

NEUROCOGNITIVE CORRELATES OF FAMILY HISTORY OF SUBSTANCE ABUSE AS  
A FUNCTION OF RECENT ALCOHOL USE

by

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(Under the Direction of Lawrence Sweet)

ABSTRACT

Parental history of substance abuse (PHA) is linked to increased risk for alcohol use problems; however, the cognitive and neurobiological mechanisms of this relationship are not well understood. Emerging research suggests PHA is associated with poorer executive functioning (EF) in adult offspring, and may also result in changes to the coherence of intrinsic neural networks, such as the frontoparietal control network (FPC), which supports EF. No studies to date have directly examined whether observed changes in neural connectivity serve as a mechanism of the effect of PHA on EF. The present study examined the direct effects of PHA on EF and FPC network coherence, as well as the indirect effects of PHA on EF via FPC coherence in a sample of 176 healthy young adults. Results demonstrated a significant inverse relationship between reported PHA and network coherence of the FPC at rest. Contrary to study hypotheses, PHA was not significantly inversely related to performance on behavioral measures of EF. Mean FPC network coherence did not significantly mediate the relationship between PHA and EF. Findings suggest that PHA may result in altered resting state neural activity; however, this did not serve as a mechanism of executive weakness in this population.

INDEX WORDS: Alcohol Use, Functional Connectivity, Executive Functioning; Mediation

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A Dissertation Submitted to the Graduate Faculty of the University of Georgia in Partial  
Fulfillment of the Requirements for the Degree

DOCTOR OF PHILOSOPHY

ATHENS, GEORGIA

2020

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August 2020

## ACKNOWLEDGEMENTS

I would like to thank Dr. Lawrence Sweet for his invaluable mentorship and support over the past six years. Thank you for your guidance, dedication to teaching, and forgiveness of my tendency to talk far too quickly. My sincere gratitude is also extended to my dissertation committee members, Dr. L. Stephen Miller and Dr. Steven Beach, for their support and insight throughout my graduate career.

I am indebted to the participants and researchers who contributed to the Human Connectome project, without whom this project would not have been possible. Thank you to my lab mates in the Clinical Neuroscience Laboratory, whose assistance and friendship are deeply appreciated.

Finally, I would like to thank my family and friends for their unwavering encouragement and support. To my friends from all walks of life, thank you for keeping me sane and sharing your unique perspectives with me. You have changed and shaped the way I see the world, and I am forever grateful. To my parents, David and Diane Murphy: thank you for believing in me, filling my life with countless wonders, and teaching me the importance of hard work and kindness. To Melanie, thank you for inspiring my curiosity, being my role model, and reminding me to laugh through all things. Finally, to Ben. There are not enough words to express my gratitude for your patience, encouragement, and love. Thank you for growing with me, grounding me, and supporting me through the years.

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## CHAPTER 1

### INTRODUCTION

Excessive alcohol use is a worldwide concern: in 2014, alcohol consumption directly accounted for 3.3 million deaths (5.9% of all global deaths; World Health Organization, 2014). Misuse of alcohol lead to nearly 90,000 deaths and 2.5 million years of potential life lost per year in the United States, with alcohol-related incidents representing 1 out of every 10 deaths among working-age adults aged 20-40 (Gonzales et al., 2014; Stahre, Roeber, Kanny, Brewer, & Zhang, 2014). Additionally, it is associated with significant economic costs: according to a 2015 study, binge and heavy drinking were associated with an estimated 249.0 billion dollars in lost productivity and healthcare costs to the United States (Sacks et al., 2015; World Health Organization, 2014).

Defined as binge drinking (i.e., 4 or more drinks in a single occasion for women, 5 or more drinks in a single occasion for men) and heavy drinking (i.e., 8 or more drinks per week for women; 15 or more drinks per week for men; Sacks, Gonzales, Bouchery, Tomedi, & Brewer, 2015), excessive alcohol use is a well-known facilitator of health risk. It has been associated with greater rates of motor vehicle accidents, violence (e.g., homicide, suicide, sexual assault, intimate partner violence), and risky sexual behaviors (e.g., unprotected sex or sex with multiple partners; Smith, Branas, & Miller, 1999; Greenfield, 1998; Mohler-Kuo, Dowdall, Koss, & Wechsler, 2004; Abbey, 2002; Naimi, Lipscomb, Brewer, & Colley 2003; Wechsler, Davenport, Dowdall, Moeykens, & Castillo, 1994). Long term consequences of excessive alcohol use include cardiovascular disease (e.g., high blood pressure, heart disease, stroke; Smith et al.,

1999; Rehm et al., 2010), liver and digestive problems, numerous types of cancer (e.g., mouth, throat, liver; Bofetta & Hashibe, 2006; International Agency for Research on Cancer, 2012). Psychosocial difficulty, including mental health problems, such as depression and anxiety, loss of productivity, unemployment, and family problems are also associated with heavy drinking (Castaneda, Sussman, Westrich, Levy, & O'Malley, 1996; Booth & Feng, 2002; Leonard & Rothbard; 1999). Given the considerable social and economic impacts, identification of risk factors for excessive alcohol use and continued examination of its outcomes is of considerable importance for developing targeted intervention and prevention programs that may ameliorate these consequences.

### **Parental History of Substance Abuse and Alcohol Use**

Parental history of substance use is well-established risk factor for subsequent alcohol dependence (Schuckit, 1985; Trim, Schuckit, Smith., 2010; Wetherill et al., 2012). Studies have demonstrated that first-degree relatives of individuals with a history of alcohol use disorder (AUD) are more likely to develop problems associated with alcohol use throughout their lives than those without this history (Barnow, Schuckit, Lucht, Joh, & Freyberger, 2002; Donovan; 2004; Dawson, Harford, & Grant, 1992; 1998; Lieb et al., 2002; Milne, Caspi, Harrinton, Poulton, Rutter, & Moffit, 2009; Kalaydjian et al., 2009; Sher et al., 1991; White, Johnson, and Buyske, 2000). Youth with a parental history of substance abuse (PHA) are at risk to begin using alcohol at a younger age, with greater severity, and with more likelihood of use converting to AUD than the general population (McGue et al., 2001; Chassin, Flora, & King, 2004; Labrie, Migluri, Kenney, & Lac, 2010). A recent meta-analytic review revealed that PHA was associated with worse alcohol consequences, including more reported symptoms of hangover, alcohol use disorder symptoms, and other drug use or dependence (Elliott, Carey, & Bonafide,

2012). Familial aggregation studies have demonstrated that substance abuse is highly heritable (approximately 50-70%), and that this familial contribution is more significant for frequent use than for nonproblematic use (Merikangas et al., 1998; Verhulst, Neale, & Kendler, 2015; Schuckit, 2009; Agrawal & Lynskey, 2008).

Despite the considerable evidence linking parental history of substance use or alcoholism to adult alcohol use, the underlying neurobiological mechanisms by which this risk is conferred remain poorly understood. Studies investigating adults with alcohol use disorder (AUD) suggest that neurobiological differences may exist prior to initiation of alcohol use that place these individuals at risk for alcohol difficulties (Herting, Schwartz, Mitchell, & Nagel, 2010; Reich et al., 1998; Spadoni et al., 2008). Preliminary studies have identified cognitive and neurobiological differences in youth with PHA (described in further details in subsequent sections) who are not consuming excessive levels of alcohol, which supports the theory that there are heritable risk factors that may result in alcohol use problems.

### **Parental History of Substance Abuse and Cognitive Functioning**

Numerous negative cognitive consequences of alcohol use and abuse have been established within the literature (e.g., Brown, Tapert, Granholm, & Delis, 2000). These deficits have long been interpreted as the result of the neurotoxic effect of alcohol on the brain; however, evidence indicates that cognitive vulnerabilities may exist prior to exposure to alcohol use. Among alcohol naïve youth, those with a positive PHA perform worse on neuropsychological tests, including aspects of executive functioning (Giancola, Zeichner, Yarnell, & Dickson, 1996; Harden & Pihl, 1997; Poon, Ellis, Fitzgerald, Zucker, 2000). Specifically, poorer performance in the domains of response inhibition (Nigg et al., 2006; Acheson et al., 2011; Saunders et al., 2008; Lovallo et al., 2006), cognitive flexibility (Corral, Holguin, & Cadaveira, 2003; Gierski et al.,

2013); and working memory (Lovallo et al., 2006) have been demonstrated among individuals with PHA compared to their peers. These EF vulnerabilities have been subsequently associated with greater alcohol use (Goldstein & Volkow, 2002; Peeters et al., 2015; Tarter et al., 2003), thus representing a potential risk factor and point of intervention. The mechanism of the relationship between EF and subsequent alcohol use is not yet well understood, but dual process models suggest that among individuals with deficits in EF, automatic impulses to drink are improperly regulated, thus drinking behaviors are guided more by impulses than careful reasoning and long-term goals (Deutsch & Strack, 2006; Hoffman, Friese, & Strack, 2009; Houben & Wiers, 2009; Thush et al., 2008; Houben, Wiers, & Jansen, 2011).

### **Executive Functions**

The executive functions (EF) are a group of top-down processes that are instrumental in reasoning, problem solving, regulation, and planning (Collins & Koechlin, 2012; Lunt et al., 2012). As such, these functions are foundational for academic and occupational success (Bailey 2007; Blair & Razza, 2007; Duncan et al., 2007), quality of life (Brown & Landgraf, 2010; Davis, Marra, Najafzadeh, Lui-Ambrose, 2010), functional ability (Lewis & Miller, 2007) and health outcomes such as obesity (Crescioni et al., 2011). Additionally, deficits in EF are implicated in drug and alcohol addiction (Baler & Volkow, 2006; Goldstein, 2004; Finn & Hall, 2004; Koob & Volkow, 2016; Nigg et al., 2006; Tapert et al., 2002). Three well established and generally agreed upon EF include inhibitory control, cognitive flexibility, and working memory, (see Figure 1, based upon Figure 4 from Diamond, 2013; Lehto et al., 2003; Blair, Raver, Berry, et al., 2014; Zelazo & Bauer, 2013; Davidson, Amso, Anderson & Diamond; 2006). These domains, which are independently influential on behavior, also work in tandem to facilitate each

other, among other cognitive functions that they support (Diamond, 2013). Each of these domains is discussed in further detail below.

Cognitive flexibility. Cognitive flexibility, which is also commonly referred to as mental set shifting, is the ability to quickly and fluidly adapt behavior to fit changing needs or situations (Diamond, 2013). It includes the ability to change perspectives interpersonally and spatially (e.g., viewing something from a different direction or point of view), the ability to adjust to changed demands or priorities, and adaptive problem solving approach (i.e., identifying new solutions when a currently used approach is no longer successful; Diamond, 2013). Tasks that estimate cognitive flexibility challenge these aspects of thinking, often by assessing the amount of time capacity to produce output quickly and according to a set of rules that may change throughout the task. During a classic example, the Wisconsin Card Sorting Task (Grant and Berg, 1948), participants are asked to match a set of cards to key cards according to sorting criteria that shift between different stimulus characteristics of the cards (e.g., color, shape, number). This task was adapted by Zelazo and colleagues in the form of the Dimensional Change Card Sort Test (DCCS; described in detail in the Method section), which estimates failures to switch between changing sorting criteria (Zelazo, Frye, & Rapus, 1996; 2003).

Cognitive flexibility improves across early development (Davidson et al., 2006; Garon, Bryson, & Smith, 2008). Studies using the DCCS have demonstrated that very young children demonstrate difficulty switching between sorting criteria and have difficulty inhibiting their predisposed response to attend to information that was previously relevant (Chatham et al., 2012; Kloo & Perner, 2005). Indeed, while children demonstrate an improved ability to flexibly switch on a trial-by-trial basis by the age of approximately seven (Davidson et al., 2006; Gupta et al., 2009); difficulty with rapidly or immediately shift flexibility are still evident in adulthood.

