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Influence of Alcohol on Cognitive Functioning and Neural Functional Connectivity in Adolescents

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

Thanh Tam Thi Nguyen-Louie

Committee in charge:

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2018

The Dissertation of Thanh Tam Thi Nguyen-Louie is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

Chair

University of California, San Diego

San Diego State University

2018

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ABSTRACT OF THE DISSERTATION

Influence of Alcohol on Cognitive Functioning and Neural Functional Connectivity in Adolescents

by

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Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2018

San Diego State University, 2018

Professor Susan F. Tapert, Ph.D., Chair

Rationale: Neurodevelopment may be shaped by environmental factors such as alcohol intake. More than 20% of U.S. high school students began drinking before age 14. Adults who initiated drinking before age 14 are four times more likely to develop

psychosocial and psychiatric difficulties than those who began drinking after turning 20. Little is known, however, about how the age of alcohol use onset influences brain development.

Design: This study prospectively examined the effects of alcohol use onset age on neurocognitive functioning in healthy adolescent drinkers. Youth underwent a neuropsychological battery and neuroimaging session at baseline (M = 13.6 years-old, SD = 0.8), before substance use initiation, and at follow-up (M = 20.2 years-old, SD = 1.5), to evaluate changes in frontoparietal context-dependent functional connectivity (cdFC) during a visual working memory task, and neuropsychological performance. Hierarchical linear regressions examined if earlier ages of onset for first and regular alcohol use adversely influenced neurocognition and functional connectivity, above and beyond baseline neurocognition, substance use severity, and familial and social environment factors.

Results: As hypothesized, an earlier age of first drinking onset predicted poorer performances in psychomotor speed and visual attention (ps<.05; N = 215) and an earlier age of weekly drinking onset predicted poorer performances in cognitive inhibition and working memory, controlling for baseline neuropsychological performance, drinking duration, and past-year marijuana use (ps<.05; N = 127). Age of first and regular drinking onset did not significantly predict follow-up frontoparietal cdFC. Exploratory whole brain analyses suggested that, as hypothesized, earlier ages of regular drinking onset were associated with higher cdFC between subcortical and fronto-temporal areas, and linked to poorer neuropsychological performance.

Conclusion: This was the first study to assess the association between age of onset on neurocognition and cdFC in adolescents. Initiation of any or weekly alcohol use at younger ages are risk factors for poorer neuropsychological functioning and subcortical-cortical hyper-connectivity. This may have important implications for public policies related to the legal drinking age and prevention programming, as this study suggests that early onset of drinking increases risk alcohol-related neurocognitive vulnerabilities. Further studies are needed to replicate these preliminary findings.

CHAPTER 1: INTRODUCTION

1.1 Adolescence is a Period of Crucial Brain Development

Although the human brain reaches 90% of its full size by age six (Reiss, Abrams, Singer, Ross, & Denckla, 1996), structures continue to develop and mature throughout adolescence and into adulthood. Regions associated with primary functions (e.g., movement and sensory performances) are the first to reach maturity (Toga, Thompson, & Sowell, 2006), while those involved in higher-order cognitive functioning (e.g., decision making and impulsivity) do not reach full maturity until late adolescence and into adulthood (Gogtay et al., 2004). Brain development begins with posterior and inferior structures and proceed anteriorly and superiorly (Huttenlocher, 1979; Sowell, Trauner, Gamst, & Jernigan, 2002). During this crucial developmental period, cortical and subcortical structures are refined and re-organized as changes in gray and white matter take place.

There is marked heterogeneity in the linear and curvilinear relationship between age and volume in cortical and subcortical structures (Østby et al., 2009). Throughout adolescence and into adulthood, gray matter volume in the basal ganglia decreases linearly with age, while structures implicated in memory and emotions (i.e., hippocampus and amygdala) exhibit an increasing curvilinear relationship, reaching developmental asymptote around early to mid-20 years (Giedd, 2004). At the same time, cortical gray matter follows an inverted U-shaped pattern of development, such that an initial increase in volume is followed by a period of decreased volume before reaching full maturation. Evidence suggests that the increased volume reflects active synaptogenesis and arborization rather than the creation of new neurons (Shaw et al., 2006). After structures

reach their peak sizes, unnecessary and unused connections are selectively pruned and eliminated (Tamnes et al., 2010). The occipital and parietal lobes show peak cortical thinning, a marker of maturation, earlier in life compared to frontal and temporal regions. In the occipital and parietal lobes, cortical thinning reaches asymptote in the early-20s, whereas temporal and frontal regions appear to continue changing until late-20s and 30 years old (Østby et al., 2009). Different modalities suggest that frontal areas take the longest to reach maturation; peak cortical thickness is reached at 25 years old, and white matter reaches full development in the early-30s. In comparison, the parietal and occipital lobes reach peak cortical thickness at 20 years old, but white matter maturity does not peak until mid- to late-20 years of age for these regions (Somerville, 2016).

Along with these neurostructural changes, adolescents exhibit better performances in higher-order cognitive domains such as memory, executive function, and visuospatial integration over time (for review, see Bava & Tapert, 2010). Supporting the development of these functions are increases in effective functional connectivity between the frontal and parietal areas from ages eight to 27 (Hwang, Velanova, & Luna, 2010). Together, evidence suggests that neurodevelopment in adolescence is not a passive nor predetermined process. Neuronal proliferation and pruning are likely to be intricately linked to environmental factors in which new synapses are formed and strengthened to accommodate learned materials. Importantly, experiences play a critical role in determining which circuits are used or not (Greenough, Black, & Wallace, 1987).

One such factor is alcohol. Considering the plasticity of the brain in response to environmental perturbations, alcohol may interact with, and disrupt, certain neurodevelopmental processes during adolescence. The effects of alcohol use are further

compounded by different maturation rates of brain structures subserving lower- versus higher-order cognitive functions (Somerville, 2016). The prematurity of structures implicated in emotional regulation and decision making likely places adolescents at an increased risk of forming maladaptive drinking behaviors (Casey, Jones, & Hare, 2008; Spear, 2000). These behaviors may then in turn further influence neural and structural changes in order to compensate for alcohol toxicity, creating a feedback loop of alcohol use behaviors and neural compensatory changes.

1.2 Alcohol Use in Adolescence

Alcohol is typically the first intoxicant a person tries in life and is the most commonly used drug among youth (Johnston, O'Malley, Miech, Bachman, & Schulenberg, 2017). In 2016, 23% of adolescents have tried alcohol by 8th grade and 61% by the end of high school. Drinking to intoxication increases at a similar rate, with 9% by 8th, 26% by 10th, and 46% by 12th grade (Johnston et al., 2017).

Although the rate of alcohol use among adolescents has decreased over the past decade (Johnston et al., 2017), of particular concern are the early ages in which adolescents initiate drinking. One in five United States (U.S.) high school students begin drinking before age 13 (Eaton et al., 2012; SAMHSA, 2013). In 2012, over 3% of U.S. drinkers aged 12 or older tried alcohol for the first time within the past year, averaging to about 12,600 new initiates each day (SAMHSA, 2013). In 2015, this has increased to 13,000 new initiates daily, half of whom are adolescents between 12-17 years of age. This initiation rate is twice that of the second most common intoxicant, marijuana (Lipari, Williams, Copello, & Pemberton, 2016). The average age of first alcohol use among individuals aged 12-49 in the U.S. was 17.6 in 2015, slightly older compared to

prior years (e.g., 17.4 in 2014). There is currently no published national data on the average age of first weekly alcohol use (i.e., the age at which youth begin drinking at least once a week). An earlier age of alcohol use onset is associated with increased likelihood of developing a substance use disorder (SUD), as 16% of adults who first drank before 14 years old eventually develop alcohol use disorder (AUD), compared to 4% who initiate after 18 (SAMHSA, 2013). Initiation of alcohol use at an earlier age is associated with more psychosocial difficulties (Falk, Yi, & Hilton, 2008; Hawkins et al., 1997; Shrier, Emans, Woods, & DuRant, 1997) and increased risk for psychiatric disorders (Kessler et al., 1997; Rohde, Lewinsohn, & Seeley, 1996; SAMHSA, 2013).

1.3 Adolescent Drinking and Neural Structure

Alcohol use in adolescence is associated with a range of neurobiological and cognitive changes that play a critical role in white matter development and maintenance. Using magnetic resonance imaging (MRI), reduced global white matter volume was found in youth with AUD, most prominently in the prefrontal cortex, a region implicated in higher-order cognitive abilities that include planning and impulsivity (De Bellis et al., 2005). Further, teens with AUD exhibit smaller hippocampal volume than non-drinking counterparts (De Bellis et al., 2005; Nagel, Schweinsburg, Phan, & Tapert, 2005). Controlling for age, ethnicity, sex, and supratentorial volume, more past-year binge drinking episodes predicted smaller frontal and parietal cortical thickness, and greater number of lifetime drinks predicted smaller central white matter volumes, larger temporal cortical volumes, and thicker insular cortex in a multisite nation-wide sample of U.S. adolescents (Pfefferbaum et al., 2016). Diffusion tensor imaging elucidates white matter fiber tract health and connectivity, providing quantifications linked to white matter

integrity. Higher fractional anisotropy and lower mean diffusivity values are associated with healthier myelination (Pierpaoli & Basser, 1996). Adolescent drinkers show indications of poorer integrity in large white matter tracts, including the corpus callosum, and in cerebellar, frontal, temporal, and parietal regions (Bava et al., 2009; McQueeny et al., 2009).

