-.297	.289
AUD* Sex→ ECN-DMN	.029 (.034)	.126	.399	-.167	.419

Note: AUD= alcohol use disorder status; ECN= executive control network; DMN= default mode network; ECN-DMN= between network connectivity.
** p<.01; *p<.05

CHAPTER 4

DISCUSSION

The current study examined associations among AUD status, resting state functional connectivity within and between the ECN and DMN, and latent EF in a sample comprised of 63 young adult men and women who met criteria for AUD and 60 matched control participants. The overall aim was to determine whether these RSFC dynamics mediate the predicted association between AUD and latent, theory-driven EF. Specifically, we first aimed to determine whether there were differences in latent EF among a sample who met criteria for AUD compared to a control group. We hypothesized that latent EF performance would be worse in the AUD group. Second, we examined the possibility of group differences in within and between network connectivity in the ECN and DMN. We expected the AUD group to exhibit weaker within and between network connectivity. Third, we examined whether latent EF was associated with RSFC. We expected there to be significant associations where increased connectivity was associated with better performance. Our final aim was to determine whether within and between network RSFC was mechanistically important in the association between AUD status and EF. We hypothesized that RSFC would mediate the association between AUD and EF.

Hypotheses were generally not supported. Specifically, EF did not differ significantly between groups, within and between ECN and DMN connectivity were not significantly associated with latent EF and there were no significant indirect effects via within or between ECN and DMN connectivity. However, part of our second hypothesis was supported in that ECN was significantly associated with AUD status such that there was reduced within ECN functional connectivity in the group of individuals who met criteria for AUD compared to the matched

control group. Two noteworthy incidental findings also emerged. First, processing speed was significantly associated with AUD status, where individuals who met criteria for AUD performed slower than matched controls. Second, follow-up analyses demonstrated that within and between connectivity of the ECN and DMN differed based on sex. Taken together, though hypotheses for only one study aim was supported, consideration of incidental findings and study characteristics may serve to clarify lack of support for study hypotheses derived from prior literature. The implications of both significant and null findings are discussed below.

EF and AUD

The first aim of the current study was to investigate differences in latent EF between groups with AUD and matched controls. Overall, there was no effect of AUD status on latent EF after controlling for differences in estimated intelligence, as measured by verbal IQ. Though this was controlled statistically, it is important to note that this represents a sampling bias. Given that deficits in EF have been described in studies of alcohol use (e.g., Tapert et al., 2004; Peeters et al., 2014; Rupp et al., 2016; Martelli et al., 2017; Houston et al., 2014), this finding was somewhat surprising. Previous effect size estimates for associations between alcohol use and EF fell within the small to medium range (Galandra et al., 2019; Chanraud et al., 2011; Müller-Oehring et al., 2015), which our sample was powered to detect if effects were present.

The lack of EF findings for the current study diverged from extant literature and the corresponding study hypotheses, but consideration of several points may help to clarify the absence of differences in EF in the present study. First, the model for the current study rests on the notion that prior published reports of lower EF performance is a consequence of AUD. It is possible that lower EF function can also precede AUD, serving as a risk factor (e.g., poor decision making). Prior literature has shown both to be likely, where the association between

AUD and EF is bidirectional (Tapert et al., 2004; Peeters et al., 2014). As such, similar demonstrated EF performances between the groups may be related to the possibility that the control group exhibited the same putative EF risk considering that they also consume alcohol, albeit at lower levels. Comparison to a non-drinking control group may have addressed this possibility. However, it is important to note that mean EF test performance scores all fell within the average range and all but the Flanker test yielded mean scores very close to population means. Thus, it is even less convincing that low prior EF is associated with alcohol consumption in our sample. Interestingly, inspection of average cognitive scores shows that performance on a task of inhibitory control (Flanker) in the AUD group diverges almost one standard deviation, on average, from verbal intelligence which is often used as a proxy for baseline, premorbid intelligence. However, both groups performed below expectation only on this test. Though a small signal, this may still yet signify that specific aspects of EF (i.e., inhibitory control) may be important as a potential risk factor and that specific characteristics of our study sample buffered against EF effects related to alcohol consumption.