Healthy, young adults demonstrate slower reaction times on switch trials, even when forewarned of the change (Diamond & Kirkham, 2005; Allport & Wylie, 2000). While a general increase in cognitive flexibility has been demonstrated through young adulthood (20-35; Best & Miller, 2010), performance has been shown to decline during advanced aging, with older adults showing poorer accuracy and longer response latencies compared to young adult controls (Kray, 2006; Meiran, Gotler, & Perlman, 2001).

*Inhibitory Control.* The domain of inhibitory control is, broadly, the ability to regulate attention, behavior, thoughts, or emotions and delay a dominant or automatic response in order to make a more appropriate response. It constitutes several components, including behavioral inhibition (i.e., self-control) and interference control (selective attention and cognitive inhibition; Diamond 2013). The former includes the ability to adapt or control one's behavior in the service of reaching a particular goal. This can include inhibiting impulses to do something that is immediately rewarding but potentially costly in the long run (e.g., overeating, cheating, stealing) or exercising the discipline to focus and complete a task in the face of extraneous temptations or other distractions (Diamond, 2013). The latter often refers to control of attention at the level of perception, in that it allows a focus on information that is salient based on our goals or intentions while ignoring other stimuli (Theeuwes, 2010; Anderson & Levy, 2009; Postle et al., 2004). Tasks that are frequently used to assess inhibitory control are numerous, and include the Stroop task (MacLeod, 1991; Banich & Depue, 2015), anti-saccade tasks (Hallett, 1987; Unsworth, Schrock, & Engle, 2004), go/no-go tasks (Simson, Vaughan, & Ritter, 1977; Langenecker, Zubietta, Young, & Nieson, 2007), and Flanker Tasks (Eriksen & Eriksen, 1974; see the Method section for additional information). These tasks share some commonalities; namely that

participants are asked to forgo a prepotent or automatic tendency (e.g., reading, looking towards a salient stimulus) in order to complete a specific task demand.

As with other aspects of EF, young children often demonstrate poor performance on tasks of inhibitory control: development of this domain continues to mature from early childhood into adolescence (Luna, 2009; Luna et al., 2004). Poor inhibitory control ability among children can subsequently affect their performance on tasks that do not specifically assess the domain by promoting slower pacing rather than impulsive responding on these tasks (e.g., theory of mind; Carlson & Moses, 2001). Similar to cognitive flexibility, peak performance within the domain of response inhibition appears to occur during young adulthood (Best & Miller, 2010; Duell et al., 2018). Aging is associated with declines in aspects inhibitory control, including poorer inhibition of visual and auditory distractions (Darowski et al., 2008; Peltsch et al., 2011), and suppressing irrelevant information (Zanto, Hennigan, Östberg, Clapp, & Gazzaley, 2010).

As a key factor in controlling our impulses, inhibitory control is of vital importance for goal-directed behavior as it facilitates careful choice and behavioral change. Children who demonstrated better inhibitory control in early childhood have better outcomes as teenagers (e.g., were less likely to be smoking or taking drugs) and as adults (e.g., healthy body weight, more law-abiding) than their peers with worse inhibitory control (Anzman & Birch, 2009; Moffitt et al., 2011; Rhoades, Greenberg, & Domitrovich, 2009;). Self-control related aspects of behavioral inhibition have been closely linked to delay discounting, or one's ability to decline an immediate reward in order to obtain a greater but later reward (Bickel & Marsch, 2001; Louie & Glimcher, 2010). Inhibitory control is implicated in substance use and addiction: a considerable literature demonstrates that poorer delay discounting has been associated with negative outcomes such as

substance use disorders, obesity, attention deficit hyperactivity disorder, and gambling problems (MacKillop et al., 2011; Reynolds, 2006; Weller, Cook, Avsar, & Cox, 2008).

*Working Memory.* The term working memory, first coined by Newell and Simon in 1972 and elaborated upon by Baddeley and colleagues, refers to the ability to mentally hold and manipulate a limited amount of modality-specific information over a brief period of time (Baddeley, 1998; Baddeley & Hitch, 1974; Davidson et al., 2006; Smith & Jonides, 1999). Tasks that estimate working memory function often require individuals to both repeat back and change a series of stimuli in some way. For example, asking individuals to mentally arrange a sequence of randomly ordered stimuli (i.e., reordering a series of objects by object size), such as the WAIS Digit Span Backwards or Letter Number Sequencing subtest (Wechsler, 2008). The List Sorting Working Memory task was used in the present study, and it is described in detail in the Method section (Diamond, 2013; Tulskey et al., 2014).

While the development of short term memory, or the ability to simply buffer information, develops in infancy and early childhood (Bell & Cuevas, 2012); working memory development and increased capacity in this domain continues into adolescence (Cowan, Rouders, Blume, & Saults, 2011; Luciana, Conkin, Hooper, & Yarger, 2005); with peak performance levels in the late 20s (Wechsler, 2008). This development co-occurs with neurodevelopment of the dorsolateral prefrontal cortex (DLPFC), a region of the brain that is notable for its prolonged development and has a demonstrated robust association with working memory performance (Darki & Klingberg, 2015; Smith and Jonides, 1999). Similar to other domains of EF, a decline in working memory associated with aging has been demonstrated (Fiore et al., 2012; Fournet et al., 2012).

Working memory facilitates day-to-day activities such as written or spoken language comprehension (e.g., buffering clauses in complex sentences in order to perceive the meaning of the entire sentence when completely spoken). More complex functions, such as planning, decision making, and updating or adjusting behavior according to one's goals, are also closely associated with working memory (Diamond, 2013). Specifically, working memory allows one to consider and update goals, available behavioral or emotional responses, and potential consequences even when faced with novel or changing situations (Finn, 2002). Unsurprisingly, given its role in these behaviors, working memory is foundational for human reasoning, as it allows us to consider multiple chunks of information and identify connections between them in a meaningful manner. It is similarly related to decision-making, as it is essential that one be able to hold relevant information in mind (e.g., the situation, one's goals and desires, related past experiences) in order to consider all of the possible outcomes of a decision before making a final choice (Diamond, 2013). Deficits in WM have been associated with reduced educational attainment, impulsivity, and poor decision-making (Bechara & Martin 2004; Hinson, Jameson, & Whitney 2003; St. Clair-Thompson & Gathercole 2006; Thush et al. 2008). As with other domains of EF, poorer working memory ability has been associated with alcohol problems and alcohol use disorders (Finn & Hall, 2004; Tapert et al., 2002).

### **Excessive Alcohol Consumption and Executive Functions**

Evidence suggests the relationship between EF and alcohol use is bidirectional: poorer EF is both a risk factor for the development of addictive behaviors and a consequence of exposure to alcohol. Exposure to alcohol during adolescence and throughout the lifespan negatively affects brain maturation in regions that underlie EF (Squeglia et al., 2015). In addition, exposure to alcohol has been shown to alter neuropsychological functioning, including

deficits in EF (Squeglia et al. 2009, Brown et al., 2000; Tapert et al., 2004), although it is important to note that these findings are somewhat mixed, with some findings suggesting no EF deficits among alcohol using youth (Boelma et al., 2016; Jacobus et al., 2015; Nguyen-Louie et al., 2015). The impact of alcohol exposure may be especially harmful to adolescents, as still developing cortical regions (i.e., prefrontal cortex) may be particularly vulnerable, leading to poorer cognitive flexibility, working memory, and response inhibition (Thush et al., 2008; Crews, Braun, Hoplight, Switzer, & Knapp 2000; Weirs, van Woerden, Smulders, & De Jong, 2002). In turn, these deficits may result in even greater levels of alcohol use, thus perpetuating a cycle of abuse. Given the bidirectionality of this relationship, when examining the effect of familial risk in adult samples it is important to consider past and current alcohol use, which may exacerbate the existing neural and cognitive deficits leading to even greater negative outcomes.

One study that has probed these interrelationships was conducted by Tapert and Brown (2000). The authors estimated the nature of the interrelationship between PHA and personal substance use on neurocognition. They found support that substance dependence moderates the relationship between PHA and neuropsychological functioning on tasks that were defined as attention (e.g., WISC-R Arithmetic, Digits Backward, the Trail Making Test Part B time) and language (e.g., WISC-R Vocabulary, Boston Naming Test) among a sample of 151 adolescents. Specifically, they noted that non-abusing teens without PHA outperformed non-abusing teens with a PHA as well as abusing teens with and without PHA (Tapert & Brown, 2000). These results suggest that PHA and alcohol use may have an additive impact on neuropsychological functioning. Relevant to the present study, the tasks that the authors defined as “attention” are consistent with those frequently given as assessments of cognitive flexibility, working memory, and behavioral inhibition, and thus contribute significantly to the basis for present hypotheses.

## Neuroimaging and Executive Functions

Structural and functional brain imaging have been widely used in recent years to investigate neural underpinnings of cognition, emotion, and behavior, leading to substantial advances in our understanding of neural systems associated with EF (Alvarez & Emory, 2006; Cabeza & Nyberg, 2000; Phan, Wager, Taylor, & Liberzon, 2002).

Task-Based fMRI. Task-based functional magnetic resonance imaging (fMRI) has provided a platform for investigators to identify brain systems that respond during performance of cognitive tasks. fMRI relies on the magnetic properties of blood to quantify changes in the oxy- to deoxyhemoglobin ratio, which is linked to local neuronal demand in a linear and additive manner (Logothetis, 2008). Specifically, task-based fMRI studies identify gray matter network nodes in which there is an increase in neural activity, as measured by increased blood oxygen level dependent signal (BOLD signal; i.e., change in oxygen ratio), that is temporally associated with presentation of an experimental condition compared to a control condition (Bandettini, Wong, Hinks, Tikofsky, & Hyde, 1992; Kwong et al., 1992; Ogawa et al., 1992). The focus on specialized processing within particular regions and identifying those that are uniquely associated with a task has been termed modularity (Seeley et al., 2007). Task-based modularity analyses have been instrumental in identifying neural networks that are associated with performance on cognitive tasks, including EF.

Evidence suggests that the nodes that comprise the bilateral FPC, which include dorsolateral prefrontal cortex (DLPFC) and posterior parietal cortex (PPC) are associated with performance on tasks of cognitive control, including cognitive flexibility, verbal and spatial working memory, and response inhibition (Aloia et al., 2009; Blasi et al., 2006; Lundqvist, 2010; Sweet et al., 2008; Spadoni et al., 2008; Buchsbaum et al., 2005). Within these regions, increased

task difficulty is associated with amplified activity, which is interpreted to represent increased cognitive demand of task completion (Smith & Jonides, 1997; Sweet, Rao, Primeau, Dugierian & Cohen, 2006). Frontal regions have been linked to executive control while parietal cortices have been associated with accurate and effortful performance (Nelson et al., 2000). DLPFC activity has also been implicated in completion of cognitive control tasks, including working memory (Curtis & D'Esposito, 2003) and response inhibition (i.e., flanker, go/no go; Blasi et al., 2006). Together, this system enables participants to remain focused on, and manipulate, presented information (Diamond et al., 2013; Awh & Jonides 2001, Gazzaley & Nobre 2012, Ikkai & Curtis 2011).

*Functional Connectivity.* Complementing task-based modularity designs, investigators have also improved understanding of functional neural systems using connectivity analyses that relate to information flow across small and large-scale brain networks (Biswal, Yetkin, Houghton, Hyde, 1995; Seeley et al., 2007). Functional connectivity MRI determines whether fluctuations in BOLD signal in proximal and distal gray matter regions significantly correlate across time by observing their temporal correlations in units of brain regions or voxels (Biswal et al., 1995; Biswal, Van Kylen, & Hyde, 1997; Auer, 2008; Buckner et al., 2009; Van Dijk, Sabuncu, & Buckner, 2012;). High correlations of neuronal activity suggest shared processing mechanisms and ultimately have been used to identify brain circuits that work in tandem to support various aspects of functioning and cognition (Raichle, 2015). Functional connectivity MRI analyses have importantly demonstrated that spontaneous actions in certain regions show differing levels of connectivity even at rest, suggesting that even when not performing a task, brain regions may be working together (Barch, 2017; Biswal et al., 1995; Greicius, Krasnow, Reiss, & Menon, 2003; Beckmann et al., 2005; Fox et al., 2005; Roy et al., 2009). These methods

have been used to identify robust intrinsic networks, that is, temporally coherent networks that demonstrate patterns of synchronized fluctuations in the BOLD signal in the absence of explicit demands (Beckmann et al., 2005; Bressler & Menon, 2010; Buckner, Krienen, & Yeo, 2013; Cordes et al., 2000; Seeley et al., 2007; Van Den Heuvel & Pol, 2010). Some have interpreted these intrinsic networks as a valid representation of the functional integrity of systems that underlie cognition; such that lower coherence between nodes may represent network disorganization and processing inefficiency (Chanraud et al., 2011; Friston, 1998; Greicius, 2008).