A younger age of onset and higher lifetime drinking duration years have independently predicted smaller bilateral hippocampal volume (De Bellis et al., 2000). Importantly, larger quantities of peak consumption are associated with smaller prefrontal cortices (De Bellis et al., 2005). Among drinkers ages 16-19, higher recent maximum drinks, consumed on an occasion significantly predicted lower gray and white matter volumes in the left hemisphere and lower gray matter volume in the right hemisphere (Lisdahl, Thayer, Squeglia, McQueeny, & Tapert, 2013). Results remained the same, even after accounting for other potential confounds such as intracranial volume, mental health (e.g., depressive symptoms), family history, and other substance use (e.g., marijuana).

Cross-sectional studies, such as those described above, suggest that alcohol use may influence the developing brain, but they do not account for pre-drinking differences. Longitudinal studies are now exploring this (e.g., Luciana, Collins, Muetzel, & Lim, 2013). At baseline, when all participants were non-drinkers, youth who later transitioned into heavy drinking had smaller volumes in the right rostral and caudal anterior cingulate, ventrolateral prefrontal cortex, and left isthmus cingulate regions, and lower white matter in the right cerebellar hemisphere (Squeglia et al., 2014). At the three-year follow-up, youth who initiated heavy drinking showed greater reductions (i.e., from intra-individual

baseline volumes) in the left ventral diencephalon, inferior and middle temporal gyri, caudate, and overall brain stem. Between 12-24 years of age, youth who transitioned into heavy drinking undergo an accelerated trajectory of gray matter reduction in frontal and temporal areas and reduced white matter in the corpus callosum and pons compared to those who remained non-drinkers (Squeglia et al., 2015). Similar pre-existing differences in brain structure and post-drinking changes have been reported in monozygotic twins, suggesting important and interrelated roles of environment and biology (Wilson, Malone, Thomas, & Iacono, 2015).

1.4 Adolescent Drinking and Cognition

Alcohol use appears to have a lasting effect on multiple neuropsychological domains. Adolescent drinkers, compared to controls, show poorer performances on tasks of attention (Boelema et al., 2016; Tarter, Mezzich, Hsieh, & Parks, 1995; Thoma et al., 2011), memory (Brown, Tapert, Granholm, & Delis, 2000), information processing (Tarter et al., 1995), visuospatial functioning (Beatty, Hames, Blanco, Nixon, & Tivis, 1996; Sher, Martin, Wood, & Rutledge, 1997), language abilities (Moss, Kirisci, Gordon, & Tarter, 1994), motor speed (Ferrett, Carey, Thomas, Tapert, & Fein, 2010) and executive functioning (Glenn & Parsons, 1992; Montgomery, Fisk, Murphy, Ryland, & Hilton, 2012; Moss et al., 1994). Controlling for pre-drinking performances, youth who drink 10 or more drinks in one occasion may be at greater risk for poorer functioning in verbal learning and memory compared to moderate drinkers who consume less than five drinkers per occasion (Nguyen-Louie et al., 2016). Importantly, learning and subsequent short- and delayed- cued and recall memory of a word list were negatively associated with estimated peak drinking occasion acute blood-alcohol level.

Drinkers 18-20 years old, with longer durations of lifetime use, exhibit poorer performances on tasks of visuomotor coordination (Trails A) and mental flexibility (Trails B) (Day, Celio, Lisman, Johansen, & Spear, 2013). Controlling for age and education, non-AUD drinkers performed *worse* than adolescents with AUD in visuospatial construction tasks at baseline. After ten years, performance remained stable for controls, while AUD youth show significantly poorer functioning and ultimately, performed significantly worse than controls at follow-up. This has been interpreted to suggest that continued problematic alcohol use may be related to greater and more rapid declines in cognitive performance in heavy drinkers (Hanson, Medina, Padula, Tapert, & Brown, 2011). Supporting this notion, recent (i.e., three months) withdrawal symptoms have been associated with poorer performances in verbal learning and memory, namely short and long delayed recall and recognition memory (Hanson, Cummins, Tapert, & Brown, 2011).

A recent prospective study examined the linear quantitative relationship between 11 individual substance use behaviors (e.g., past-year and 3-month frequency and quantity, post-drinking effects) and 19 neuropsychological task variables, controlling for age, socioeconomic status (SES), gender, drinking status (i.e., control, moderate, heavy drinkers), and baseline cognitive functioning in 234 participants (Nguyen-Louie, Castro, Squeglia, Brumback, & Tapert, 2015). More past year heavy episodic drinking days, more overall drinking days, and higher maximum drinks per occasion were predictive of poorer follow-up verbal memory. More past month alcohol use days predicted poorer visuospatial performance, and more instances of hangover/post-drinking effects predicted poorer performance in psychomotor speed. Together, these results suggest that youth

with sub-diagnostic alcohol use symptomology may still be at risk for developing subtle, but detectable, neuropsychological changes after alcohol use begins and escalates. This is an important public health consideration. In 2012, 43% of youth aged 12-25 reported current alcohol use, but only 9% met criteria for AUD (SAMHSA, 2013). It is possible that young drinkers who do not meet diagnostic criteria for AUD (American Psychiatric Association, 2000) may still exhibit subtle cognitive difficulties.

1.5 Adolescent Drinking and Neural Activation

Differences in neural activation in adolescent drinkers compared to controls have been documented using several behavioral tasks, including spatial working memory (SWM) and visual working memory (VWM). SWM tasks examine networks that include the premotor cortex, dorsolateral prefrontal cortex (DLPFC), ventrolateral prefrontal cortex, anterior frontal lobe, parietal cortex, and cerebellum (Cohen et al., 1997; Owen, McMillan, Laird, & Bullmore, 2005). Despite performing at a similar level to controls in accuracy and reaction time, AUD teens (15-17 years old) exhibit greater task-related blood oxygen level dependent (BOLD) responses, suggesting that adolescent heavy drinkers recruit more neural resources to perform at the same level as controls. More drinks consumed and more withdrawal symptoms in the past three months predicted greater SWM BOLD response in the left frontal, right caudate, left temporal and left cerebellar regions (Tapert et al., 2004b). Similarly, young adult binge drinkers show more activation bilaterally in the pre-supplementary motor area during a VWM task than non-binge drinkers (Campanella et al., 2013). It is possible that the effects of alcohol on neural activation changes with age and with heavier engagement in drinking (Tapert et al., 2004b), which underscores the importance of examining and controlling for pre-

drinking neural activity in longitudinal designs.

1.6 Age of Drinking Onset and Neurocognition

Evidence strongly suggests an unfavorable trajectory of cognitive development for adolescent drinkers. Imaging studies have identified numerous brain areas implicated in alcohol use. The literature suggests that areas involved in higher-order cognitive functioning appear most at risk, possibly because these areas have not reached full maturity by adolescence (Squeglia, Jacobus, & Tapert, 2009). The hippocampus, cerebral cortex, prefrontal cortex, and white matter are especially vulnerable (Bava et al., 2009; De Bellis et al., 2005; Nagel et al., 2005). Adolescence is an important period for experience-dependent maturation of fronto-cortical areas and their interconnections (Ernst & Fudge, 2009; Petanjek et al., 2011). Disruption to areas responsible for learning, memory, and executive function may produce a feed-forward loop that further increases drug-seeking behavior, such as increased impulsivity and poor decision making (Jennison, 2004).

It has been suggested that adolescence is a critical period for alcohol-related neural vulnerabilities, evidenced by decreased sensitivity to the adverse social and behavioral aspects of alcohol use coupled with increased sensitivity to its neurotoxic effects (Crews, Vetreno, Broadwater, & Robinson, 2016). In rodents, adolescents show decreased sensitivity to sedation, social inhibition, motor impairment, withdrawal, and taste aversion effects of alcohol (Doremus, Brunell, Varlinskaya, & Spear, 2003; Silveri & Spear, 1998; Varlinskaya & Spear, 2002; White et al., 2002). In general, adolescent drinkers are less likely to experience the negative pharmacological and social effects of acute alcohol intoxication, a mechanism that, in adults, likely serves as experiential

feedback to curb maladaptive drinking patterns (for review, see Crews et al., 2016). Further, adolescents may be at increased vulnerability for neurotoxic effects of alcohol. For example, ethanol dose-dependently reduces dendritic pruning in the somatosensory cortex (Chandler, 2003) and neurogenesis in male adolescent rats in the forebrain and hippocampal areas while increasing widespread neuronal apoptotic markers (Crews, Mdzinarishvili, Kim, He, & Nixon, 2006; Morris, Eaves, Smith, & Nixon, 2010).