Another possible explanation for lack of difference in EF performance is that the participants who met criteria for alcohol use disorder in the current study may not have experienced chronic and significant exposure to a degree that would result in neurological changes that precipitate cognitive changes. While time since first drink for the control group was not collected, in the AUD group, average time since onset of problematic alcohol use was 9.7 years. According to data that examined per capita consumption of alcohol using beverage sales data, Americans (both male and females) consume 1.34 gallons of ethanol per year, which translates to approximately 9.5 drinks per week (Slater & Alpert, 2021). When adjusted to consider only adults over the age of 18, this equates to approximately 13.6 drinks per week. Compared to this estimate, the AUD

group consumes approximately two times this amount (25.04 drinks) while our control group consumes considerably less (4.55 drinks). Though the level reported by our AUD group clearly exceeds these estimated norms, NIAAA guidelines, and reflect clinical significance as indicated by AUD diagnosis, the lack of EF findings in the current study raise questions regarding if and when alcohol imparts changes to cognitive functions.

While indirect neurotoxic effects of alcohol on the brain via malnutrition (i.e., thiamine deficiency), liver disease, metabolite toxicity, or electrolyte imbalance (Neiman, 1998) have been well described, alcohol also has direct neurotoxic effects for which clinical significance related to cognitive changes beyond acute intoxication are less clear. Direct effects are thought to be mediated through NMDA receptors of glutamatergic neurons, where alcohol inhibits these receptors, in turn spurring upregulation of receptors with repeated, chronic alcohol exposure. The upregulated receptors are uninhibited in the absence of acute alcohol intake, which results in excessive stimulation of NMDA receptors, and subsequent influx of calcium which has cytotoxic effects (Verbaten, 2009). The frontal lobes and subcortical structures (e.g., hippocampus), where glutamatergic neurons are densely populated, are particularly vulnerable to these cytotoxic effects (Verbaten, 2009). Despite extensive characterization of mechanisms that underlie alcohol's effects on peripheral systems (i.e., liver, heart, lungs, gut), even animal studies have not been able to definitely characterize mechanisms by which neurotoxic effects of alcohol affect neural functioning. More recent research has contested the notion that alcohol alone is neurotoxic to a degree that would severely disrupt neurological functioning. Rather, observed neurological disruption has been proposed to be a function of indirect effects via nutritional deficiency, namely thiamine (Vedder et al., 2015; Zahr et al., 2016).

Taken together, though 9.7 years is a considerable amount of time and the AUD group clearly exceeds average population and NIAAA recommended alcohol guidelines, it is possible that duration and consumption levels alone may not impart substantial neural effects that would result in cognitive changes in the absence of nutritional deficiency. However, differences found in the ECN in our sample suggest that it is still plausible that individuals in the current study sample have experienced some degree of neural changes related to alcohol use. Conversely, this may reflect development and premorbid risk for onset of AUD. Also important to consider is, that if the onset of direct neurotoxic effects begins at low drinking intensity thresholds, these effects may already be expressed to some degree in our control group, which excluded non-drinkers. This could also have reduced the expected EF differences between our groups.

Another compelling and perhaps more likely explanation for lack of EF differences between AUD and controls in the current study sample is the possible role of cognitive and brain reserve. The importance of reserve has been well described in aging literature (Brickman et al., 2011). Reserve is typically differentiated into brain reserve, which refers to the brain's capacity to withstand more substantial pathological damage, and cognitive reserve, which refers to one's ability to maintain a similar level of functioning despite more substantial pathological damage. This resilience is thought to be due to factors such as premorbid intelligence and education, occupational attainment, and social engagement (Richards & Sacker, 2003; Stern 2009).

In the current study sample, there were significant differences between verbal intelligence and education between AUD and control groups, but both were well-educated (AUD M = 14.76 years, SD = 2.72; control group M = 16.14 years, SD = 2.62) and of average estimated verbal intelligence (AUD M = 100.90; control group M = 110.36). Unsurprisingly verbal intelligence was significantly associated with higher-order EF measures. Despite the fact that education and

verbal intelligence are only proxies for reserve, they still likely represent a mechanism that may have buffered the effects that alcohol might have on higher-order cognitive functions. Future investigation of the role of cognitive reserve as it pertains to alcohol use might provide valuable knowledge regarding vulnerable populations and how treatment targets might vary.