Several methods are commonly used to examine functional connectivity in resting state BOLD data. Model-free methods, including principal and independent component analyses, examine whole-brain connectivity patterns by examining general and unique patterns of connectivity without the definition of *a priori* regions of interest (Viviani, Gron, & Spitzer, 2005; Beckmann et al., 2005; DeLuca et al., 2006; van de Ven et al., 2004; van den Huevel & Pol, 2010). In contrast, model-dependent methods, also referred to as a seed-based approaches, estimate correlations among prespecified brain regions. In this approach, *a priori* regions of interest (i.e., seeds) are identified, typically based on prior literature. Across studies, these regions vary in size, from the level of a single voxel to a cluster of voxels, which might be defined by prior fMRI findings or neuroanatomical boundaries. The mean BOLD signal of the voxels within the established seed region are calculated over the time course of the imaging run. BOLD signal variation is then examined for strength of association with that of other voxels using correlations (Fox & Raichle, 2007; Vincent et al., 2008) or general linear models with covariates that represent spurious variance, such as observed motion, band pass filtering, parameters estimating head motion, global signal associated with respiration-induced signal

fluctuations, and known error signal from a ventricular region of interest (Bartels & Zeki, 2005; Birn et al., 2006; Fox et al., 2005; Vincent et al., 2008). Based on the resulting parameter estimates between the seed region and the voxels comprising target network nodes the strength and direction of connectivity is determined, such that regions with mean parameter estimates that are highly positively associated are considered to be functionally synchronous, and those exhibiting inverse relationships are considered anticorrelated.

Functional connectivity within networks has been successfully linked to attributes measured outside of the scanner both when BOLD acquisition occurs while participants are performing tasks (e.g., Thomas-Yeo et al., 2013) and at rest (Seeley et al., 2007; Vincent et al., 2008). The latter indicate that individual differences in intrinsic connectivity strength correlate to actual cognitive performance and other behaviors associated with the networks examined. Indeed, a 2007 study demonstrated that connectivity between regions within a central executive network was significantly and inversely correlated with performance on a set shifting task, such that greater functional connectivity was associated with improved performance (Seeley et al., 2007). Similarly, the FPC, including the DLPFC and PPC have been linked to cognitive ability (Prado, Carp, & Weissman, 2001; Sridharan, Levitin, & Menon, 2008).

As a result of increased interest in understanding functional connectivity and its relationship with cognition and behavior, efforts have been made to improve methodology and replicability in connectivity research. The Human Connectome Project (HCP) is a large-scale initiative that aimed to improve methods of data acquisition and analysis to characterize and quantify brain connectivity and function across the lifespan (Uğurbil et al., 2013; Van Essen et al., 2013; Smith et al., 2013). The project sought to map functionally distinct areas of the human brain and better understand how they are connected, contribute to behavior, and ultimately relate

to neurodevelopmental, neuropsychiatric, and neurological disorders (Barch, 2017; Van Essen et al., 2012). The project was awarded 30 million dollars in grant funding through the National Institute of Health in September of 2010 to complete the first phase of the project. Funding was dispersed to an academic consortium of ten institutions in the United States and Europe led by researchers at Washington University and the University of Minnesota. In its first phase, team members across 10 institutions collected comprehensive evaluations from healthy young adults between Fall of 2010 and Spring of 2012. Evaluations included standardized acquisition of structural MRI, task and resting state functional MRI, MEG, as well as numerous behavioral measures. Recruitment efforts resulted in 1100 individuals with complete data collection and an additional 100 with out-of-scanner behavioral data (Van Essen et al., 2012). The full dataset was released for access on March 1st, 2017.

Given the open source nature of the HCP, the data has resulted in numerous publications and presentations covering a vast array of topics. Authors have examined topics including the association of intelligence with global network efficiency (Kruschqitz, Waller, Daedelow, Halter, & Veer, 2018), neural connectivity after traumatic brain injury (De Simoni et al., 2017), and age-related connectivity differences in individuals with attention deficit and hyperactivity disorder (Hong, Park, Cho & Park, 2017), among others. Several authors have published investigations aimed to elucidate relationships between neural structure, functioning, and substance use or abuse. Structural studies have demonstrated links between substance use and cortical thickness, with alcohol use disorders linked to larger cortical thickness in the left insula and right fusiform gyrus (Zhao, Zheng, and CCC, 2017) and frequency of heavy drinking and global cortical thickness (Morris et al., 2019). Functional neuroimaging studies using the HCP have demonstrated greater insula reactivity to negative stimuli among cigarette users (Dias, Peechatka,

& Janes, 2016). However, to date no authors have examined the relationship between resting state functional connectivity, executive functioning, and substance use.

### **Neuroimaging, PHA and Alcohol**

Structural and functional MRI studies have been used to probe the neural associates that may result from a family history of alcohol use and precede alcohol problems. Documented neurobiological associates of parental history of alcoholism include differences in brain volume, white matter microstructure, and behaviorally assessed brain functioning (Cservenka, 2016; Cservenka, Herting, & Nagel, 2012; Cservenka and Nagel, 2012; Mackiewicz Seghee, Cservenka, Herting, Nagel, 2013; Silveri, Rogowska, McCaffrey, & Yurgelun-Todd, 2011). Functional neuroimaging studies have similarly demonstrated differences in neural activity and connectivity among individuals with a PHA: samples of non-drinking individuals with a PHA demonstrated aberrant frontoparietal functional connectivity when completing spatial working memory tasks compared to matched controls (Herting et al., 2010; Pfefferbaum et al., 2001; Rangaswamy et al., 2004; Schweinsburg et al., 2004; Squeglia & Cservenka, 2017). Among a sample of 72 adolescents (age 12-14), lower fMRI measured neural responses in the posterior cingulate, cingulate gyrus, and medial frontal gyrus were demonstrated during a vigilance task among youth with higher rates of PHA compared to those with fewer family members with AUD (Spadoni et al., 2008).

A growing body of empirical evidence suggests that parental history of alcohol use may be associated with altered functional connectivity of the FPC. Adolescents with a PHA have significantly different resting state synchronicity between the left nucleus accumbens, left orbitofrontal cortex, bilateral inferior frontal gyri, and left post-central gyrus according to a 2014 study (Cservenka, Casimo, Fair, & Nagel, 2014). Pertinent to the present study, a 2013 study by

Wetherill and colleagues examined the association between PHA and connectivity of the frontoparietal network among substance naïve youth using functional connectivity analyses during a working memory task and diffusion tensor imaging (DTI). The authors demonstrated that youth with PHA had reduced functional connectivity between the DLPFC and PPC compared to their peers without a parental history of substance use. They noted that this may represent a neurobiological marker for alcohol use disorders, as well as a neurodevelopmental delay whereby youth with a positive PHA had weaker connections between more distal nodes. In addition, functional connectivity between the DLPFC and PPC was negatively correlated with overall performance on an attention task, suggesting that that these connections may underlie attentional deficits observed among youth with PHA (Knopik, Jacob, Haber, Swenson, Howell, 2009). In contrast, DTI results did not demonstrate altered white matter architecture in the tracts associated with this functional circuitry, which authors interpreted to indicate that variations or delays in synaptic transmission, rather than myelination, account for differences in frontoparietal connectivity. The findings of this study have several implications for the present study, which seeks to expand these findings to adults and examine relationships between PHA, connectivity, EF, and adult alcohol use.

### **Aims and Hypotheses**

While separate bodies of research have linked parental history of substance use, heavy drinking, functional connectivity, and executive functions, none to date have directly tested the mediating role of connectivity of the FPC in the relationship between parental history related risk and EF, and how alcohol use may moderate these relationships. The Human Connectome Project's large sample size and lengthy resting state data acquisition provides a unique platform for investigation that is beyond the statistical power of what has been available in previous FMRI

studies. Characterization of the neural and cognitive profiles of individuals with a PHA and the interrelationships between these factors may help determine potential premorbid markers in the brain functioning of individuals who develop AUD and how these factors contribute to increased risk. Identification of the mechanisms behind these outcomes is needed to inform future attempts to develop prevention and intervention strategies that may reduce rates of problematic alcohol use and associated consequences. In addition, given that the present study utilizes an adult sample, we are uniquely positioned to probe the moderating effect of adult heavy drinking on the relations between PHA and neurocognitive functioning (Tapert & Brown, 2001).

The present study had four primary aims expected to extend prior findings that separately link PHA to executive dysfunction and altered neural connectivity, determine whether network coherence in the FPC mediate this relationship, and assess if these relations occur as a function of heavy alcohol use frequency over the past 12 months. The first aim was to demonstrate that direct effect of PHA on executive functioning and FPC network coherence in the present sample. Consistent with the existing literature, it was hypothesized that reported parental history would be inversely correlated with performance across a battery of three EF measures (i.e., Card Sorting Task, Flanker Task, and Visual Working Memory Task), such that those with a parental history performed more poorly than their counterparts without PHA. Additionally, it was hypothesized that those with a parental history of substance abuse would show decreased resting state coherence of the FPC derived from *a priori* seed-region analyses.

The second and third aims of the study focused on testing the inter-relationships between study variables via simple and conditional mediation analysis. Specifically, the third aim was to demonstrate partial mediation of the direct effect of PHA on EF through FPC network coherence. It was hypothesized that there would be a significant indirect effect of FPC

connectivity, such that PHA is significantly inversely associated with FPC coherence, resulting in poorer EF. Finally, the fourth aim was to determine the extent to which heavy alcohol use moderated the direct effect (PHA to EF) and indirect effect (PHA to FPC). This aim accounted for the potential moderating effect of heavy alcohol use on these relationships through a moderated-mediation model. More specifically, it was hypothesized that heavy alcohol use would significantly moderate the relationship between PHA and EF as well as the relationship between PHA and FPC network coherence. We hypothesized that PHA would be associated with worse EF among individuals who report a higher rates of drinking compared to those who report lower rates of drinking and that PHA would be associated with decreased network connectivity among those who reported drinking more heavily than those who did not.

## CHAPTER 2

### METHOD

#### **Participants**

Resting state functional connectivity magnetic resonance imaging, parental history of substance abuse, current alcohol use, and EF performance data were collected from 1100 participants as a part of the Young Adult Human Connectome Project (HCP; <http://www.humanconnectome.org>). The participant pool comprised racially, socioeconomically, and genetically diverse U.S. citizens between the ages of 22 and 35 (see Table 1 for participant demographic information). The Young Adult HCP sample recruited individuals born in Missouri to families that included siblings and twins; however, not all participants who were included had siblings within the study. Data were collected between August 2012 and October 2015 and were released on March 1, 2017. All data were de-identified prior to release as described by Van Essen and Barch (2015; Hodge et al., 2016).

Participants were screened for suitability during a brief telephone interview. Exclusion criteria included neurodevelopmental disorders (e.g., autism), a history of severe psychiatric (e.g., schizophrenia), neurological (e.g., traumatic brain injury, epilepsy, stroke), or medical disorders (e.g., cardiovascular disease). Severity was operationalized as 1) participant report of diagnosis by treating physician, 2) hospitalization for two days or longer, or 3) pharmacological or behavioral treatment by a cardiologist, psychiatrist, neurologist, or endocrinologist for a period of 12 months or longer. Exclusion criteria also included history of any genetic disorder (e.g., cystic fibrosis), and current or past chemotherapy or radiation that may have affected the

brain. Additionally, participants were excluded if they endorsed MRI contraindications such as unsafe metal implants, pregnancy, or claustrophobia. Substance use (e.g., alcohol, drugs, tobacco) was not exclusionary. For additional information regarding the telephone screening process, inclusion, and exclusion criteria, see Van Essen et al., 2013, Supplemental Table 1.