Considerably less is known about how the age at which an individual begins drinking influences subsequent brain development and neurocognitive functioning. To date, six studies on the relationship between age of onset and neurocognition outcome have been published with mixed findings (Bjork, Hommer, Grant, & Danube, 2004; De Bellis et al., 2000; Demir, Ulug, Ergun, & Erbas, 2002; Joos et al., 2013; Kist, Sandjojo, Kok, & van den Berg, 2014). Among adolescent drinkers who begin drinking at 10-16 years old, an older age of alcohol use onset predicted significantly decreased resting-state functional connectivity between the bilateral nucleus accumbens and right DLPFC, inferior parietal lobule, dorsomedial prefrontal cortex, and left middle temporal gyrus (Weissman et al., 2015). An older age of AUD onset is associated with larger hippocampal volumes (De Bellis et al., 2000), suggesting that late onset may be better for brain development than early onset. However, among adult drinkers, those with an early age of AUD onset (<25 years old) performed better than those with late onset (≥ 25 years old) on tests of executive functioning, memory, and attention (Joos et al., 2013). Yet another study found no difference in cognitive performance among individuals with early, late, and very late (≥ 45 years old) AUD onset (Kist et al., 2014). Similarly, Bjork et al. (2004) reported that in adults, age of heavy drinking onset (defined as having

consumed 90 drinks in one month) was negatively correlated with years of heavy drinking, self-reported impulsivity, and aggressive behaviors, but was not significantly related to a measure of immediate and delayed memory. Compared to non-AUD controls, adults with alcohol dependence showed reduced frontal perfusion and poorer performances on tasks of novel-problem solving (i.e., Wisconsin Card Sorting Task), visual memory, and spatial attention (i.e., Wechsler Memory Scale Visual Reproduction and Spatial Span subtests). However, no differences were found in cerebral blood flow and neurocognitive performance among individuals with early AUD onset (i.e., diagnosed with alcohol dependence by 20 years old) and late AUD onset (i.e., diagnosed with alcohol dependence after 20 years of age) (Demir et al., 2002).

A recent study (Boecker-Schlier et al., 2016) examined the effects of pubertal (i.e., consumed first drink at Tanner stages 2-3.9, *M*=13.5 years old) and post-pubertal (i.e., consumed first drink at Tanner stages ≥4, *M*=15.0 years old) drinking onset on reward processing in healthy adults. Compared to individuals with post-pubertal onset, those who begin drinking at or before puberty showed decreased functional MRI (fMRI) activity in frontal cortical regions during reward anticipation and increased activity in the left caudate during reward delivery. To date, only two studies have examined age, or analogous pubertal stage, of drinking onset as a continuous variable (De Bellis et al., 2000; Weissman et al., 2015). Others have treated all onset age before 25 years (or in one study, before 20 years (Demir et al., 2002)) as a single category, so the marked physical, behavioral, psychosocial, and neuromaturational changes that occur throughout adolescence and emerging adulthood are not fully considered. Important differences in performance and neurostructure as a function of onset age may have been overlooked

(Giedd, 2004; Østby et al., 2009; Reiss et al., 1996; Somerville, 2016).

To date, no prospective study has examined the influence of age of first drinking onset (i.e., the age of first consuming at least one standard drink) on adolescent neurocognitive functioning. Importantly, few studies have examined age of onset as a continuous quantity rather than as early, late, and very late onset groups. When examining age of first drinking onset (AFDO), one must consider the variability in drinking trajectory among youth. For example, an individual who consumed her first drink at 14 years old and has less than 10 drinking occasions per year is likely at lower risk than a counterpart who initiated at 14 years old and has 52 drinking occasions per year. In this example, both individuals have the same AFDO, but dissimilar drinking patterns. Further, youth who tried alcohol once and thereafter abstain from drinking are not expected to show the same neurocognitive changes as continuous drinkers, even among those with equivalent AFDOs. Thus, in addition to examining AFDO as a predictor of neurocognition in adolescent drinkers, it may be relevant to examine the age of *regular* drinking onset (i.e., the age at which an individual first begins drinking on a regular, or weekly, basis) (Brown et al., 1998). Youth who have initiated ongoing patterns of alcohol use are at greater risk for psychosocial difficulties than occasional drinkers, as evidenced by increased rates of conduct disorder, negative drinking consequences, and other substance use (Grant et al., 2005; Pechansky, Szobot, & Scivoletto, 2004). Considering the dynamic neuromaturational processes taking place throughout adolescence, it is crucial to understand if, and how, alcohol-related neurotoxicity may be influenced by the age at which youth begin drinking. Examination of both first and weekly drinking onset ages will allow for a more comprehensive

understanding of how such effects may differ for individuals who recently initiated drinking versus sustained moderate-heavy drinkers.

1.7 VWM Tasks for Understanding Neurodevelopment

The current study utilized a VWM task (Luck & Vogel, 1997) to explore the impact of AFDO and age of weekly drinking onset (AWDO) on neurocognition. Working memory continues to develop and mature throughout adolescence and into adulthood (Crone, Wendelken, Donohue, van Leijenhorst, & Bunge, 2006; Isbell, Fukuda, Neville, & Vogel, 2015), providing an important construct for understanding the effects of alcohol use on neurodevelopment. The neural basis of VWM has been explored in detail (Benn et al., 2014; Christophel & Haynes, 2014; Courtney, Ungerleider, Keil, & Haxby, 1996; Fougnie & Marois, 2006; Smith & Jonides, 2003; Ungerleider, Courtney, & Haxby, 1998) and involves lower-level cognitive processes and higher-order functions, including attention, processing speed, and goal-oriented behaviors (Christophel & Haynes, 2014; Tapert et al., 2001; Wager & Smith, 2003).

Compared to fixation trials, active engagement in the task has been associated with increased neural response in visual object recognition regions (i.e., frontal eye field, inferior temporal gyrus, premotor, and occipital regions), DLPFC, and parietal regions (Berryhill & Olson, 2008; Pessoa, Gutierrez, Bandettini, & Ungerleider). Prefrontal regions appear key to successful completion of VWM trials, as monkeys with lesions to the DLPFC exhibit significantly impaired performances (Bauer & Fuster, 1976), and single-cell recordings show that prefrontal neurons respond specifically to the presentation and offset of stimulus in VWM tasks (for review, see Funahashi, 2006; Miller, Erickson, & Desimone, 1996). The involvement of both frontal and parietal

regions appears critical for optimal VWM functioning. For example, neuronal firing activity in the parietal and frontal lobes are decreased by 30% if either region is rendered non-functional during a memory saccade task in monkeys (Chafee & Goldman-Rakic, 2000).

Cross-sectional studies have shown that adolescent drinkers appear to perform more poorly on VWM tasks (Paulus, Tapert, Pulido, & Schuckit, 2006; Tapert, Pulido, Paulus, Schuckit, & Burke, 2004a). Binge drinkers, compared to controls, have shown greater activation in frontal and parietal regions to this task (Campanella et al., 2013; Maurage, Bestelmeyer, Rouger, Charest, & Belin, 2013; Schweinsburg, Schweinsburg, Nagel, Eyler, & Tapert, 2011). Heavy drinkers showed differential activation patterns to high versus low VWM conditions in frontal, parietal, and occipital regions compared to controls, after accounting for baseline activation differences (Squeglia et al., 2012). Thus, a parametric VWM task with varying working memory load conditions serves as an ideal paradigm to explore the relationship between alcohol use and neurocognition, as it has been shown in prior studies to involve brain areas that may be particularly vulnerable to adolescent drinking (Wetherill et al., 2012; Wetherill, Castro, Squeglia, & Tapert, 2013).

Much prior research on the influence of alcohol on adolescent neurocognitive functioning has focused on BOLD task-based activation patterns, while the association between adolescent drinking and functional connectivity remains to be explored in detail. Adolescent frontoparietal circuitry may be particularly vulnerable to the neurotoxic effects of alcohol, as seen with tasks of inhibition (Dodds, Morein-Zamir, & Robbins, 2011; Fassbender et al., 2006), working memory (Tapert et al., 2004b; Wager & Smith, 2003), and processing speed (Walter & Dassonville, 2011). In response to a VWM task,

heavy-drinking teens show greater activation in frontoparietal areas (i.e., bilateral middle frontal gyrus and right inferior parietal lobe) than non-drinking controls (Wetherill et al., 2013), suggesting a possible link between frontoparietal circuitries and alcohol exposure.

1.8 Summary

Compared to non- and light-drinking controls, heavy drinkers show differences in neuropsychological performance and task-based neural activation patterns. However, there is a gap in the literature on the prospective influence of age of first drinking onset and, perhaps more importantly, age of regular, or weekly, drinking onset on later neurocognitive functioning in adolescents. This study aimed to longitudinally examine the influence of AFDO (onset ages 10-20; follow-up ages: 18-25) and AWDO (onset ages 14-23; follow-up ages: 18-26) on follow-up neuropsychological performance and context-dependent functional connectivity (cdFC) between the DLPFC and posterior parietal cortex (PPC) during a VWM task (Besseling et al., 2012) (see Table 1), while controlling for baseline neuropsychological performance and cdFC and other potential biological and environmental confounding factors.

Higher AFDO and AWDO (i.e., older ages of first and weekly drinking onset) were hypothesized to linearly predict better performances in neuropsychological measures. In youth who initiated between 10-16 years of age, an earlier age of alcohol use onset has been found to be associated with increased resting-state functional connectivity between the nucleus accumbens and prefrontal, right inferior parietal, and medial temporal regions (Weissman et al., 2015). Based on these findings, it was hypothesized that higher AFDO and AWDO would linearly predict *decreased* cdFC between the DLPFC and PPC during a VWM task at follow-up. This study also aimed to

elucidate the association between cdFC patterns and neuropsychological performance in adolescents at follow-up, as few studies have examined the intercorrelation among these important and complementary measures of cognitive functioning. As higher AFDO and AWDO were expected to predicted *better* neuropsychological performance and *decreased* cdFC, it followed that *better* neuropsychological performance was hypothesized to be associated with *decreased* cdFC. This prediction was supported by prior evidence suggesting that indices that have been associated with better neuropsychological functioning (e.g., older age and AUD family history negative) are also linked to decreased cdFC (Spadoni, Simmons, Yang, & Tapert, 2013).