Planned follow-up analyses were conducted to investigate whether differences in specific aspects of EF were present, as there is consensus that there is unity and diversity in the EF construct (Snyder et al., 2015). Cognitive flexibility as measured by the Cart Sort task and, possibly, inhibitory control as measured by the Flanker task appeared to exhibit a small effect between the AUD and control group and, though they did not necessarily reach significance, might be worthy of further exploration in a larger sample. Still, these effects did not persist when analyses controlled for baseline intelligence. Thus, this may simply reflect shared variance attributable to education and estimated premorbid functioning.

Another possible explanation for absence of EF differences is that the expected AUD effect on EF was masked by processing speed. Interestingly, AUD status was associated with slower processing speed, even when accounting for effects of verbal intelligence. Further, follow-up exploratory mediation analyses indicated that processing speed was a significant mediator for associations between AUD and inhibitory control and AUD and cognitive flexibility. Within neuropsychology literature, processing speed is consistently found to be sensitive to brain dysfunction (Larrabee et al., 2008). Processing speed, particularly psychomotor processing speed, has been found to decline with normal aging and is an important substrate that underlies age-related decline in other cognitive functions, including EF (Hoyer et al., 2004; Liebel et al., 2017; Salthouse, 2000). This effect is thought to be mediated through frontal white matter integrity (Bartzokis et al., 2010; Schiavone et al., 2009), and is apparent in a number of

neurological disorders including multiple sclerosis, traumatic brain injury, cerebrovascular disease, and other dementias (Rao, 1996).

Compared to higher order aspects of EF, processing speed is a relatively foundational cognitive domain. Though measurement of any cognitive domains is not necessarily "pure," where even simple processing speed tasks involve abilities such as language, visual discrimination and motor performance, it requires considerably less integration of complex cognitive skills than aspects of EF such as cognitive flexibility, inhibitory control, or working memory. In a research study sample with a high level of reserve, processing speed may be a sensitive marker for frontal dysfunction given that pathways for compensatory processes for speed may be limited compared to those possible for higher-order functions. In other words, the complex pathways that support EF mean that weaknesses in one area may be compensated for by another. Further, using processing speed as a potentially sensitive marker for dysfunction in AUD is logical given its sensitivity not only to white matter disruption, but to frontal lobe functioning. This is due to the role of the frontal lobe in reaction time, error correction, and response adjustment (Alexander et al., 2007; Chee et al., 2009; Modirrousta and Fellows, 2008, Righart et al., 2013). Taken together, processing speed seems to be an important domain that may serve as a screening target to detect subtle changes and risk for further brain changes in high-functioning individuals with AUD.

Functional Connectivity and AUD

The presence of intrinsic brain networks at rest has been well characterized, providing evidence that supports the notion that brain regions are synchronized even in the absence of tasks (Biswal et al., 1995; Greicius et al, 2003; Fox et al., 2005; Raichle 2011). Studies have demonstrated convergence of functional connectivity with structural connectivity and there is

general consensus that resting state networks are valid and reliable substrates of cognition (Seeley et al., 2007; Greicius et al., 2009; van den Heuvel & Sporns, 2011). The ECN and DMN were the focus of this investigation. The ECN is consistently described as a key substrate in facilitating behavioral responses and representing and maintain goals during motivated behavior, which are among core components of EF (Badre, 2008; Miller & Cohen, 2001). Connections between the DLPFC and parietal cortices have been shown to be dominant components of the ECN, representing its "structural core" (Shen et al., 2020). The DMN, which is comprised of medial prefrontal cortex and precuneus, supports self-directed and self-referential cognitive processes important for regulatory functions (Murray et al., 2012; Northoff et al, 2006; Greicius et al., 2003).

Consistent with the published literature on functional connectivity at rest, node-to-node correlations within the ECN in the present study were generally significantly correlated in our sample. Left to right DLPFC connectivity appeared to be less synchronous with other node-to-node connectivity within the ECN, though separate correlation analyses for AUD and control participants demonstrated that this appeared to be driven by AUD participants. Overall, effect sizes were in the medium to large range suggesting good network coherence, particularly in the control sample. Similarly, node-to-node correlations within the DMN were significant, with effect sizes in the medium to large range. Unlike the ECN, differences in connectivity strength were not apparent between the AUD and control group. There was more variability in ECN-DMN between-network connectivity, where effect sizes ranged from small to large. Similar to the ECN, this appeared to be driven by the AUD group. Coherence between the left posterior parietal cortex and DMN nodes did not appear to be significantly associated with other node-to-node connections broadly, and particularly for node-to-node coherence that involved prefrontal

regions. Still, node-to-node correlations were generally significant overall and consistent with expected levels for resting state functioning.