For the present analyses, the overall sample (n= 1100) was sub-sampled to include all individuals who endorsed a history of substance abuse in either parent. A visual display of the sub-sampling approach is presented in Figure 1. Notably, some participants who endorsed PHA were not included in the present study due to incongruence of report from included siblings. This served as an additional level of verification of responses. Participants were only included if they and a majority of their siblings were concordant in their responses of parental history (i.e.,  $\geq 2/3$  siblings reporting same responses). Upon selection of individuals with a parental history, age, gender, and race matched control participants were selected individually. When multiple possible matches were available, control participants were chosen at random using a random number table. When exact matches were unavailable, priority was given to gender and race. In this case, control participants could be included only if they were within two years of the selected participants age (i.e., 2 years older or younger).

## **Procedure**

Informed consent was obtained from all participants. For additional information regarding the consenting process, see Van Essen et al., 2013. Participants completed the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA, Bucholz et al., 1994). This measure is used to assess prior psychiatric illness and subthreshold psychiatric symptoms, including DSM-III-R and DSM-IV symptoms of alcohol dependence or abuse. Recruited individuals participated in several components of data collection in two 7 hour assessments over

two days at Washington University in St. Louis. Prior to undergoing any MRI scanning participants practiced in a mock scanner to acclimate to the scanning environment. Resting state fMRI data were acquired in four 15-minute runs, two on each day of data collection. During fMRI data acquisition participants were asked to relax while keeping their eyes fixated on a projected cross-hair presented on a dark background. In addition, participants completed an extensive out-of-scanner behavioral assessment that took place upon completion of the collection of MRI data (for a comprehensive description of this battery see Barch et al., 2013, Tables 2 and 3). Included in these evaluations were assessments of EF using the NIH Toolbox (<http://www.nihtoolbox.org/>) on the first day of the evaluation, and assessments of parental history of substance abuse on the second day (Van Essen et al., 2013; Barch et al., 2013).

## **Measures**

Six assessments were used to address study hypotheses, including a quantification of PHA, participants' frequency of heavy alcohol use, three behavioral assessments of EF, and FPC network coherence through functional MRI.

### *Parental History of Substance Abuse (PHA)*

Participants completed a questionnaire addressing family history of psychiatric and neurologic disorders (e.g., schizophrenia, bipolar disorder, Alzheimer's disease). History of substance abuse was classified dichotomously based on participant report of if either parent had a history of drug or alcohol problems. To assess for the validity of this responses, familial level responses within the sample were assessed. Of participants who completed survey data, 90.37% of siblings provided concordant reports with their siblings. Participants with discordant responses were excluded unless there was majority agreement among siblings (i.e., greater than or equal to 2/3 of siblings provided identical results). Notably, the reliability and validity of self-report of

family psychiatric history has been demonstrated in numerous studies, with demonstration of high reliability and validity for history of substance abuse across studies (Hardt & Franke, 2007; Weissman et al., 2000).

#### *Assessment of Alcohol Use and Severity*

Two estimate of current alcohol use and severity were included in the present analyses. Responses were based on self-report during the SSAGA. Participants reported frequency of heavy drinking (i.e., five or more beverages) in the last 12 months and during their heaviest period of alcohol consumption. Collected data for both variables was coded categorically, and variables reflect ranges of the number of days with 5 or more alcohol beverages consumed rated as follows: 1 = never; 2 = 1-11 days per year; 3 = 1-3 days per month; 4 = 1-2 days per week; 5 = 3 plus days per week or greater. Inclusion of this variable was based on prior research identifying relations between heavy drinking and EF deficits (Houston et al., 2014; Morris et al., 2019). To account for both recent and historical heavy drinking, participant responses on both measures were summed into a composite heavy alcohol use variable.

#### *Assessment of Executive Functions (EF)*

Three tasks from the NIH Toolbox (described in further detail below) that are designed to assess EF were used in the present study. The NIH Toolbox was the result of an initiative to develop a standardized research assessment of various domains across the lifespan (e.g., cognitive, emotional, motor functions; Gershon, Wagster, Hendrie, Fox, Cook, & Nowinski, 2013; Hodes, Insel, & Landis, 2013; Weintraub et al., 2013). Instruments were selected based on considerations such as psychometric soundness (e.g., reliability, content validity), applicability in diverse settings and with different groups, nationally normed for individuals between 3 and 85, and field tested for inclusion in the final battery (Gershon et al., 2013). Based on the existing

literature, the present study focuses on three components of EF: cognitive flexibility, response inhibition, and working memory, as they have been linked to alcohol use in prior studies (Bechara & Martin 2004; Nigg et al., 2006; Noël, Bechara, Dan, Hanak, & Verbanck, 2007; Stephan et al., 2017). Age adjusted scores (e.g., compared to the nationally representative NIH toolbox sample) were calculated by the NIH toolbox and were converted to z-scores based on sample means and standard deviations. Outliers ( $n=3$ ) were excluded when task performance fell more than 3.29 standard deviations (SD) from mean performance on the task (Tabachnick & Fidell, 2007). As performance across the three administered EF measures did not demonstrate moderate correlation ( $r$  values between .3 and .7), all subsequent analyses were also completed for individual tests rather than a composite of EF functioning.

*Cognitive Flexibility.* The Dimensional Change Cart Sort (DCCS) is an established measure of cognitive flexibility. The assessment was initially designed by Zelazo and colleagues (Frye, Zelazo, & Palfai, 1995; Zelazo, 2006) and was adapted for use in the NIH Toolbox (Zelazo et al., 2013). The task takes approximately four minutes to complete. During this time, participants are presented with two target pictures that vary along two dimensions (e.g., color and shape) and asked to match a series of stimuli (e.g., blue circle) to the target pictures. Sorting of the pictures occurs first according to one dimension (e.g., color) and then, after a pre-determined number of trials, the other dimension (e.g., shape). Participants are asked to switch the dimension by which they are matching, thus utilizing cognitive flexibility to rapidly and accurately adjust choices of the appropriate targets. A single performance score was calculated using the NIH toolbox algorithm that integrates accuracy of target matching and reaction time (Weintraub et al., 2013).

*Inhibitory Control.* The Flanker task, originally developed by Eriksen & Eriksen (1974) was adapted for use in the Attention Network Test and subsequently for use in the NIH Toolbox (Rueda et al., 2004; Zelazo et al., 2013). The task assesses inhibitory control and attention by asking participants to attend to a series of stimuli presented in succession while inhibiting attention to distractor items that surround a target. Specifically, during the three-minute task participants are asked to focus on a central stimulus (i.e., an arrow for adult participants) and indicate a response as to the direction it is facing while inhibiting attention to stimuli that are flanking it (also arrows in the present study). The middle stimulus is either congruent with the arrows that flank it (i.e., facing the same direction) or incongruent (i.e., facing the opposite direction). A single score was calculated for each participant using the NIH Toolbox algorithm which weights and integrates response accuracy and reaction time for adult participants (Weintraub et al., 2013).

*Working Memory.* The List Sorting Working Memory test from the NIH Toolbox was used to assess the storage and manipulation of a limited amount of information over short periods of time (Baddeley, 1992). The task requires participants to sort and sequence a series of visually and orally-presented stimuli (i.e., foods and animals displayed with written text and a sound clip (Tulsky et al., 2014). Stimuli are presented for 2 seconds and participants are asked to remember each stimulus in each series while mentally reordering them according to the task demands across “1-list” and “2-list” conditions. In the “1-list” condition, participants are required to sort the objects (either food or animals) in size order from smallest to largest. In the “2-list” condition participants are required to sort by category prior to sequencing the stimuli: they are presented both food and animals and asked to report the food in size order, followed by the animals in size order (for additional information on task parameters, see Tulsky et al., 2014).

Participants in the present study were given two practice items per condition, in which the images briefly flash sequentially on the screen. A single score consisting of total items correct across all trials was used (Weintraub et al., 2013).

### **Neuroimaging: Resting State fMRI**

*Data acquisition.* High-resolution structural images were collected on a 3T Siemens Skyra scanner (Siemens AG, Erlanger, Germany) with a 32-channel head coil. In total the HCP collected four 15-minute resting state imaging runs across two days of assessment. For the purposes of the present analyses, two 15-minute imaging runs collected on the same day were used. Data were completed using the following acquisition parameters: TR = 720 ms, TE = 33.1 ms, flip angle = 52°, FOV = 208 × 180 mm, 72 sagittal slices, and slice thickness = 2 mm, resulting in 2.0 mm isotropic voxels. A multi-band acceleration factor of 8 was used, Echo spacing = 0.58 ms, BW=2290 Hz/Px. This resulted in a total of 2400 resting state fMRI volumes per subject from two sessions of 1200 volumes each. Structural (T1-weighted) images were also acquired in order to aid data preprocessing and provide neuroanatomical reference. Additional details about data acquisition can be found in the HCP S900 Release reference manual (WU-Minn, 2017), and they are outlined in detail in Glasser et al., 2013, Smith et al., 2013, and Uğurbil et al., 2013.

*Image Processing.* Data were downloaded in an unprocessed format from the HCP website. Although four 15 minute resting state scans were collected across two days, only two scans were used for the present analysis. This results in a total of 30-minutes of data (2400 volumes), which is significantly longer than published recommendations (5-10 minutes; Shehzad et al., 2009; Van Dijk et al., 2012). Additionally, more recent studies have demonstrated that 25

minutes of data are needed to reliably detect individual differences in patterns of intrinsic connectivity (Anderson et al., 2011; Elliot et al., 2019; Hacker et al., 2013; Lauman et al., 2015).

Data were preprocessed using Analysis of Functional Neuroimages software (AFNI; Cox, 1996). Using a previously published-upon pipeline (Nusslock et al., 2019) functional data were prepared for subsequent analysis through despiking, slice time correction, and alignment to T1 data collected on the same day as fMRI data. Data were de-obliques and registered into Montreal Neurological Institute standardized space. The initial four volumes of each run were removed to ensure steady state MRI signal. Volumes were censored due to 1) greater than 25% of voxels identified as outliers and 2) Excessive intervolumes movement ( $>0.2\text{mm}$  along any axis). Data were spatially smoothed using a 6-mm Gaussian filter. To remove low- and high-frequency noise, bandpass filtering was applied (0.01-0.08 Hz). Additionally, six standard motion parameters and their temporal derivatives were included as regressors in the deconvolution.

*Functional Connectivity Analyses.* To test study hypotheses, seed regions of interest (ROI) in the FPC were defined based evidence of a unified executive control network. FPC ROIs included four regions, including bilateral dorsolateral prefrontal cortex (DLPFC) and the bilateral posterior parietal cortex (PPC; Vincent et al., 2008; Buchsbaum et al., 2005; Chen et al., 2013; Seeley et al., 2007; Wetherill et al., 2012). ROIs centered around coordinates identified from Neurosynth (neurosynth.org), a large-scale platform that extracts and aggregates the results of published neuroimaging studies to identify activation coordinates associated with terms of interest (e.g., ‘cognitive control network;’ Yarkoni, Poldrack, Nichols, Van Essen, & Wager, 2011). Coordinates were identified using the search terms “dorsolateral prefrontal” and “posterior parietal.” These search terms yielded 36216 activations based on 1049 studies and

18933 activations based on 476 studies, respectively. For both regions, results from these studies were used to form an association statistical inference map, which tells whether activation in a given voxel or region occurs more consistently for studies that mention the search term than for studies that do not. Based on this inference map, the coordinates that represented the center of the region most consistently linked to the descriptive term were used for subsequent analysis. Five mm spheres were drawn around each set of coordinates to create *a priori* seed regions (see Table 1 for coordinates). These regions were confirmed using the Glasser HCP anatomical atlas in AFNI (Glasser et al., 2016).