In addition to examining the two *a priori* regions of interest (ROIs), exploratory analyses also examined whole-brain cdFC among other regions that showed significant differences in follow-up BOLD activation during the VWM task as a function of AFDO and AWDO. Higher AFDO and AWDO were hypothesized to linearly predict decreased follow-up VWM BOLD activation throughout cortical and subcortical brain regions and decreased cdFC among these exploratory regions.

Chapter 1, in part, is published in Nguyen-Louie T.T., Simmons, A.N., Squeglia, L.M., Infante, A.M., Schacht, J., Tapert, S.F. (2018) Earlier alcohol use onset predicts changes in functional connectivity. *Psychopharmacology*, 235, 1041-1054 and Nguyen-Louie T.T., Matt, G.E., Jacobus, J., Li, I., Castro, N., Cota, C., Tapert, S.F. (2017) Earlier alcohol use onset predicts poorer neuropsychological functioning in young adults. *Alcoholism: Clinical and Experimental Research*, 41, 2082-2092. The dissertation author was the primary investigator and author of these papers.

CHAPTER 2: METHODS

2.1 Participants

Data for this study were a subsample of an existing larger longitudinal study on neurocognitive effects of substance use in adolescents (R01 AA13419, PI: Tapert, 9/2002- 8/2018). At baseline, participants were recruited through flyers sent to households of students attending public middle schools in the San Diego area (Nguyen-Louie et al., 2015; Squeglia, Schweinsburg, Pulido, & Tapert, 2011). Potential participants between 12-15 years of age were screened by trained psychometrists. Parents were then asked to provide verbal telephone consent, and assent from youth, to undergo screening procedures, at which time inclusion and exclusion criteria were assessed. Informed consent and assent documents were then mailed to interested and eligible families and reviewed by phone with parent and youth. Eligible participants were assessed using a detailed youth screening procedure; parents underwent a similar, parallel screen (see Measures section). Each participant was administered a comprehensive neuropsychological battery and MRI scan at baseline and follow-up.

Youth and parents were then followed annually after baseline. To maintain a high follow-up rate, youth were contacted by phone every 6 months for a brief (15-20 minutes) interview on substance use and general functioning. Annual birthday cards and semiannual informational newsletters were also disbursed to participants (Twitchell et al., 1992). Follow-up rates exceeded 95% in this study. Follow-up phone interviews included a structured clinical interview, Family History Assessment Module, Revised Socioeconomic Index of Occupational Status Measure, a structured diagnostic mental health interview, the Customary Drinking and Drug Use Record, and Timeline Follow-

back (see Measures section). Parents were administered a brief follow-up interview that included the Family History Assessment Module, Revised Socioeconomic Index of Occupational Status Measure, Timeline Follow-back of youth's use, and, for youth under 18 years of age, a parent version of a diagnostic mental health interview. At follow-up, youth who transitioned into alcohol use were brought back into the lab for a repeat neuropsychological and neuroimaging session.

Baseline inclusionary criteria. At baseline, participants must be between 12-15 years old and have a close relative or parent to act as informant on drinking patterns and family history of substance use for youth's first- and second-degree relatives. Twelve to 15 years old is an important age group for entry into the parent study. Epidemiologically, less than 20% of adolescents report drinking alcohol (past several sips) before the age of 13 (Eaton et al., 2012). At baseline, participants had minimal experience with alcohol and drugs. Neural development of frontal lobe brain regions is intensified during this time but the brain is developed enough to allow for longitudinal comparisons without gross structural changes (Giedd, Blumenthal, et al., 1999; Sowell et al., 1999). Therefore, 12-15 years of age is an ideal period to capture developmental differences in adolescent drinkers. Assessing neuropsychological and neuroimaging information in adolescents during this baseline period allowed for examining inter-individual differences in neurocognition after substance use has started. To ensure that a sufficient portion of the sample will transition into drinking in follow-up years, youth with risk factors for alcohol use problems (i.e., family history of SUD, externalizing disorders, tried alcohol before age of 14) were over-sampled. At baseline, approximately 50% of youth had family history of AUD and/or conduct disorder symptom(s).

Baseline exclusionary criteria. At baseline, potential participants were excluded if they reported drinking more than ten total times in their life or consumed more than two drinks within a week. Other drug use exclusionary criteria included: >5 lifetime experiences with marijuana and any use in the past three months, >1 cigarette per week, or any history of other intoxicant use.

Other exclusionary criteria included: (1) prenatal exposure to alcohol (>2 drinks during a given week), tobacco, or illicit drugs; (2) history of chronic medical illness; (3) any neurological (e.g., seizure disorder, migraines) or Diagnostic and Statistical Manual of Mental Disorders (DSM) IV (American Psychiatric Association, 2000) Axis I disorder other than oppositional defiant or conduct disorder; (4) head trauma or loss of consciousness of >2 minutes; (5) learning disabilities or intellectual disability; (6) parental history of psychiatric disorders that are not substance-related; (7) colorblindness or non-correctable vision or hearing problems; (8) left handedness, as brain lateralization for these individuals differs from that of right-handed individuals; (9) current use of medications that may potentially affect the brain or cerebral blood flow; (10) premature birth (i.e., born prior to 35th gestational week); (11) current or expected pregnancy; (12) arriving to the scan appointment intoxicated on alcohol or other drug, confirmed via breathalyzer and urinalysis; (13) inadequate comprehension of English, which may produce inaccurate results in the participant's assessment performance; (14) youth does not have a biological parent or other close relative available for consent and corroborating substance use and family history information; (15) claustrophobia; (16) irremovable metal implants, or (17) the adolescent and/or parent/guardian do not both provide informed assent and consent, respectively.

Follow-up eligibility. Inclusion criteria at follow-up for the current study included: (1) youth must have initiated alcohol use (i.e., have had at least one standard drink) by follow-up; (2) have available neuropsychological performance data at baseline and follow-up; (3) have available VWM fMRI data at baseline and follow-up; and (4) have available substance use, demographic, and mental health self-report data at baseline and follow-up. Participants were excluded from the present study if any of the following were endorsed at follow-up: (1) history of chronic medical illness; (2) any neurological (e.g., seizure disorder, migraines) disorder; (3) head trauma or loss of consciousness (>2 minutes); (4) pregnancy; and (5) contraindications to MRI (e.g., irremovable metal implements).

Sample size: neuropsychological assessments. The parent study recruited 295 participants at baseline, of which two passed away prior to 2016, one person sustained a severe traumatic brain injury, and eight individuals withdrew from the parent study. Of the remaining sample, 254 participants had at least one standard drink and 30 remained non-drinkers by follow-up in 2016. Baseline neuropsychological assessment data was available for all 254 individuals who have transitioned into alcohol use. Among them, follow-up neuropsychological assessment data were not available for 39 participants: 18 moved outside of the Southern California area, 20 remained in San Diego but were unable to come into the laboratory due to scheduling conflicts, and one individual was on an extended trip outside the United States. Overall, for the present study, 215 individuals have had at least one standard drink, met other follow-up inclusion criteria, and had valid neuropsychological, substance use, and self-report data at baseline and follow-up. Among these 215, 127 participants transitioned into weekly drinking and had valid

neuropsychological, substance use, and self-report data at baseline and follow-up.

Sample size: neuroimaging. Of the 254 participants who have transitioned into any drinking, 69 participants were not administered the VWM task during baseline brain imaging, and another 42 did not receive follow-up MRI scanning. Three additional participants were excluded due to below chance (i.e., <50% correct) performance on the VWM task, and four participants were excluded due to excessive and uncorrectable motion artifacts. In total, at follow-up, 136 participants had consumed at least one standard drink, met follow-up inclusion criteria, and had valid MRI data for imaging analyses, substance use, and self-report data at baseline and follow-up. Among these 136, 73 participants transitioned into weekly drinking (see Table 1).

2.2 Measures

Initial screens. At baseline, the study was briefly described to youth and parents interested in the project by phone. The study purpose, procedures, potential risks and benefits and issues relating to confidentiality were reviewed, and eligibility criteria were assessed. Brief functioning and demographic information were obtained to assess for exclusionary criteria. Eligible participants (youth and parents) were then administered a detailed clinical interview with the measures below. At follow-up, youth and parents were administered similar forms to assess changes in social functioning and demographics factors.

Psychosocial functioning. The Structured Clinical Interview (Brown, Myers, Mott, & Vik, 1994) was administered to youth at baseline and follow-up to assess academic functioning, activities involved (e.g., video games, extracurricular, jobs), peer relations, attitudes towards substance use, living arrangements, medical functioning, and

career goals.