The second aim of the present study was to determine whether there were differences between AUD and control groups in within and between network connectivity in the ECN and DMN. Findings demonstrated that ECN within network connectivity was significantly associated with AUD status. Specifically, the AUD group exhibited decreased connectivity within the ECN when compared to matched control participants. This effect remained significant even when controlling for variance associated with verbal intelligence and sex. These findings are broadly consistent with extant literature and models for AUD, as altered ECN function is thought to be central in AUD (Zilverstrand, 2018). Dual-process theories of addiction, namely the iRISA model, have emphasized the role of the prefrontal cortex in onset and maintenance of addiction (Goldstein & Volkow, 2011; 2016). The prefrontal cortex is a critical hub of the ECN that directs attention, inhibits limbic reward-driven behavior, and supports higher-order cognitive and motivational processes. This has been supported by meta-analysis of task-based studies of ECN response to alcohol-related cues (Myrick et al., 2004) as well as resting-state studies (Müller-Oehring et al., 2015).

While it is accepted that aberrant connectivity within the ECN is linked to AUD and heavy drinking, the literature remains mixed with regard to directionality and implications of such aberrant connectivity. Several studies have found decreased ECN connectivity to be associated with alcohol-related variables such as failed control of consumption and AUD severity in active drinkers as well as groups differences in abstinent alcoholic individuals (Weiland et al., 2014; Camchong et al., 2013; Müller-Oehring et al., 2015). Others, however, found there to be increased within ECN connectivity in individuals with AUD compared to controls (Zhu et al.,

2017). Studies finding increased functional connectivity within the ECN attributed findings to reflect compensatory mechanisms, purporting that the brain of heavy drinkers require additional resources given structural disturbances to gray and white matter related to long-term effects of alcohol (Jansen et al., 2014; Momenan et al., 2012; Durkee et al., 2013). Decreases in functional connectivity within the ECN in AUD are broadly conceptualized to reflect suboptimal connectivity related to disruption of prefrontal regions sensitivity and preferential attention to alcohol-related cues (Volkow et al., 2004). Our findings support the latter notion, and support existing theories that dysfunction in key ECN nodes increase risk of maintenance of alcohol misuse. Though the current study modeled AUD to predict RSFC, it is important to emphasize that the majority of studies, the present included, examine RSFC cross-sectionally. Thus, while there is converging evidence of aberrant connectivity, it is certainly plausible that disruptions in functional connectivity serves as a risk factor that precedes AUD. Conclusions regarding causality cannot be drawn in the absence of longitudinal study design.

Planned follow up correlation analyses further elucidated specific node-to-node (i.e., seed to target) connectivity among regions of interest within the ECN. In a sample of individuals who met criteria for AUD, there was decreased connectivity between the left DLPFC and right posterior parietal cortex, right DLPFC and left posterior parietal cortex, right DLPFC and right posterior parietal cortex, left posterior parietal cortex and left DLPFC, right posterior parietal cortex to left DLPFC. Though these five comparisons were significant, seven were not. Broadly, it appeared that connections between DLPFC to and from posterior parietal regions were significantly less synchronized among the AUD group, both inter- and intrahemispherically. However, connectivity between left and right DLPFC and left and right posterior parietal regions did not appear to be significantly related to AUD status. Though consideration of average

network connectivity is a well-accepted and valid method of RSFC analysis (Weiland et al., 2014), these findings suggest that representation of networks may benefit from more careful consideration of the nature in which regions within each network interact such that fronto-parietal connections may be meaningful, while commissural communication are less relevant to AUD.