The goal of the functional connectivity analyses within the present study was to identify a single estimate of overall network connectivity, as well as exploratory analysis of the unique relations between nodes identified within the FPC. Thus, identified regions served as both seed and target regions. For each of the two 15-minute acquisition runs of resting state fMRI, BOLD signal was first preprocessed and denoised separately. Data was then concatenated and raw time-series data for each voxel was demeaned and converted to a percent-signal-change score to reduce variability between participants. In other words, BOLD activity within each ROI was averaged across all time points to create a mean wave form for that ROI over time. ROI seed data was calculated as the average percent signal change for all voxels in each respective region. This average percent signal change was used to quantify the correlation between regions, with the correlation of the average time series in each seed ROI with all other ROIs in the network (Biswal, et al., 1995; Joel, Caffo, Zijl, & Pekar, 2011). Correlations for all ROI relationships within a particular network are computed (e.g., right DLPFC to right PPC). Pearson correlations ( $r$  values) were converted to  $Z$ -scores using Fischer's  $r$  to  $z$  transformation at the individual level in order to achieve distributional normality.  $Z$ -values across across all possible connections of

the FPC were averaged to produce an overall connectivity estimate for the network as a whole. Outliers (n=1) were excluded when network coherence fell more than 3.29 standard deviations (SD) from mean (Tabachnick & Fidell, 2007). Additionally, to determine whether specific ROIs drive anticipated results each of the direct links between respective nodes were correlated with study variables of interest. Z-scores were used as continuous variables in group level analyses and hypothesis testing regression models.

### **Statistical Analyses**

Descriptive and group level analysis for hypothesis testing were conducted using the Statistical Package for Social Sciences (SPSS 21.0 for Windows, IBM, Chicago, IL). Prior to conducting hypothesis testing, assumptions for multiple linear regression and multiple mediation were examined. Specifically, linear regression assumes normal distribution of data, homoscedasticity (i.e., error terms have the same variance across conditions), there is a linear relationship between variables, and that there is little or no multicollinearity (i.e., independent variables are not highly correlated with each other; Cohen, Cohen, West, & Aiken, 2003). Data were normally distributed across included variables, therefore non-linear transformations were not performed (e.g., log-transformation; Cox and Small, 1978). Variance inflation factors were assessed and no multicollinearity between variables was identified (i.e., Aiken & West, 1991).

Bivariate correlations were examined to determine the extent of the relation between study variables. As existing literature suggests differential gender effects on the relationship between PHA cognitive and behavioral outcomes (Tapert & Brown, 2000; Pihl, Peterson, and Finn, 1990), exploratory analyses examined relationships in men and women separately. Subsequently, we proposed to test Aims 3 and 4 using the PROCESS SPSS macro (Hayes, 2012; 2017). The PROCESS macro is a publicly-available plug-in which provides a modernized

framework for assessing complete and partial mediation effects. The present study proposed to utilize a basic mediation (Aim 3) and conditional (moderated) mediation approach that has been adapted from simple mediation (Aim 4; Hayes, 2017; Preacher, Rucker, & Hayes, 2007). As described below, this type of conditional process analysis incorporates the tenants of both mediation and moderation.

In 1986, Baron and Kenny outlined a multi-step process of mediation used to detecting indirect effects, now commonly referred to as mediation. The approach, labeled a “causal steps approach” indicated that mediator ( $M$ ) is a variable that accounts for the relation between a predictor and an outcome that have a demonstrated relationship, or direct effect. Simple mediation (see Figure 2) is demonstrated when (1) an independent variable ( $IV$ ) significantly predicts a dependent variable ( $DV$ ) directly (path  $c$ ), (2) the  $IV$  significantly predicts the  $M$  (path  $a$ ) and (3)  $M$  significantly predicts the  $DV$  (path  $b$ ) while controlling for the  $IV$  (path  $c'$ ). In Baron and Kenny’s original discussion, perfect mediation occurred if  $c'$  became non-significant when controlling for  $M$ . The authors proposed that through this series of regression analyses one could determine mediation; however, shortcomings in this approach have been identified (Preacher and Hayes, 2004; Zhao, Lynch, & Chen, 2010).

To address limitations to the causal steps approach, adaptations to the original approach and statistical tests for determining the significance of an indirect effect have been developed. For example, the Sobel test is a statistical method that is often used in conjunction with the causal steps approach to determine the significance of an indirect effect by comparing the strength of the indirect effect ( $a*b$ , or  $c-c'$ ) to a null hypothesis (Hayes, 2009; Sobel, 1986). More recently, bootstrapping techniques have been employed to address limitations of the Sobel test, namely that it assumes a normal sampling distribution of the indirect effect (Hayes, 2009).

Bootstrapping is used to create a sampling distribution of the indirect effect through resampling with replacement  $k$  times, mimicking the original sampling process. The paths within the indirect effect (i.e.,  $a$  and  $b$ ) are estimated and the product of the path coefficient is used for statistical testing of significance.

Bootstrapping approaches have also allowed for further adaptation of the causal steps approach set forth by Baron and Kenny. For example, in the original model mediation could only be tested in the setting of a demonstrated significant direct effect of the predictor on the outcome variable. This meant that even in the setting of an a priori theoretical rationale for an expected direct effect, if that was not demonstrated researchers were told to discontinue analysis (Hayes, 2009). Although the intention was to avoid identifying spurious mediators, this often resulted in the assumption of no indirect effect, this did not account for theoretical explanations for the lack of significant direct effect (Zhao et al., 2010). Therefore, currently it is considered acceptable to assess and identify mediation between variables even if the direct effect was not significant (Hayes 2009; Shrout & Bolger, 2002).

Moderation analysis aims to determine the extent to which the strength, size, or direction of the relationship between a given  $X$  and  $Y$  is influenced by a third variable of interest,  $W$  (Hayes, 2017; Cohen, Cohen, West, & Aiken, 1983).  $W$  is said to be a significant moderator if the effects are influenced by the inclusion of the variable and an interaction term ( $W \times X$ ) within the model. This is commonly termed as a significant interaction between  $X$  and  $W$ . The identification of moderators helps to establish the boundary conditions of the effect. For example, in a situation in which an effect is moderated by sex, the  $X$  variable may be significantly influential to an outcome among women but not men. Moderation has been established and demonstrated in countless studies across the field of psychology, including

demographic factors that moderate treatment completion for substance use disorders (Stahler, Mennis, and DuCette, 2016) and trauma exposure and addictive behaviors (Schimmenti et al., 2017).

The present study used the PROCESS macro, which includes bootstrapping techniques ( $k = 5000$ ) to yield a bootstrap confidence interval that allows investigators to state with a particular level confidence that the indirect effect is not zero (Hayes, 2009). Specifically, simple mediation analysis was used to test the indirect effect of FPC network on the relationship between PHA and performance on tests of EF. As with simple mediation originally described by Baron and Kenny (1986), the direct association between PHA and EF was determined (the  $c$  path). The indirect effects of the mediation variable (FPC coherence) was estimated in accordance with the process described above. In the event of a significant mediation model, we proposed to use a conditional process analysis to investigate the extent to which a moderator (alcohol use) effects the direct and indirect effects of PHA on EF (see Figure 1). Moderated mediation aims to assess the extent to which a variable,  $M$ , influences both the direct effect of  $X$  on  $Y$  and the indirect effect of  $X$  on  $Y$  (see figures 12.4 and 13.1 in Hayes, 2017). For the present study, we proposed to assess the interaction effects of PHA and reported alcohol use (PHA x Heavy Drinking) on FPC coherence and EF, respectively.

*Power Analyses.* In order to ensure that the available sample size will be sufficient to detect the hypothesized effects, power analyses were conducted with the G\*Power software package (Erdfelder, Faul, Lang, & Buchner, 2007). Power analyses indicated that a total sample of 392 participants would be needed to detect small effects ( $f^2 = .02$ ), 55 participants would be needed to detect medium effects ( $f^2 = .15$ ), or 25 participants to detect large effects ( $f^2 = .35$ ) for

linear multiple regression and mediation analyses with 0.80 power using a two-tailed alpha of 0.05.

## CHAPTER 3

### RESULTS

#### **Descriptive Statistics**

Sample characteristics are presented overall and stratified by self-reported PHA status in Table 2. The study sample comprised young adults between the ages of 22 and 35 from racially and ethnically diverse backgrounds. Individuals who reported PHA did not differ significantly from those who did not report PHA on any matched variable (age, gender, and racial or ethnic background). Groups differed significantly in their reported years of completed education, with individuals who reported PHA reporting significantly fewer years of formal education than non-PHA counterparts. All variables were normally distributed ( $\text{skew} < |1|$ ). All zero-order correlations pertinent to study variables can be found in Table 3, while partial correlations controlling for the effect of education are presented in Table 4.

#### **PHA and Executive Function**

To determine if PHA was negatively correlated with EF (Aim 1, Hypothesis 1), we assessed the relationships between PHA and performance on a pre-selected battery of EF tests including the NIH toolbox DCCS for cognitive flexibility, Flanker for inhibitory control, and List Sort for working memory. When controlling for the effects of years of education, no significant associations were observed between PHA and performance on the DCCS ( $r = -0.053$ ,  $p = 0.491$ ) or Flanker ( $r = -0.096$ ,  $p = 0.209$ ). Although zero-order correlations between PHA and performance on the List Sort were significantly inversely related ( $r = -0.150$ ,  $p = 0.048$ ), with those reporting a family demonstrating poorer performance on the task, this effect appeared

almost entirely attributable to participants' education and was no longer observed after controlling for education ( $r = -0.070, p = 0.364$ ).

Exploratory analyses examined whether gender impacted the effect PHA had on EF. Among women, the relationships between PHA and EF were similarly non-significant but demonstrated small effects in expected directions across tasks when controlling for the influence of education. Specifically, PHA was inversely related with performance on the DCCS ( $r = -0.119, p = 0.319$ ), Flanker ( $r = -0.158, p = 0.186$ ), and List Sort ( $r = -0.084, p = 0.486$ ), though none reached the threshold of statistical significance. The pattern of small inverse PHA effects observed among the women was weaker to negligible among the men included in the sample (DCCS:  $r = 0.001, p = 0.997$ ; Flanker:  $r = -0.051, p = 0.614$ ; List Sort:  $r = -.056, p = 0.583$ ).

### **PHA and FPC Network Coherence**

The frontoparietal control network demonstrated significant resting state functional coherence in the present sample. Node-to-node correlations calculated in functional connectivity analyses were significantly related to each other, suggesting that individuals' patterns of connectivity were consistent at the group level and across included nodes. Correlations between coherence values can be found in Table 3.

To determine if PHA was significantly inversely related to FPC network coherence (Aim 1, Hypothesis 2), we first examined its relation to the overall network coherence value. When controlling for the effect of education, PHA was significantly negatively correlated with overall network coherence among the four nodes of the FPC ( $r = -0.172, p = 0.023$ ), such that those who endorsed PHA demonstrated less coherence in the network as a whole.

To probe this overall effect, additional analyses examined how individual node-to-node coherence related to reported PHA. Of the six included node-to-node coherence values, three

were significantly inversely related with PHA. Specifically, coherence between the right PPC and right DLPFC ( $r = -0.190, p = 0.012$ ), left DLPFC and left PCC ( $r = -0.196, p = 0.010$ ) and right DLPFC and left PPC ( $r = -0.235, p = 0.002$ ) were significantly negatively correlated with PHA. The remaining node-to-node coherence values were not significantly related, including the right PPC and left DLPFC ( $r = -0.121, p = 0.111$ ), right PPC and left PPC ( $r = -0.037, p = 0.631$ ), and left DLPFC and right DLPFC ( $r = -0.058, p = 0.449$ ).