Family history. The Family History Assessment Module (FHAM; Rice et al., 1995) was administered to youth and parent at baseline and follow-up to assess family history of SUD of first- (i.e., biological parents) and second- (i.e., biological grandparents, siblings, aunts, and uncles) degree relatives. Data obtained from the FHAM were used to assess familial history density, a continuous measure of biological risk for SUD. Familial history density was calculated as the weighted sum of all first- (i.e., biological parents and siblings, weighted 0.5) and second-degree relatives (i.e., biological grandparents, aunts, and uncles, weighted 0.25) who endorsed two or more AUD and/or SUD symptoms (Zucker, Ellis, & Fitzgerald, 1994).

Socioeconomic status. SES was assessed using the Revised Socioeconomic Index of Occupational Status measure (Stevens & Featherman, 1981), from which a Hollingshead Index of Social Position score (Hollingshead, 1965) was calculated for each participant using parental socioeconomic background information (i.e., educational attainment, occupation, and salary of each parent) to characterize the youth's rearing environment. Higher values indicate lower SES.

Psychopathology. The National Institute of Mental Health (NIMH) Diagnostic Interview Schedule for Children Version IV (C-DISC-IV; Lucas et al., 2001; Shaffer, Fisher, Lucas, Dulcan, & Schwab-Stone, 2000) is a computerized structured diagnostic interview administered at baseline to assess over 30 psychiatric diagnoses in children and adolescents aged 17 years and under based on the classification systems of the DSM-IV (American Psychiatric Association, 2000) and the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10) (World Health

Organization, 1995). Categories of psychopathology assessed included anxiety, mood, schizophrenic, behavioral, and substance use disorders. At baseline, youth were administered the DISC-Y, and parents were administered a parallel version (Robins, Cottler, Bucholz, & Compton, 1996). The two versions assessed for the same behaviors and psychopathology symptoms using different pronouns in the youth (i.e., "Did you feel…") and parent (i.e., "Did he seem…") versions.

At follow-up, participants were administered the computerized Mini International Neuropsychiatric Interview (M.I.N.I.; Sheehan et al., 1998), a structured diagnostic interview that assessed for psychopathy based on the DSM-5 (American Psychiatric Association, 2013) and ICD-10. Parent versions for assessment of youth psychopathology were not administered for participants 18 years and older. The disorders assessed included major depressive disorder, dysthymia, generalized anxiety, mania/hypomania, panic, agoraphobia, social phobia, obsessive-compulsive disorder, posttraumatic stress disorder, substance use, psychosis, anorexia nervosa, bulimia nervosa, and antisocial personality disorder. Recent (i.e., past month) and lifetime suicidality were also assessed. Any youth who endorsed recent suicidal ideation were provided with appropriate resources (e.g., hotline phone number), and if necessary, contacted by a licensed clinical psychologist research staff member.

Youth level of externalizing symptomology were assessed with the parent report Child Behavior Checklist (Achenbach, 1991) at baseline, and, at follow-up, the parallel Adult Self Report (for ages 18 or older; Achenbach & Rescorla, 2003) to obtain continuous normed indices of Externalizing (i.e., Rule-Breaking Behavior and Aggressive Behavior Problems) problem symptoms. Higher scores indicated more

symptoms.

Substance use. The Customary Drinking and Drug Use Record (CDDR; Brown et al., 1998) is a structured interview that examines the pattern and severity of alcohol, nicotine, marijuana, and other drug use (amphetamines, barbiturates, hallucinogens, benzodiazepines, cocaine, inhalants, opiates, ecstasy, ketamine, gamma-hydroxybutyric acid, phencyclidine, and recreational use of prescription drugs). Age of onset, average and peak frequency and quantity of use, withdrawal symptoms, and DSM-IV and DSM-5 SUD criteria were assessed.

The Timeline Follow-back (TLFB; Medina, Nagel, Park, McQueeny, & Tapert, 2007; Sobell & Sobell, 1992; Sobell, Maisto, Sobell, & Cooper, 1979) examined detailed frequency and quantity of substance use during the past 30 days. Youth were administered the TLFB three times for each follow-up time point: during the detailed phone interview, neuropsychological assessment appointment, and the MRI scanning appointment. Information from all three TLFB sources and CDDR were then integrated and coded by trained psychometrists to ensure accuracy.

Neuropsychological battery. A comprehensive neuropsychological battery was administered at baseline and follow-up to assess cognitive functioning. At baseline, the assessment battery included: Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) Color Word Interference and Trail Making (TMT) subtests; California Verbal Learning Test - Children's Version (CVLT-Children; Delis, Kramer, Kaplan, & Ober, 1994); Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999) Block Design subtest; Wechsler Intelligence Scale for Children – Third Edition (WISC-III; Wechsler, 1991) Digit Symbol-Coding and Digit Span subtests; and the Rey-

Osterrieth Complex Figure task (Rey & Osterrieth, 1993). At follow-up, participants 18 years and older were administered the adult versions of the CVLT - Second Edition (CVLT-II; Wechsler, 1997) and Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Delis, Kramer, Kaplan, & Ober, 2000) Coding and Digit Span subtests.

2.3 Procedures

Imaging. Participants were scanned in a 3-Tesla GE Discovery MR750 short bore Excite-2 MR system with an 8- channel phase-array head coil. The imaging center was equipped with eight high bandwidth receivers for ultra-short repetition times (TR) to reduce signal distortions and ventromedial signal dropout. Scan sessions began with scout scans (10 seconds) that assured good head placement and slice selection covering the whole brain. A high-resolution 2d T1-weighted sequence permitted volumetric analyses of white matter, gray matter, and tracing brain ROIs. A sagittally acquired spoiled gradient recalled sequence was used (FOV 24 cm, 256x192 interpolated to 256x256 matrix, .94x.94x1 mm voxels, 176 slices, TR=20 ms, TE=4.8 ms; flip angle 12˚, 7:26). Field map acquisitions employed two different echo times to assess field inhomogeneities and signal distortions under the same parameters as echo-planar image acquisition. This information was applied to the fMRI acquisitions to minimize warping and signal dropouts (4 minutes total). BOLD fMRI signal was measured with T2*-weighted axially acquired echo-planar imaging sequences (FOV=24 cm, 64x64 matrix, 3.75x3.75x3.8 mm voxels, 32 slices, TE=30 ms, flip angle 90˚, ramped bandwidth 250 KHz). Task stimuli were back projected from a laptop to a screen at the foot of the scanner bed visible via an angled mirror attached to the head coil. Accuracy and reaction time data were logged with a response box designed for MRI studies. Each task was identical for all

participants.

Visual Working Memory fMRI task. The VWM task consisted of 30 trials of an array of 2, 4, or 6 colored dots presented briefly (100 ms, see Figures 1 and 2). After a 1,000ms delay, the subsequent trial included the same number of dots presented in the same location and were either the same color array or one-color different. For each trial, participants pressed "1" if the color array was identical, and "2" if not. The paradigm was set up such that 50% of the trials have identical color arrays while 50% had a one-color dot difference. The human working memory system can hold three to four distinct pieces of information at a given moment (Paulus et al., 2006), thus the 6-dot condition was considered supra-span (i.e., higher than most people's working memory span), and the 2-dot condition was sub-span (i.e., within most people's working memory load capacity). The measure of interest from this task was the cdFC difference during the 6-dot array relative to the 2-dot array (high load vs. low load condition), interpreted as cdFC between ROIs and exploratory regions in response to increasing working memory load. A larger, more positive, cdFC fit coefficient was interpreted as higher positive temporal correlation between the ROIs or exploratory whole-brain analysis regions to complete the supra-span (6-dot) trials.

2.4 Data Analysis

Covariates and moderators. To control for pre-drinking neurocognitive functioning, analyses included baseline performances on the same tasks (i.e., neuropsychological assessments or cdFC in response to 6-2 dot VWM task in the same regions) as covariates. To better understand the effects of AFDO and AWDO on neurocognition, independent of other substance use related risk factors, analyses

controlled for the duration of drinking years, past year drinking frequency, past year tobacco and marijuana use frequency and marijuana use recency. Drinking duration was defined as the number of years between onset and follow-up in which participants were not classified as a control (i.e., have consumed ≥2 drinks per occasion and had ≥10 drinking occasions in the past year). Past year drinking frequency was defined as the number of drinking days in the past year prior to follow-up. Past year tobacco and marijuana use indicated the number of days participants have used tobacco and cannabis within the past year, respectively. Marijuana use recency assessed the number of days since the last cannabis use occasion prior to neurocognitive testing or MRI scan. Neuropsychological assessments and MRI scans occurred either on the same day or within five days (i.e., one week) apart.

Social and environmental factors were included as potential covariates in initial analyses to account for possible social rearing effects on neurocognitive performances. Familial density of SUD and SES were examined, as youth from higher SES households and of lower familial SUD density are more likely to perform better on neuropsychological tests (Hill et al., 2000; Raizada & Kishiyama, 2010; Roberts, Bornstein, Slater, & J., 1999). Externalizing symptomology have been associated with risky drinking and poorer cognitive functioning (Finn et al., 2009) and was therefore examined in initial analyses as a potential covariate. Models were first estimated with all proposed covariates and the independent variable of interest (i.e., AFDO or AWDO). Predictors that did not account for any significant variance in the outcome variable and/or independent variable were removed from the final models. All hierarchical regression analyses were carried out in SPSS (Rel. 21.0.0. 2012. IBM, Chicago, IL).