In contrast to significant ECN findings, there were no significant differences in DMN within network connectivity or ECN-DMN between network connectivity. These findings diverge from much of the literature on AUD. Similar to ECN connectivity, several studies found increases in within network connectivity for the DMN (e.g., Müller-Oehring et al., 2015) while others found AUD to be associated with decreased connectivity (e.g., Chanraud et al., 2011). A recent study using machine learning to classify AUD with rs-fMRI found little contribution of DMN connectivity to AUD classification (Vergara et al., 2022). Based on findings from another study, it was hypothesized that DMN regions were more affected by nicotine use than alcohol use and that relative lack of effect observed for the DMN was due to absence of nicotine users in this sample (Vergara et al., 2017). Another possible reason for null findings for the DMN could be the impact that sobriety may have on network changes. Many studies that found DMN differences were conducted in a sample of abstinent participants. For example, one study stipulated that individual recruited for their alcohol group had a period of abstinence of at least a week, with an average of 26.9 days (Zhu et al., 2018). Another study included individuals who were in early remission, with an average of 16 weeks since meeting criteria for dependence (Müller-Oehring et al., 2015). Further, the sample for this study included significantly more individuals with alcohol use who met nicotine dependence criteria (54%) compared to controls (12%). Fede and colleagues (2019) similarly found DMN to predict AUDIT scores in an

abstinent sample where 67% were recruited from an inpatient setting. There are clearly many comorbid factors associated with alcohol use that might contribute to changes in the DMN, and presumably similarly explain, in part, lack of findings for ECN-DMN between network connectivity. Future research clarifying these dynamics across the cycle of alcohol use and recovery may help to further elucidate targets for treatment at each unique stage.

Despite little support for RSFC hypotheses overall, we found resting state connectivity within and between the ECN and DMN to differ based on sex. Specifically, there was reduced connectivity within the DMN in males compared to females. In contrast, males exhibited greater connectivity within the ECN and between ECN and DMN. Structural differences in male and female brains have been described, with females exhibiting greater proportion of gray matter compared to white matter and males exhibiting larger global brain volume (Gur et al., 1999). Females have been shown to exhibit greater overall cortical thickness, while males have more variation in regional volumes, gyrification, and cortical thickness (Ritchie et al., 2018). Task-based functional studies have similarly identified differences between males and females on visuospatial tasks that are reflected in cognitive literature showing better performance in males, but females demonstrating better performance on tasks of verbal fluency, recognition memory, and episodic memory (Miller & Halpern, 2014; Gur et al., 2000). Findings regarding intrinsic network connectivity, however, have reflected considerable uncertainty. Though some studies failed to find such differences and suggested that sex was not a relevant variable in resting state functional connectivity (Weissman-Fogel et al., 2010), several have found sex to be an important biological factor for intrinsic networks. In healthy, typically developing adults, several studies have found sex-related differences in fronto-parietal connections (Biswal et al., 2010; Zuo et al., 2010) and DMN (Jamadar et al., 2018). One study in a large sample of 650 healthy young adults

found sex to significantly relate to intrinsic network RSFC, particularly the DMN and task-positive control networks (de Lacy et al., 2019). Whether increased connectivity is reflective of better baseline coherence or possibly a compensatory process remains poorly understood. Additionally, whether these are inherent to developmental trajectories, are secondary to sex, or related to differences in experiences related to culturally-defined gender roles remains unclear. Nevertheless, this provides evidence that converges with prior literature that sex should be modelled in resting state functional connectivity studies.

Functional Connectivity and EF

Within and between ECN and DMN connectivity were not significantly associated with latent EF. Follow-up analyses to investigate whether specific measures might be more sensitive to functional connectivity within and between the ECN and DMN were performed. There were no significant associations between network connectivity and individual cognitive measures. Overall, these findings diverge from previous literature that has linked EF to task-based and resting state studies (e.g., Sweet et al., 2008; Niendam et al., 2012; Jansen et al., 2015; Kim et al., 2012; Crittenden et al., 2015; Müller-Oehring et al., 2015). Overall, this may suggest that resting state connectivity is not a strong marker of EF performance when challenged with behavioral tasks. Importantly, this does not necessarily mean that resting state connectivity is not a useful marker for certain constructs, as the ECN was found to be significantly different between AUD and control groups. Despite the fact that it remains synchronous in the absence of task, seemingly to prepare for task engagement, it may not fully reflect the importance and complexity of dynamic interactions that support task engagement (Greicius et al., 2009; Seeley et al., 2007). Fjell and colleagues (2017) found that in healthy aging, EF decline was more strongly associated with white matter volume changes and brain connectivity together, but almost entirely

unrelated to functional connectivity alone. The discussion above regarding cognitive and brain reserve is certainly relevant here, as connectivity at rest may not be sophisticated enough to detect compensatory processes that occur in a high-functioning sample.