Exploratory analyses were also performed to examine the relationship between PHA and FPC network coherence stratified by gender. Among women, PHA and overall network coherence were not significantly related ( $r = -0.112, p = 0.350$ ). Consistently, none of the six node-to-node coherence values were significantly related to PHA. In men, however, overall coherence was significantly inversely related with PHA ( $r = -0.220, p = 0.027$ ), driven primarily by significant associations between PHA and coherence of the left DLPFC and left PCC ( $r = -0.247, p = 0.013$ ) and right DLPFC and left PPC ( $r = -0.290, p = 0.003$ ). The remaining node-to-node correlations were not significantly related with PHA: right PPC and right DLPFC ( $r = -0.180, p = 0.071$ ), right PPC and left DLPFC ( $r = -0.087, p = 0.386$ ), right PPC and left PPC ( $r = -0.062, p = 0.541$ ), and left DLPFC and right DLPFC ( $r = -0.104, p = 0.299$ ).

### **FPC Network Coherence and EF Performance.**

The direct relationship between FPC network coherence and EF across measures was assessed to determine the appropriateness for use in mediation models. FPC network coherence was not significantly related to performance on any of the included cognitive tests of EF, as shown in Table 3. Likewise, exploratory analyses stratified by gender did not reveal significant relationships between FPC coherence and EF performance on any administered tasks.

## **Alcohol Use and Study Variables**

To determine the potential modifying effect of participant's substance use on present analyses, an estimate of heavy alcohol use was calculated. Participants' reported frequency of heavy drinking was not significantly related to PHA, FPC network coherence, or performance on included cognitive tasks (Table 3).

## **Multiple Regression and Mediation Analyses**

Although study variables did not indicate the presence of a significant relationship between FPC coherence and EF, mediation analyses were conducted using PROCESS macros in SPSS (Hayes, 2012) to test Aim 3 with the benefit of bootstrapped resampling methods. Simple mediation models were computed to determine if overall FPC network coherence significantly mediated the relationship between PHA and EFs. Three models were used to evaluate the potential mediating role of network coherence in the relation between PHA and performance on each test of EF. Education was included as a covariate in all mediation models. Results are presented in Table 5.

For the DCCS, the overall model fit and total effect were non-significant ( $R^2 = 0.038$ ,  $F(3,171) = 2.236$ ,  $p = 0.058$ ). Findings for the Flanker test were similarly non-significant ( $R^2 = .012$ ,  $F(3,171) = 0.712$ ,  $p = 0.546$ ). Finally, for the List Sort test, overall model fit was significant ( $R^2 = 0.100$ ,  $F(3,169) = 6.275$ ,  $p = 0.001$ ); however, this was attributable to a significant contribution of education ( $B = 1.639$ ,  $p = 0.004$ ), rather than the direct effect of PHA or the indirect effect of network coherence.

As heavy alcohol use was unrelated to all study variables, no moderated mediation analysis was conducted.

## CHAPTER 4

### DISCUSSION

The present study examined the direct and indirect influence of PHA on performance on three measures of EF and resting state functional coherence of the FPC network in a sample of young adults. Although prior studies have demonstrated poorer EF among individuals with a PHA (Tapert & Brown, 2000; Nigg et al., 2004), no studies to date have examined the direct relationship between PHA and resting state FPC connectivity. Additionally, the present study extends approaches used in the existing literature by examining the indirect effect of FPC network coherence on the hypothesized relationship between PHA and EF. We first assessed whether PHA was inversely correlated with performance on three EF tasks (Aim 1, Hypothesis 1) and network coherence in the FPC (Aim 1, Hypothesis 2). Aims three and four represent the first known attempt to assess whether neural network coherence serves as a mediator of the relationship between PHA and EF.

Partial support for the hypotheses of Aim 1 was demonstrated in the present study. While PHA was not significantly inversely correlated with performance on any of the administered executive tasks (Hypothesis 1), those who reported PHA demonstrated less network coherence of the FPC network as a whole (Hypothesis 2). Multiple regression and mediation analysis were applied to test Aim 2 (Hypothesis 3); however, across all administered cognitive tasks, resting state FPC network coherence did not serve as a significant partial mediator of the relationship between PHA and EF. Finally, Aim 3 (Hypothesis 4) was not supported, as reported levels of heavy alcohol use were not significantly related to PHA, FPC coherence, or EF. Therefore,

moderation analyses were not completed. Overall, the present study demonstrated support for one study hypothesis, providing evidence that PHA results in altered network coherence among the four nodes of the frontoparietal control network, but results did not support the other hypotheses. Implications and possible explanations for these findings are discussed below

### **Parental History of Substance Abuse and Executive Functioning**

PHA was not significantly correlated with executive performance assessed using tests of cognitive flexibility, response inhibition, and working memory. This finding is surprisingly divergent from the existing literature, which has consistently demonstrated an inverse relationship between these variables in samples of adolescents and young adults (Lovallo et al., 2006; Nigg et al., 2006; Acheson et al., 2001; Gierski et al., 2013). Several factors may reconcile the present study's findings with prior findings. First, there is limited consistency across studies in terms of which tests are used to assess EF. For example, Lovallo and colleagues (2006) used the Stroop task to measure cognitive inhibition, while Nigg and colleagues (2006) used a version of a Stopping Task (Logan, 1994). While prior findings appear to be largely robust in the face of different EF measures, variability in measure selection may limit the generalizability to some EF assessments, including the NIH Toolbox subtests used presently. A second possible contributor is limited variability in EF performance in the present study. The sample included healthy young adults who were carefully vetted for inclusion in the HCP project. As exclusion criteria included neurodevelopmental disorders, severe psychiatric conditions, and medical/neurological disorders (Van Essen et al., 2013), some typical variability in executive performance that may have, in part, been related to PHA, may have been removed.

Although these factors may contribute to the discrepancy of present findings, results may also be a true representation of the relationship between PHA and EF performance in young

adults. Most of the existing literature on the effect of PHA on EF has been conducted in adolescents who are still in the midst of neural and cognitive development (Brown et al., 2000; Acheson et al., 2011; Saunders et al., 2008). Therefore, our sample of young adults may represent a different point of development at which PHA has less impact. Indeed, as early adulthood represents the culmination of frontal lobe development and expected optimization of EF (Conklin, Luciana, Hooper, & Yarger, 2007; Fuster, 2002; Jurado & Rosselli, 2007; Romise & Reynolds, 2005; Zelazo & Muller, 2002) variability in EF performance among healthy young adults may be lower than that of adolescent samples. Thus, it may be the case that individuals with PHA demonstrate early EF deficits, but are able to “catch up” with their peers in terms of neural and cognitive development as they age. This is consistent with the assertion that PHA may result in a prolonged period of neural development which can account for observed EF weaknesses in adolescents (Spadoni et al., 2008; Hingson et al., 2006; King & Chassin, 2007). Individuals with PHA may simply develop executive skills later in their developmental trajectories than peers without a family history of substance abuse.

Additionally, as years of education accounted for the observed link between PHA and performance on the working memory task, it may also be the case that access to external factors that support cognition, such as education, ameliorate the effect of PHA for some individuals, including those in the present sample. Although some prior studies examining the relationship between PHA and EF in adolescent samples control for years of education (Tapert et al., 2000), the contribution may be mitigated in adolescent samples given legal mandates to attend school in the United States. Thus, prior findings linking PHA to EF may be the result of differential engagement in the education system, but these findings are washed out as all students are assigned equal education levels based upon enrolment. Years of post-secondary education may

be a better estimate of the confounding effect of educational attainment given the increased freedom to select into ongoing education. Consistently, in another sample of young adults, level of academic achievement as measured by years of post-secondary education differed as a function of PHA (Lovallo et al., 2008), with those reporting PHA reporting less post-secondary education than peers without PHA. Future research is necessary to determine the extent to which development and other factors, such as education, contribute to this change.

A final point of interest related to PHA and EF is the discrepancy in gender suggested by findings in the present sample. Although findings did not reach the level of significance, women showed inverse effects that were small in magnitude but in the expected direction for tasks of cognitive flexibility and inhibition, while these effects among their male counterparts were approximately half or negligible. While we are cautious to not over-interpret these findings, this discrepancy suggests that gender may play a role in differentiating the effect of PHA on EF. This tentative interpretation is consistent with a several existing studies that have shown a similar pattern. Silveri and colleagues (2004) demonstrated that history of familial drug abuse impacted emotional and cognitive development to a greater degree in adolescent girls compared to boys. Similar findings have been demonstrated on other cognitive tasks, including decision-making (Petry, Kirby, & Kranzler, 2002), language, and attention (Tapert & Brown, 2000).

### **Neural Network Coherence of the FPC at Rest**

The existence of a FPC network that includes the bilateral PPC and DLPFC has been consistently demonstrated in task-based fMRI (Coull, Frith, Frackowiak, & Grasby, 1996; Dodds, Morein-Zamir, & Robbins, 2011) and in the resting state functional connectivity literature (Kong et al., 2013, Zanto & Gazzaley, 2013). During external EF task demands, these regions show a coherent increase in neural activity compared to baseline or neutral control tasks,

suggesting that both increased activity and synchronicity of the network are associated with EF (He et al., 2007). At rest, these regions remain in communication, demonstrating a continuous pattern of coherent activity despite being relatively suspended (Rosazza & Minati, 2011). Consistent with this literature, the present study demonstrated that node-to-node network coherence scores were significantly correlated in our sample, supporting the notion of a coherent FPC network that is synchronized at rest. Indeed, the medium to large effect sizes between node-to-node coherence values suggests that individuals who showed greater connection between two given nodes were likely to show similarly elevated synchronicity in other nodes.

In the present study, coherence of the FPC network at rest was significantly inversely related with PHA, such that those who reported PHA showed less overall coherence of the network than those who did not. This finding is consistent with our hypothesis, which was based on an existing literature that suggests decreased coherence throughout the brain, including regions of the FPC network in substance-naïve youth with PHA (Cservenka, Casimo, Fair, & Nagel, 2014; Mackiewicz Seghete, Cservenka, Herting, & Nagel, 2013; Wetherill et al., 2012). The observed relationship in our study provides further support that neural networks may be sensitive to PHA. As abnormal resting state functional connectivity has been linked to poorer performance on cognitive tasks (Chai et al., 2011; Cservenka et al., 2014; Fox, Snyder, Vincent, & Raichle, 2007; Mennes, Kelly, Zuo, Di Martino, Biswal, Castellanos, & Milham, 2010; Van Den Huevel, Stam, Kahn, & Pol, 2009), this may represent neural inefficiency; however, additional research is needed to better understand the relationship between decreased resting state connectivity and other outcomes of interest. Additionally, although the observed inverse relationship suggests a possible alteration in neural functioning, we cannot comment on whether this finding is related to an inherited biological predisposition to lowered connectivity, changes

in their environment as a result of PHA, or both. Nevertheless, these findings provide evidence that adds to an existing literature that has suggested changes in neural activity among individuals with PHA.

Exploratory analyses showed a discrepancy in the effect of PHA on network coherence as a function of gender. In contrast to the pattern of findings demonstrated in the relationship between PHA and EF, which showed a stronger link between PHA and EF in women than in men, it was the men that accounted for the overall significant relationship between PHA and lower network coherence. Indeed, no significant link between PHA and network coherence was demonstrated among the women sampled, while a significant inverse correlation between PHA and overall FPC coherence was seen among men. This was true despite a smaller sample size of men in the study ( $n = 74$ ). This finding suggests that men experience disruptions to neural activity as a function of PHA, while women may not. As men are disproportionately at risk for substance use disorders (Nolen-Hoeksema, 2004) this gender difference may implicate a yet unexplored neural vulnerability among men with PHA that may be unrelated to their EF.

It is notable that although overall network coherence was significantly inversely related, probing of individual node-to-node correlations revealed that only 3 of these 6 relationships were significantly related to PHA. This highlights a potential means of improving the specificity of future resting state functional connectivity studies of PHA. Although averaging the intensity values across nodes creates a mean value that serves as a useful index, with precedent (Nusslock et al., 2019) for simplifying network coherence, it may negate or wash out meaning differential inter-node effects. As efforts to link functional connectivity to behavior continue to increase, investigators may be better served by examining fewer and more targeted network node relationships in addition to an overall network estimate.