Power analysis. Using G-Power (Vogel, Woodman, & Luck, 2001), *a priori* analyses suggested that a total sample size of $N = 52$ was needed to achieve power of $1\text{-}\beta = .80$ (medium effect size of $f=.40$, two-tailed $\alpha = .05$) with one variable of interest (i.e., AFDO or AWDO) and a total of nine potential predictors (i.e., eight possible covariates) in a linear regression model. A total sample size of $N = 107$ is needed to achieve the same parameters in a model with all nine predictors included (see Table 1 for post-hoc power achieved).

Neuroimaging: regions of interest analysis. All baseline and follow-up imaging data were processed and analyzed using Analysis of Functional NeuroImages (AFNI; afni.nimh.nih.gov). BOLD activity: Motion (i.e., three rotational and three linear displacement parameters) was estimated for each participant and used to control for task-related analyses (Bandettini, Jesmanowicz, Wong, & Hyde, 1993). Outliers (i.e., motion) in the six motion parameters were detected and outputted (*3dToutcount*) to a file and visually inspected for each participant. Datasets with significant task-correlated or bulk motion were excluded. Acquisitions with significant outliers were censored (i.e., removed from further processing). On the remaining data, significant outliers in the voxel time series data were replaced using *3dDespike*. Acquisitions with outliers making up >3% of the time series data were also excluded from further analysis. Artifacts and abnormal signals were removed and time series data were temporally aligned and co-registered to a maximally stable base volume with an iterated least squares algorithm (*3dvolreg*) (Cox & Jesmanowicz, 1999). Spatial smoothing was applied using a Gaussian filter (full-width half maximum 6 mm with *3dBlurToFWHM*). The time series for each task condition (2-, 4-, and 6-dot) was entered as a regressor and convolved with an ideal hemodynamic

response function in a general linear model (GLM; *3ddeconvolve*) (Cohen et al., 1997), covarying for baseline, linear trends and motion correction parameters (x,y,z, roll, pitch, yaw). The first three TRs were ignored, as were censored volumes as specified above. Results of the GLM included, for each voxel, 1) a fit coefficient that represented change in signal between 6- and 2-dot conditions, 2) percentage signal change and 3) threshold (T) statistics. Each individual's functional and anatomical data sets were co-registered and warped to standardized Talairach space (Talairach & Tournoux, 1988) to reduce effects of anatomical variability (*3dAllineate*). Functional data were resampled into isotropic (3 mm^3) voxels (*3dfractionize*). Co-registration was examined for each subject (*3dABoverlap*). Any participant with a misalignment of greater than 10% was excluded from analysis if realignment attempts were unsuccessful (AFNI's *align_epi_anat.py*).

Context-dependent functional connectivity: Context-dependent functional connectivity was assessed using the psychophysiological interaction (PPI) method (Friston et al., 1997; Jo, Saad, Simmons, Milbury, & Cox, 2010), which estimates the inter-region neuronal temporal connectivity as a function of the VWM task (i.e., 6-2 dot contrast). The average time series was extracted for the DLPFC (i.e., Brodmann areas BA 46, ventral BA 9, and poster BA10) (Zhou et al., 2007), which served as the seed ROI, and any trends were removed (*3dDetrend*), followed by deconvolution of the seed time series into neural timing with a gamma basis function (*Waver* and *3dTfitter*). To examine changes in functional connectivity between ROIs (DLPFC and PPC) as a function of the VWM 6-2 dot contrast, a psychophysiological interaction regressor was created by multiplying the deconvolved time series (i.e., "the physiological" neural activity) with the behavioral task (i.e., the "psychological" task) and then re-convolved with a gamma basis

function. The resulting interaction terms (one for 6-dot, and one for 2-dot) and a main task effect regressor (i.e., detrended time series across all conditions) were entered into a GLM that included the regressors from the task-based fMRI analysis (see above). Additional regressors were included to model the six motion parameters and baseline, linear, quadratic, and cubic trends (i.e., polort 4). The first five TRs were ignored. The resulting PPI parameter (Fisher z-transformed correlation coefficients) of interest represented the measure of cdFC between the DLPFC and all other regions of the brain under the VWM task 6-2 dot contrast. An atlas-based anatomical mask was applied for the PPC (i.e., the superior parietal cortex, supramarginal gyrus and angular gyrus) (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008) in order to examine cdFC between the DLPFC and PPC, masking out all other brain regions. PPI parameters representing the cdFC between the two ROIs (R^2) were transformed into correlation coefficients (i.e., R) and then, to account for skewness and deviations from a normal distribution, into Fisher's Z.

To test the hypotheses that age of onset (AFDO and AWDO) predicted cdFC activity between the two ROIs at the follow-up time point, above and beyond covariates, Fisher's Z for the contrast of interest (i.e., 6-dot minus 2-dot conditions) was averaged across voxels for each subject and region, extracted, and exported for analysis in SPSS (Rel. 21.0.0. 2012. IBM, Chicago, IL). Baseline cdFC for the same regions was entered in step 1 of a hierarchical linear regression, followed in step 2 with other covariates that showed significant relationship with either cdFC outcome (i.e., Fischer's Z correlation maps) or AFDO/AWDO. In step 3, AFDO or AWDO was entered into the regression to examine its association with cdFC above and beyond covariates.

Neuroimaging: whole-brain exploratory analyses. Exploratory cluster-based analysis was conducted to test the hypothesis that age of onset (AFDO and AWDO) significantly predicted cdFC between other brain regions other than *a priori* specified ROIs at the follow-up time point. To control for multiple comparisons and Type I error, noise smoothness in the x, y, and z dimensions was first estimated (*3dFWHMx*) with a Gaussian and mono-spherical autocorrelation function (acf). Parameters from this model were then entered into Monte Carlo simulations (*3dClustSim*) that accounted for the estimated smoothing to determine cluster size thresholds that met the following criteria: bi-sided thresholding, first-nearest neighbor clustering, uncorrected (per-voxel) $p<.01$, and corrected (whole volume) $\alpha = .01$. Only regions with 20 or more voxels were retained in fMRI and functional connectivity group-level analysis.

To determine seed regions for cdFC analysis, a whole-brain regression analysis was first conducted in AFNI (*3dMEMA*) to determine clusters that showed a significant relationship between BOLD activation to the VWM task (6-2 dot contrast) and age of onset. A separate regression was conducted for each predictor of interest: AFDO and AWDO. Spherical anatomical masks were created for regions that showed a significant relationship in BOLD activation with age of onset and applied to each participant's follow-up and baseline BOLD dataset. Each spherical region was then used as the seed in follow-up cdFC. Data extraction and analysis for BOLD activity and context-dependent fcMRI followed an identical plan as in ROI-based analyses, described above.

Data reduction of neuropsychological test battery. To account for possible Type I error and redundancy among outcome measures, 26 neuropsychological test variables for each time point (i.e., baseline and follow-up) were subjected to a principle

components analysis using varimax rotation with Kaiser normalization (see Table 2). A nearly identical factor structure was confirmed with oblique, direct oblimin rotation for baseline and follow-up. Thus, all following analyses were conducted using the varimax rotation structure. Results yielded six cognitive domains: verbal learning and memory, cognitive inhibition, psychomotor speed, working memory, visual attention, and visuospatial planning. Internal consistency was assessed with Cronbach's alpha coefficients (see Table 3). All time to completion measures (i.e., D-KEFS Color Word Interference and Trails Making Test, Digit Vigilance Test tasks) were multiplied by -1 so that higher scores indicated better performance. After transformation, higher scores indicated better performance for all neuropsychological domains.

Neuropsychological performance and context-dependent functional connectivity. The association between neuropsychological performance (i.e., cognitive domains) and cdFC (i.e., Fisher's *Z*) at follow-up was examined in zero-order correlations (Pearson's *r*). Correction for multiple comparisons was carried out based on the false discovery rate controlling procedure (Benjamini & Hochberg, 1995), q-value = 0.05 using the *multproc* package (Newson, 2003) in Stata (Version 14; StataCorp LP, College Station, TX). Nominal (uncorrected) *p*-values are also presented for comparison.

Neuropsychological performance and age of onset. Examination of the relationship between neuropsychological functioning and age of onset was conducted using hierarchical linear regressions in SPSS (Rel. 21.0.0. 2012. IBM, Chicago, IL). Each neuropsychological domain was analysed in a separate model. AFDO and AWDO were examined in different models as independent predictors, assessing and controlling for the eight previously described covariates. Baseline neuropsychological performance, a robust

predictor of follow-up performances (Nguyen-Louie et al., 2015; Tapert, Granholm, Leedy, & Brown, 2002), was entered in step 1 of the regression, followed in step 2 with other covariates that showed significant relationship with either neuropsychological outcome or age of onset. In step 3, AFDO or AWDO was entered into the regression model to examine its association with cognitive performances at follow-up above and beyond covariates. For neuropsychological domains that showed significant associations with age of onset, follow-up hierarchical regressions were conducted to better understand this association for each individual neuropsychological test that comprised each latent domain. Effects sizes were assessed using R^2 (full model) and $R^2\Delta$ (increase in variance accounted for at each step).