The importance of specific patterns of connectivity within a network may be related to specific node-to-node coherence associations with AUD, as well as with specific cognitive measures. Increased connectivity between left posterior parietal cortex and left DLPFC was found to be significantly associated with better working memory performance when controlling for sex and verbal intelligence. The current study utilized the List Sort task, a language-based working memory measure, from the NIH Toolbox. Beyond left hemisphere lateralization for language-based tasks, there has also been research that suggests that the left ECN is more strongly related to approach behaviors AUD, which may impair ability to control use (Krmpotich et al., 2014; Weiland et al., 2014). Increased connectivity between both left to right and right to left posterior parietal cortices were associated with better performance on a measure of inhibitory control. This finding fits well with prior literature as posterior parietal connectivity has been found to facilitate effortful cognitive performance (Nelson et al., 2000). Thus, in this high functioning sample, posterior parietal-support engagement of effort may be more relevant than frontal control systems on a task without a high degree of complexity. It is important to note is that this association does not reflect task activation and thus conclusions about activation of this region during the task cannot be drawn.

Limitations

There are several additional limitations that are important to note. First, the study design was cross sectional in nature. Thus, conclusions about causality regarding AUD and resting state functional connectivity within the ECN cannot be drawn. Though we modelled AUD as a

predictor of ECN connectivity, it is equally plausible that dysfunction in the ECN can serve as a risk factor that makes individuals more vulnerable to develop AUD. Second, the sample size to detect effects must be considered. Though the proposed analyses were powered to detect small to medium effects, as expected from a review of the extant literature, characteristics in our sample might have buffered against these effects. Specifically, our sample was well-educated. Therefore, levels of reserve were likely to be higher. Additionally, our sample was recruited from the community rather than inpatient settings. Though not definitive, this likely resulted in a sample that was characterized by relatively lower levels of severity than samples utilized in previous studies. The combination of higher levels of reserve and lower levels of severity may help to clarify the relatively smaller observed effects in the current study compared to past literature.

Contributions, Future Directions, and Conclusions

Overall, the results of this study contribute to the limited and equivocal body of literature that investigate RSFC and cognitive performance in AUD. Importantly, our study filled an important gap in the literature, which primarily consists of studies in college-aged students and adults with severe levels of drinking requiring inpatient treatment. We found support for only one study hypothesis, which was the prediction of reduced connectivity within the ECN in our AUD group. We did not find evidence in support of latent EF, within DMN connectivity, or ECN-DMN between network connectivity differences between groups. We also did not find RSFC to mediate the association between AUD and EF.

Despite limitations, this study nevertheless lends important contributions to the literature and directions for future investigation. First, the ECN at rest shows decreased coherence in individuals with AUD compared to controls. Though the ECN at rest was not found to be a marker of EF when the brain is challenged with a task, and EF was not found to be associated

with AUD, several factors that were found to be relevant in our study raise interesting lines of investigation for future work. Longitudinal studies that investigate how resting state networks change over time may prove to be important. Greater specificity in mechanisms of alcohol use onset, maintenance and relapse throughout the addiction cycle (binge/intoxication, withdrawal/negative affect, preoccupation/anticipation/craving) may inform more targeted treatments. Second, we found that ECN and DMN connectivity differed based on sex. Though it is unclear whether this reflects developmental trajectories secondary to sex, environmental differences secondary to culturally-defined gender roles, or differential susceptibility to the effects of AUD, this provides further support that studies should delineate effects between men and women in AUD and RSFC studies. Further, factors that influence this effect, such as gender identity, occupation, weight, brain volume, and other health factors may further elucidate this finding. Importantly, whether these are inherent to developmental trajectories secondary to sex or related to differences in experiences related to culturally-defined gender roles remains unclear. Finally, though EF is often the focus of AUD studies, the results from the current study suggest that, similar to other bodies of literature for neuropsychiatric disorders, processing speed is an important marker for lower levels of AUD severity and high-functioning, well-educated populations.

Taken together, it is unlikely that functional connectivity, alone, accounts for the variability and complexity that contributes to multifinality of cognitive outcomes associated with AUD. The current study serves as additional evidence that, though the effect of alcohol on peripheral systems is well characterized, chronic effects on the brain remain nebulous and highlights the critical need to continue research that attempts to clarify risk and protective factors for outcomes associated with AUD.

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