Although previous studies have linked FPC network activity to EF performance during both task-based (Thomas-Yeo et al., 2013) and resting state (Amboni et al., 2015; Seeley et al., 2007; Vincent et al., 2008) fMRI paradigms, in the present study resting state FPC coherence was unrelated to performance across EF measures of cognitive flexibility, response inhibition, and working memory. Lack of significant associations in this large neuroimaging sample refutes our hypothesis and suggests that resting state coherence in these regions may not be a useful marker of performance on behavioral EF assessments. This may be related to the fact that resting state functional coherence is not synonymous with levels of network activity when engaged and that networks do not work in isolation when they are engaged. Although the FPC continues to demonstrate synchronous activity at rest, suggesting continued coherence in the absence of a task, it is still relatively suspended (Greicius et al., 2003; Hasson, Nusbaum, & Small, 2009; Seeley et al., 2007; Smith et al., 2009). Therefore, even though we observed functional coherence in our sample suggesting that the intrinsic FPC network maintains synchronous “communication” at rest, the level of communication may not be representative of the effectiveness of the network as a whole to engage in EFs. Indeed, although coherence values in the sample were high, this addresses neither the efficiency of response of these regions to EF task demands nor how efficiently they interact with other networks such as emotion and motivation networks. Thus, present findings highlight an important limitation to the resting state functional connectivity approach, and speak to the importance of further investigations aimed at determining what network coherence at rest indicates about effectiveness of the network when recruited before drawing inferences about how it may be related to performance on cognitive tasks.

## **Hierarchical Regression and Mediation Analysis**

Initially hierarchical regression was proposed for this project to examine simple mediation and conditional (i.e., moderated) mediation of the PHA-EF relationship. Specifically, we aimed to determine whether 1) the relationship between PHA and performance on tasks of EF was partially mediated by FPC network coherence, and 2) whether this mediation would be significantly moderated by heavy alcohol use. Across all cognitive tasks, simple mediation was not supported. As mediation analyses were non-significant, moderated mediation was not conducted. Taken together, these findings suggest that coherence of the FPC at rest does not account for variability between PHA and EF in the present sample. Notably; however, education accounted for a significant amount of variance in predicting working memory performance in the final model. As education was related to lower PHA and positively correlated with performance on the working memory task, it is possible that education may serve as a mechanism by which PHA exerted influence on cognition in prior studies. In contrast, it also may be that education alone accounts for variability in performance on the included working memory task.

## **Strengths, Limitations, and Future Directions**

The present study has several strengths and limitations that warrant consideration. The sample in the present study was individually matched and large ( $n = 176$ ) compared to prior studies of resting state connectivity in those with and without PHA (Wetherill et al., 2011,  $n = 40$ ). Although well powered to detect medium and large effects, this study was underpowered to detect small effects, which may have resulted in Type II error for small effects. While Type II error is of great importance, it is also necessary to consider potential utility of detection of such small effects. This is particularly relevant when considering performance on tests of EF, for which typical variability around average scores is expected. As performance on cognitive tests

are considered primarily in reference to deviation from the average range, very small decrements in EF as a function of PHA may represent only subtle effects that would be unlikely to negatively impact everyday functioning. Thus, in the absence of extreme scores or performance deficits in the present sample, even significant small effects may have had limited real world utility.

Consideration is also given to the strengths and limitations of the recruited sample characteristics. Participants were heterogenous in terms of race ethnicity, though the dearth of individuals from Asian American/ Pacific Islander, and Hispanic backgrounds pose potential problems with generalizability. Additionally, as the HCP sample was comprised of healthy young adults, it is possible that those with cognitive deficits or severe substance use problems may have been excluded from the present analyses based on age or health status, thus restricting the range of the data tested. Similarly, these findings may not generalize to older adults. Finally, our sample was more female than male, which may limit generalizability, as evidence suggests that more men than women develop alcohol use problems (Nolen-Hoeksema, 2004; Wagner & Lloyd 2002). To address these limitations related to sampling, future studies may wish to sample individuals who are even more heterogeneous in terms race/ethnicity, current psychopathology and social functioning, as this may more accurately capture the picture of offspring of individuals with substance abuse histories. Furthermore, future studies may focus on examining samples that are equally split across gender or proportionate to base rates of alcohol use disorders.

An additional important limitation to consider in interpreting present findings was the simplicity of the self-report assessment of PHA. Although self-report measures have demonstrated reliability in assessing family history of psychiatric difficulties, with specifically

high levels of reliability and validity for substance use (Hardt & Franke, 2007; Weissman et al., 2000), the use of a dichotomous PHA variable in this study may have oversimplified a complex construct. Indeed, factors such as severity and duration of alcohol use and environmental changes related to substance abuse (e.g., family violence) have been shown to be uniquely predictive in understanding outcomes among individuals with PHA (Chermack, Stoltenberg, Fuller, & Blow, 2000). As such, future studies should probe additional factors related to parental use, as this may better explain variation in FPC coherence, as well as alcohol use and EF.

Finally, although resting state functional connectivity research is a promising technique, the findings from the present study suggest the need for caution when interpreting its association with neurocognitive function or behavior (e.g., impulsivity, substance use). Although a robust evidence base has found support for consistent networks that show coherence both at rest and when completing a task (Beckmann et al., 2005; Bressler & Menon, 2010; Buckner, Krienen, & Yeo, 2013; Cordes et al., 2000; Seeley et al., 2007; Van Den Heuvel & Pol, 2010), interpretation of the relationship between activity at rest and response while engaged in a targeted task remains unclear. Future studies may aim to quantify similarities and differences between task-based fMRI and resting state fMRI coherence in a given network, to elucidate how activation or suppression of these regions are related. Furthermore, although there is a growing body of research examining the relationships between resting state coherence and cognition, additional work is needed to determine if this truly can serve as a neurobiological marker of functioning when the system is engaged in a particular function. Continued development in this area may allow for the use of this relatively simple, low-stress, and efficient methodology to serve as a reliable and valid proxy for neural functioning.

## Conclusions

Broadly, results of this study add to the limited research base investigating the important relationship between familial substance use, neural functioning, and cognitive and behavioral outcomes. Despite its limitations, the present study was the first attempt to examine the intertwining relationships of resting state functional connectivity changes, PHA, and EF in a sample of generally healthy young adults. Our hypotheses were only partially supported with evidence that PHA accounts for a reduction in network coherence in the FPC network in men but not women. In contrast, we found no support for a statistically significant inverse relationship between PHA and EF in either men or women. Furthermore, network coherence did not significantly mediate the relationship between PHA and EF. Despite not supporting some of the study hypotheses, these findings hold value in several regards. First, decreased resting state coherence of the FPC as a function of PHA provides additional support to the existing literature suggesting that this reflects a neural vulnerability among individuals with parental history that is unrelated to their own use of alcohol. Further probing of this relationship may elucidate the mechanisms by which this influence is exerted. Regarding EF, findings of null effects in a racially/ethnically diverse and relatively large sample of young adults may indicate a true lack of influence of parental history after individuals have had the time to reach a point of neural maturation that supports peak executive functioning ability. As this differs from the findings in adolescents, this may speak to different developmental trajectories among those with PHA, as well as the potential influence of protective factors (e.g., education). Thus, the present study may serve as a basis for future research examining factors that support resilience in the setting of PHA.

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## APPENDIX

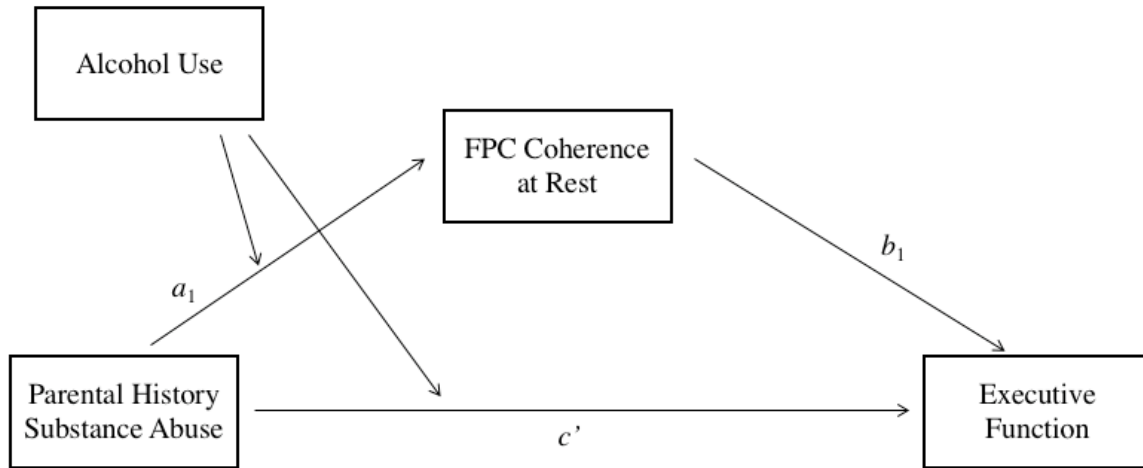


Figure 1. Proposed Model to Test Hypothesis Four

**Note.** Conceptual model of the conditional process analysis path diagram depicting the direct effect and causal paths linking parental history of substance abuse (PHA) to executive functioning as mediated by frontoparietal control network (FPC) coherence at rest as a function of alcohol use. Hypotheses predicted that PHA would be negatively related to FPC connectivity, which would be associated with poorer executive functioning (EF) performance on tests of cognitive flexibility, response inhibition, and working memory. We also hypothesized that alcohol use would moderate the relationship between PHA and EF, such that higher rates of reported drinking increases the impact of PHA on EF. Similarly, we hypothesized that higher rates of reported alcohol use would increase the impact of PHA on FPC connectivity, adding to this relationship.

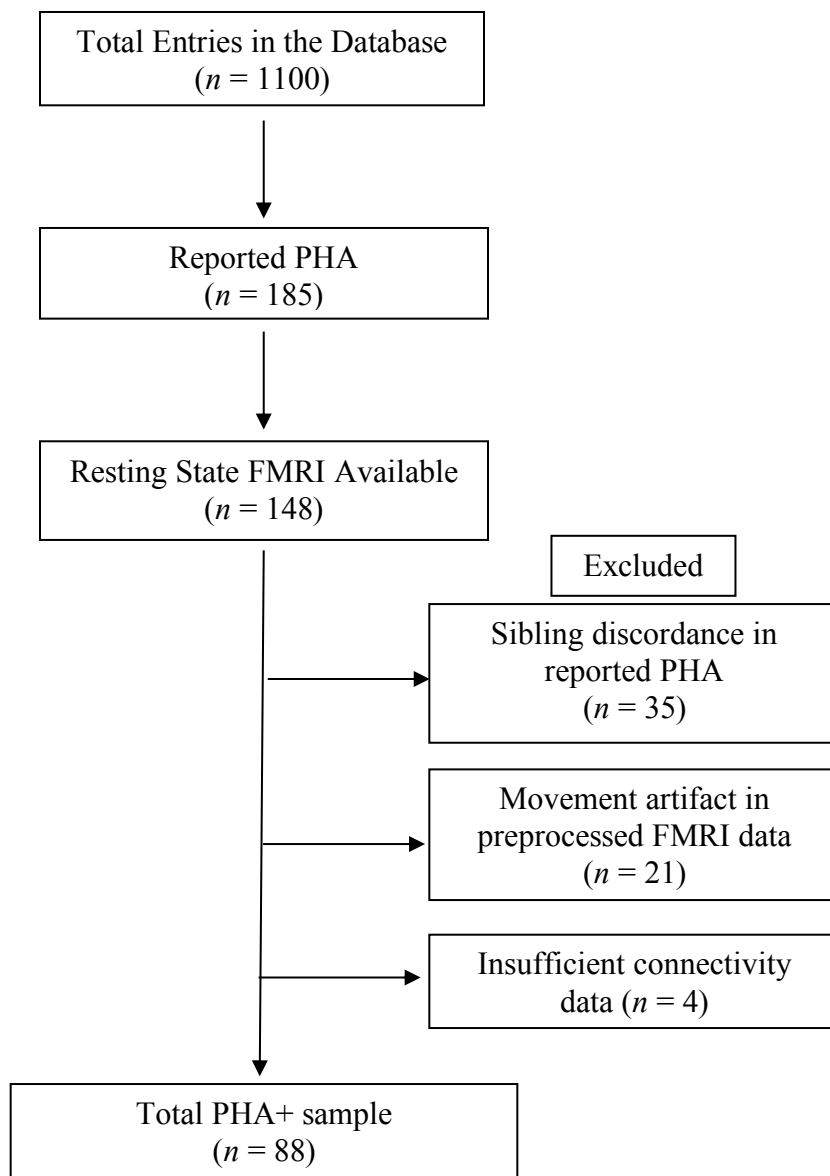


Figure 2. Flowchart of Participant Inclusion

**Note.** PHA = parental history of substance abuse; FMRI= functional magnetic resonance imaging. Sibling discordance was any sibling groupings in which a minority (<67%) endorsed a family history of parental substance abuse.