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CHAPTER 3: RESULTS

3.1 Description of Sample

Of 295 participants initially enrolled in the parent project (see Table 4), 215 adolescents have transitioned into first use of alcohol, and among them, 127 individuals have transitioned into weekly alcohol use by follow-up in 2016. At baseline, participants (*N*=215) were between 12-15 years of age (*M* = 13.6, *SD* = 0.77). The subsample who later initiated weekly drinking (*N*=127) were statically identical in age at baseline as the total sample (AWDO youth baseline age: *M* = 13.7, *SD* = 0.79). At follow-up, participants were on average age 20.2 (*SD* = 1.48); the subsample who transitioned into weekly drinking (*N* =127) was *M* = 21.3 years of age (*SD* = 1.76) at follow-up. On average, the age of first drinking onset in the whole sample was *M* = 16.1 years (*SD* = 2.04, range = 10.00 – 22.83). Youth who later transitioned into weekly drinking had their first standard drink at *M* = 15.6 years of age (*SD* = 2.0), while youth who has never initiated weekly drinking (*N* = 88) were significantly older at the time of first drinking onset, *M* = 16.9 years of age (*SD* = 1.9; $T_{189.06}$= 4.58, *p*<.0001). The average age of weekly drinking onset was *M* = 18.4 years (*SD* = 1.70, range = 14.00 – 23.17), consistent with epidemiological studies, in which the age of alcohol use initiation was 17.6 years overall (Lipari et al., 2016) and 16.2 years for those who initiated prior to age 21 (SAMHSA, 2013).

3.2 Task Performance

No significant differences were detected in performance (i.e., percent correct) for the 2-dot condition between baseline and follow-up (*N*=215). On average, participants were correct on 93% of trials at baseline (*SD*= 6.0; range: 68-100; response time of *M* =

2384.0ms, *SD*= 185.3) and in *M* = 94% of trials at follow-up (*SD*= 6.0; range: 61-100; *M* = 2213.2ms, *SD*= 118.2). On the 6-dot condition, participants were significantly more accurate (T_{116}= -5.14, *p* <.0001) and responded at a quicker rate at follow-up (*M* = 82% correct *SD*= 11.0; range: 52-100; of *M* = 2354.5ms, *SD*= 143.1) compared to baseline (*M* = 77% correct; *SD*= 9.2; range: 52-100; *M* = 2550.3ms, *SD*= 190.2).

Among participants who have transitioned into weekly drinking (*N* = 127), significant effects of time were found for performance on both the 2-dot (T_{54}=-2.26, *p*=.03) and 6-dot (T_{54}=-4.10, *p*=.0001) conditions, with better performance at follow-up than baseline. On the 2-dot task, participants were correct in *M* = 91% of trials at baseline (*SD*= 6.0; range: 77-100; response time *M* = 2373.0ms, *SD*= 181.8), and 94% at follow-up (*SD*= 6.1; range: 71-100; *M* = 2227.1ms, *SD*= 121.8). On the 6-dot condition, participants were correct on 78% of trials at baseline (*SD*= 9.4; range: 52-100; *M* = 2531.1 ms *SD*= 192.8), and 82% at follow-up (*SD*= 11.1; range: 75-100; 2364.0.1ms, *SD*= 143.8).

3.3 cdFC and Task Performance

At baseline and follow-up, no significant bivariate correlation was found between task performances on the VWM 6- and 2-dot conditions and 6-2 dot contrast cdFC between the DLPFC and PPC.

3.4 cdFC and Neuropsychological Performance

Among youth who have transitioned into weekly drinking, negative correlations were found among 6-2 dot contrast cdFC in the right posterior cingulate to inferior frontal gyrus, left parahippocampal gyrus to supramarginal gyrus, and left parahippocampal gyrus to superior frontal gyrus with cognitive disinhibition, psychomotor speed, verbal

attention, and visuospatial abilities ($p < .05$; see Table 5). For all regions and domains, *lower* cdFC was associated with *better* neuropsychological performance. Verbal learning and memory showed no significant correlation with cdFC. No pairwise correlation remained significant after adjusting for a false discovery rate of q=0.05 (Benjamini & Hochberg, 1995).

3.5 Relationship Among Predictors at Follow-up

AFDO was significantly correlated with AWDO, follow-up age, SUD familial density, drinking duration, externalizing symptomology, past year tobacco, alcohol, and marijuana use days, ps < .01, but not with SES or marijuana use recency. AWDO was significantly correlated with follow-up age, externalizing symptomology, and past year tobacco and alcohol use days (ps<.01) but not with SUD familial density, SES, drinking duration, and marijuana use days and recency. AFDO and AWDO were the most highly correlated predictors (r = .56), followed by drinking duration and follow-up age (r = .49). These associations remained significant after multiple comparisons correction with a false discovery rate of q = .05. Sensitivity analyses suggested minimal concern for multicollinearity among predictors. In final models reported below, the variance inflation factor of predictors ranged from 1.01 to 1.35 (tolerance range: 0.74-0.99).

3.6 Age of Onset and Neuropsychological Performance

Age of first drinking onset and neuropsychological performance. In results described below, drinking duration exhibited a suppression effect on the predictor of interest, AFDO. AFDO was a significant predictor of outcome neuropsychological data only if the model also accounted for drinking duration. Drinking duration did not account for any significant variance in the outcome of interest, neuropsychological performance.

Higher AFDO predicted better visual attention functioning at follow-up (T_{214} = 2.0, $\hat{\beta}$= .106, p <.05), controlling for baseline visual attention and drinking duration (see Figure 3). In step 1, baseline visual attention accounted for 47.2% of the variance of follow-up visual attention functioning; in step 2, drinking duration did not account for any additional variance; in step 3, AFDO accounted for an overall 48.3% of the variance. No interaction effects were found. Follow-up hierarchical regressions of individual neuropsychological tests in this domain showed that higher AFDO predicted better performance on D-KEFS CWI Word Reading above and beyond covariates (T_{214} = 2.05, $\hat{\beta}$= .116, p <.05; R^2 = .414; ΔR^2 AFDO = .011). No relationship between AFDO and other subtests in this domain was found, p >.05.

Higher AFDO predicted better psychomotor speed at follow-up (T_{214} = 2.6, $\hat{\beta}$= .116, p <.04), controlling for baseline psychomotor speed and drinking duration. In step 1, baseline psychomotor speed accounted for 40.7% of the variance in follow-up psychomotor speed; in step 2, drinking duration did not account for any additional variance; in step 3, the addition of AFDO accounted for an overall 41.9% of the variance. No interaction effects were found. Follow-up hierarchical regressions of individual neuropsychological tests in this domain showed that higher AFDO predicted better performance on D-KEFS TMT Motor Speed above and beyond covariates (T_{214} = 3.3, $\hat{\beta}$= .205, p <.001; R^2 = .189; ΔR^2 AFDO = .042). No relationship between AFDO and other subtests in this domain was found, p >.05.

Domain-level analyses suggested a trend towards significance such that higher AFDO predicted better working memory functioning at follow-up controlling for baseline

working memory and drinking duration (T_{214} = 1.8, $\hat{\beta}$= .120, p = .079). No interaction effects were found. Follow-up hierarchical regressions of individual neuropsychological tests in this domain showed that higher AFDO predicted better performance on Digit Span Backwards above and beyond covariates (T_{214} = 1.12, $\hat{\beta}$= .211, p <.05; R^2 = .219; ΔR^2 AFDO = .044). No relationship between AFDO and other subtests in this domain was found, p >.05.

Age of weekly drinking onset and neuropsychological performance. Higher AWDO predicted better working memory at follow-up (T_{208} = 2.59, $\hat{\beta}$= .304, p <.05), controlling for baseline working memory and past year marijuana use (see Figure 3). In step 1, baseline working memory accounted for 33.8% of the variance of follow-up verbal working memory; in step 2, past year marijuana use accounted for an additional 2.2%; in step 3, AWDO accounted for an additional 9.1%. No interaction effects were found. Follow-up hierarchical regressions of individual neuropsychological tests in this domain showed that, above and beyond covariates, higher AWDO predicted better performances on Digit Span Backwards (T_{214} = 2.28, $\hat{\beta}$= .317, p <.05; R^2 = .206; ΔR^2 AFDO = .099). No relationship between AWDO and other subtests in this domain was found, p >.05.

Higher AWDO predicted better cognitive inhibition ability at follow-up (T_{208} = 2.26, $\hat{\beta}$= .313, p <.05), controlling for baseline cognitive inhibition, past year marijuana use, and recency of marijuana use. In step 1, baseline cognitive inhibition accounted for 15.7% of the variance of follow-up verbal working memory; in step 2, past year marijuana use and recency of marijuana use accounted for an additional 4.6%; in step 3,

AWDO accounted for an additional 9.3%. No interaction effects were found. Follow-up hierarchical regressions of individual neuropsychological tests in this domain showed that, above and beyond covariates, higher AWDO predicted better performances on D-KEFS TMT Switching ($T_{214} = 2.35$, $\hat{\beta} = .302$, $p < .05$; $R^2 = .363$; ΔR^2 AFDO = .084). No relationship between AWDO and other subtests in this domain was found, $p > .05$.

3.7 Neuroimaging: Regions of Interest Analyses

No significant relationship was found between AFDO or AWDO with cdFC during the VWM task 6-2 dot contrast between the hypothesized regions DLPFC and PPC at follow-up or baseline.