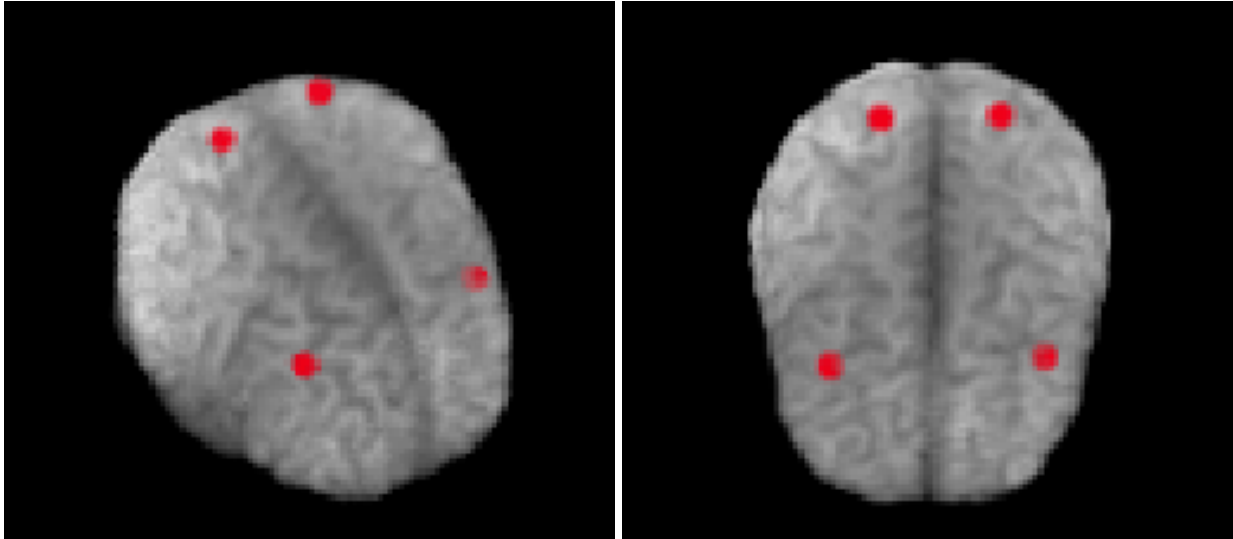


Figure 3. Regions of Interest Used to Quantify the Frontoparietal Control Network

*Note.* Names and locations of regions are presented in Table 1.

TABLE 1

## Coordinates for Frontoparietal Control Network Nodes

Region	x	y	z
L. Dorsolateral Prefrontal Cortex	-42	26	36
R. Dorsolateral Prefrontal Cortex	40	32	38
L. Posterior Parietal Cortex	-24	-64	58
R. Posterior Parietal Cortex	22	-62	58

*Note.* L = Left, R = Right. Coordinates were derived from the Neurosynth Database; presented in MNI space and represent center of 5 mm (19 voxel) sphere; LPI orientation

TABLE 2

## Descriptive Data for Study Variables

	Total Sample ( <i>n</i> = 176)	PHA+ ( <i>n</i> = 88)	PHA- ( <i>n</i> = 88)	<i>p</i> value ( <i>t</i> -test)	Effect size (Cohen's <i>d</i> )
<i>Biopsychosocial variables</i>					
Age (years: mean, <i>SD</i> )	29.2 (3.8)	29.4 (3.9)	29.0 (3.8)	0.409	0.123
Sex (N, %)				--	--
Female	102, 58%	51, 58%	51, 58%	1.000	0.000
Male	74, 42%	37, 42%	37, 42%	1.000	0.000
Race/Ethnicity (N, %)				0.863	0.086 <sup>+</sup>
White	113, 65%	56, 63.6%	57, 65%	0.875	0.012 <sup>+</sup>
Black/ AA	48, 27%	25, 28.4%	23, 26%	0.865	0.013 <sup>+</sup>
Asian/ Pacific Islander	6, 3%	3, 3.4%	3, 3.4%	1.000	0.000 <sup>+</sup>
Latinx/Hispanic	5, 2.8%	3, 3.4%	2, 2.2%	0.650	0.034 <sup>+</sup>
Multiracial	4, 2.2%	1, 1.1%	3, 3.4%	0.312	0.076 <sup>+</sup>
Education (years: mean, <i>SD</i> )	14.6, 2.0	14.0, 2.1	15.1, 1.7	0.000*	0.613
<i>Brain Activity</i>					
FPC Resting State Coherence	0.37 (0.16)	0.34 (0.15)	0.40 (0.17)	0.013*	0.374
<i>Cognition (mean, <i>SD</i>)</i>					
DCCS	101.5 (9.9)	100.5 (10.0)	102.5 (9.6)	0.181	0.204
Flanker	101.23 (9.5)	100.5 (10.5)	101.97 (8.4)	0.307	0.155
List Sort	102.3 (11.6)	100.6 (11.3)	104.0 (11.6)	0.048	0.297
<i>Alcohol Use</i>					
Heavy Drinking	5.17 (2.4)	5.27 (2.4)	5.06 (2.4)	0.568	0.088

**Note.** AA = African American; PHA = Parental history of substance abuse; Cognitive variables are age-adjusted scores. DCCS = Dimensional change card sort. Presented *p*-values and effect sizes are related to *t*-tests or chi-square tests. <sup>+</sup> = Cramer's *V*; \* *p* < 0.05

TABLE 3  
Zero-Order Bivariate Correlation Matrix for Study Variables

	PHA	FPC <sub>c</sub>	FPC <sub>1-2</sub>	FPC <sub>1-3</sub>	FPC <sub>1-4</sub>	FPC <sub>2-3</sub>	FPC <sub>2-4</sub>	FPC <sub>3-4</sub>	CS	FL	LS	Alc
PHA	1	-.173*	-.108	-.191*	-.038	-.087	-.189**	-.221**	-.102	-.077	-.150*	.045
FPC <sub>c</sub>		1	.742**	.721**	.727**	.767**	.741**	.776**	-.051	-.017	.098	.092
FPC <sub>1-2</sub>			1	.560**	.382**	.446**	.607**	.439**	-.095	-.115	.083	.064
FPC <sub>1-3</sub>				1	.355**	.407**	.400**	.682**	-.166*	-.090	.123	.044
FPC <sub>1-4</sub>					1	.543**	.315**	.393**	.041	.121	-.011	.153
FPC <sub>2-3</sub>						1	.469**	.487**	.045	.059	.135	.036
FPC <sub>2-4</sub>							1	.619**	-.007	-.096	.065	.016
FPC <sub>3-4</sub>								1	-.144	-.047	.082	.054
CS									1	.474**	.181*	.015
FL										1	.083	.151
LS											1	.025
Alc												1

*Note.* \*  $p < 0.05$ ; \*\*  $p < 0.01$ . FPC<sub>c</sub> = Frontoparietal control network coherence; FPC<sub>1-2</sub> = Right posterior parietal cortex and left dorsolateral prefrontal cortex coherence; FPC<sub>1-3</sub> = Right posterior parietal cortex and right dorsolateral prefrontal cortex coherence; FPC<sub>1-4</sub> = Right posterior parietal cortex and left posterior parietal cortex coherence; FPC<sub>2-3</sub> = Left dorsolateral prefrontal cortex and right dorsolateral prefrontal cortex coherence; FPC<sub>2-4</sub> = Left dorsolateral prefrontal cortex and left posterior parietal cortex coherence; FPC<sub>3-4</sub> = Right dorsolateral prefrontal cortex and left posterior parietal cortex coherence; Alc = heavy alcohol use.

TABLE 4

## Partial Correlations Controlling for Education

	PHA	FPC <sub>c</sub>	FPC <sub>1-2</sub>	FPC <sub>1-3</sub>	FPC <sub>1-4</sub>	FPC <sub>2-3</sub>	FPC <sub>2-4</sub>	FPC <sub>3-4</sub>	CS	FL	LS	Alc
PHA	1	-.172*	-.121	-.190*	-.037	-.058	-.196**	-.235**	-.053	-.096	-.070	.004
FPC <sub>c</sub>		1	.744**	.721**	.727**	.769**	.742**	.777**	-.057	-.016	.094	.097
FPC <sub>1-2</sub>			1	.561**	.382**	.452**	.607**	.439**	-.092	-.116	.096	.061
FPC <sub>1-3</sub>				1	.355**	.406**	.400**	.683**	-.174*	-.089	.119	.049
FPC <sub>1-4</sub>					1	.546**	.315**	.393**	.040	.122	-.014	.156*
FPC <sub>2-3</sub>						1	.471**	.491**	.026	.065	.108	.054
FPC <sub>2-4</sub>							1	.619**	.006	-.095	.066	.017
FPC <sub>3-4</sub>								1	-.144	-.048	.090	.053
CS									1	.491**	.135	.004
FL										1	.102	.116
LS											1	.068
Alc												1

*Note.* \*  $p < 0.05$ ; \*\*  $p < 0.01$ . FPC<sub>c</sub> = Frontoparietal control network coherence; FPC<sub>1-2</sub> = Right posterior parietal cortex and left dorsolateral prefrontal cortex coherence; FPC<sub>1-3</sub> = Right posterior parietal cortex and right dorsolateral prefrontal cortex coherence; FPC<sub>1-4</sub> = Right posterior parietal cortex and left posterior parietal cortex coherence; FPC<sub>2-3</sub> = Left dorsolateral prefrontal cortex and right dorsolateral prefrontal cortex coherence; FPC<sub>3-4</sub> = Right dorsolateral prefrontal cortex and left posterior parietal cortex coherence; Alc = heavy alcohol use.

TABLE 5

Path analyses of the associations between PHA, FPC coherence, and EF

5A. Cognitive Flexibility		
<b>Paths</b>	<i>B (SE)</i>	<i>95%CI of B</i>
<b>Direct Effects</b>		
PHA → CF	-1.145 (1.571)	[-4.245, 1.955]
PHA → FPCc	-0.056 (.024)	[-.104, -.008]*
FPCc → CF	-4.226 (4.892)	[-13.882, 5.431]
<b>Indirect Effect</b>		
PHA → CF	.236 (.308)	[-.336, .914]
5B. Response Inhibition		
<b>Paths</b>	<i>B (SE)</i>	<i>95%CI of B</i>
<b>Direct Effects</b>		
PHA → CI	-1.986 (1.531)	[-5.007, 1.036]
PHA → FPCc	-0.055 (.024)	[-.102, -.008]*
FPCc → CI	-2.052 (4.789)	[-11.507, 7.402]
<b>Indirect Effect</b>		
PHA → CI	.112 (.304)	[-.565, .705]
5C. Working Memory		
<b>Paths</b>	<i>B (SE)</i>	<i>95%CI of B</i>
<b>Direct Effects</b>		
PHA → WM	-1.429 (1.785)	[-4.952, 2.094]
PHA → FPCc	-0.052 (.024)	[-.099, -.004]*
FPCc → WM	6.002 (5.610)	[-5.073, 17.077]
<b>Indirect Effect</b>		
PHA → WM	-.310 (.349)	[-1.158, .210]

Note: \*  $p < 0.05$ ; PHA = parental history of substance abuse; FPC = frontoparietal control network coherence; EF = executive functioning; CF = cognitive flexibility; CI = cognitive inhibition; WM = working memory