3.8 Neuroimaging: Whole-brain Analyses

A significant negative relationship between AWDO and 6-2 dot BOLD response contrast (i.e., higher AWDO predicted lower BOLD activation) were found throughout the brain in cortical and subcortical areas at follow-up: the frontal (left medial, middle, and inferior frontal regions), parietal (right inferior region), temporal (right superior, right middle), occipital (left middle), and subcortical (right parahippocampal gyrus, right posterior cingulate, left globus pallidus) regions (see Table 6, Figure 4). No significant positive relationships were found between AWDO and BOLD activation (i.e., youth who initiated weekly drinking at a later age did not show greater BOLD activation during the VWM task in any brain regions). No exploratory whole-brain cdFC analyses were conducted to examine the relationship between AFDO and follow-up cdFC, as no regions showed significant differences in 6-2 dot BOLD activation as a function of AFDO at follow-up, and thus no seed regions were selected for cdFC analyses.

Regions that showed a significant relationship between AWDO and BOLD

response 6-2 dot contrast at follow-up were used as seed regions in 6-2 dot contrast cdFC analyses. In total, 10 spherical atlas-based regions (Talairach & Tournoux, 1988) were used as seeds: right posterior cingulate, right inferior parietal lobule, right lingual gyrus, left medial frontal gyrus, left straight gyrus, left paraphippocampal gyrus, left middle occipital gyrus, left globus pallidus, left superior temporal lobule, and left middle frontal gyrus. Among these seeds, regions that showed significant association between follow-up 6-2 dot contrast cdFC and AWDO were the right posterior cingulate, left parahippocampal gyrus, and left globus pallidus (see Figure 5 and Table 6).

Seed: right posterior cingulate. Higher AWDO predicted lower cdFC between the right posterior cingulate to right inferior frontal gyrus ($F(1,72) = 35.53$, $p < .0001$, $R^2 = .324$). Of the eight covariates examined, none were not significant predictors of cdFC between these regions and removed from the final model.

Seed: left parahippocampal gyrus. Higher AWDO predicted lower cdFC between the left parahippocampal gyrus to right supramarginal gyrus ($F(1,72) = 7.78$, $p < .01$, $R^2 = .086$) and right superior frontal gyrus ($F(1,72) = 18.59$, $p < .0001$, $R^2 = .196$). Of the eight covariates examined, none were not significant predictors of cdFC among these regions and removed from the final model.

Seed: left globus pallidus. Higher AWDO predicted lower cdFC between the left globus pallidus to right cingulate gyrus ($F(1,72) = 18.59$, $p < .0001$, $R^2 = .196$) and greater cdFC between the left globus pallidus to left superior temporal gyrus ($F(2,71) = 13.47$, $p < .0001$, $R^2 = .257$), above and beyond baseline cdFC between these regions. Of the eight covariates examined, none were not significant predictors of cdFC among these regions and removed from the final model.

No significant relationship between AWDO and cdFC were found with other seed regions.

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CHAPTER 4: DISCUSSION

Using neuroimaging and neuropsychological techniques, this study aimed to ascertain the effects of alcohol on the brain as a function of the age at which youth began any drinking (i.e., AFDO) and began drinking on a regular, weekly basis (i.e., AWDO). Six neuropsychological domains, comprised of 26 individual test scores, were assessed. As hypothesized, youth who began drinking at later ages (i.e., higher AFDO) performed better on tasks of psychomotor speed and visual attention than early onsetters. Youth who began drinking weekly at later ages (i.e., higher AWDO) showed better performances on tasks of cognitive inhibition (i.e., more successful at inhibiting pre-potent responses) and working memory than early weekly onsetters. No relationship between AFDO and AWDO were found with verbal learning and memory and visuospatial ability, possibly because these cognitive domains reach near adult-level maturation comparatively earlier in life (Ardila & Rosselli, 1994; Gathercole, 1998), or the impact of drinking may be consistent throughout adolescence.

AFDO and AWDO were not associated with context-dependent functional connectivity between the hypothesized ROIs (DLPFC and PPC) at follow-up. However, exploratory whole-brain analyses suggested that later weekly drinking onsetters showed *lower* (i.e., more negative) cdFC between the left parahippocampal gyrus to the right supramarginal and superior frontal gyri, right posterior cingulate to the right inferior frontal gyrus, and left globus pallidus to the left superior temporal and right cingulate gyri, relatively to the early onsetters. Further, *lower* cdFC is correlated with *better* performances in neuropsychological tasks, suggesting that lower cdFC may be a more favorable outcome. These findings represent an important advancement in the

understanding of alcohol use onset age and its effects on neurocognitive functioning in young, high-functioning youth with minimal co-occurring medical or psychiatric distress.

Higher AFDO and AWDO were hypothesized to be associated with decreased cdFC between the DLPFC and PPC, as prior work has found that adolescents with earlier drinking onset ages and greater lifetime drinking duration showed decreased subcortical-cortical resting-state functional connectivity (Weissman et al., 2015). Frontoparietal connectivity has been found to be implicated in various aspects of alcohol use. For example, substance-naïve youth with a family history of AUD showed less cdFC than those without such familial background (Wetherill et al., 2012). Among adult men, heavier drinkers (defined as consuming ≥ five a day on ≥ three occasions per week) showed lower resting-state frontoparietal functional connectivity compared to normal controls (i.e., light drinkers with no more than one drink per day) (Shokri-Kojori, Tomasi, Wiers, Wang, & Volkow, 2016). Differences in methodology may account for the unexpected null findings with the specified ROIs in this study. Prior studies have focused either on heavy drinkers with AUD (De Bellis et al., 2000) or substance-naïve youth with and without AUD family history (Spadoni et al., 2013; Wetherill et al., 2012). In the current study, participants entered as healthy, non-treatment seeking adolescents who exhibited a range of drinking patterns at follow-up. It is possible that as a risk factor, age of onset exhibits differential effects on neural patterns than family history and drinking severity.

Whole-brain analyses were conducted to further understand if, and how, age of onset is related to differences in cdFC in regions other than the DLPFC and PPC. In this study, participants completed an fMRI-based VWM task; thus, it was not surprising that

significant differences in activation and connectivity were found in brain regions important to working memory. The globus pallidus, for example, is key to distinguishing between distractor versus target stimuli, freeing working memory capacity (McNab & Klingberg, 2008; Todd & Marois, 2004). Particularly in VWM tasks, the superior frontal gyrus may also be involved in the planning and executive control aspects of working memory when the load surpasses the typical span of 3-4 items (du Boisgueheneuc et al., 2006). Other regions that showed a relationship between cdFC and AWDO have been involved in emotional regulation and social functioning behaviors. For example, youth with higher AWDO showed lower and more negative cdFC between the left globus pallidus and left superior temporal gyrus, an important structure for auditory language processing, and part of a social cues perception pathway that includes the amygdala, fusiform face area, and inferior frontal gyrus (Green, Horan, & Lee, 2015). Other regions that showed significant relations with AWDO, the right posterior cingulate, inferior frontal gyrus, left parahippocampal gyrus, and right superior frontal gyrus have been found to be important areas in affective facial perception. Notably, the parahippopcampal gyrus and posterior cingulate are limbic structures implicated in emotional and social processing (Aminoff, Kveraga, & Bar, 2013; Sabatinelli et al., 2011; Vuilleumier & Pourtois, 2007).

Similarly, the right supramarginal gyrus may be important in avoiding social judgements and biases due to egocentricity bias, the tendency to attribute one's mental state onto other individuals (Silani, Lamm, Ruff, & Singer, 2013). Together, youth who begin drinking weekly at an earlier age may have differential cdFC than peers with later onset ages. Further, individuals with higher AWDOs show more negative correlations

between regions, which has been referred to as an anticorrelation or antiphase relationship in the literature. Preliminary evidence suggests that greater negative cdFC between areas may be related to more consistent behavioral task performance (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008). In the case of a VWM task, this would suggest that youth who engaged in weekly drinking at older ages and showed more negative cdFC between regions may be more consistent in their pattern of discerning whether the two stimuli trials are the same or different colors. However, the literature on this phenomenon is in its infancy and requires further exploration.

An important limitation that should be noted is that these results are *exploratory* in nature and were obtained from a data-driven approach. Although methods for clustering and thresholding were used (e.g., Monte Carlo simulations) to decrease Type I error, the process of selecting seed regions based on areas found to be activated in BOLD analysis is not free from bias. For example, regions that showed activation differences in relation to age of onset in BOLD analyses are also more likely to show an association with the same predictor in cdFC analyses. For these reasons, the reported variance accounted for (R^2) is likely inflated, and should be interpreted with caution. Additional research is needed to replicate these findings. The current findings of whole-brain exploratory analyses should be viewed as a foundation for future studies examining the relationship between age of onset and cdFC. Cross-validation of the regions found in this study with a separate, independent sample, is necessary to ascertain the generalizability of the reported results. Another possible future direction is to better understand the role of social cognition and emotion in age of drinking onset by examining cdFC among these regions during an emotional face recognition task (e.g., Hariri, Bookheimer, & Mazziotta,

2000).

Higher AFDO predicted better performances on psychomotor speed and visual attention at follow-up, controlling for duration of drinking and baseline performances in the same domains. Higher AWDO predicted better performances on tasks of cognitive inhibition and working memory, controlling for baseline performances and marijuana use days and recency. Taken together, results suggest that a later age of drinking onset act as a protective factor for poorer neuropsychological functioning in young adult drinkers. Currently, few studies have examined this issue and results are mixed (e.g., Kist et al., 2014). The present analyses offered additional evidence to support the deleterious effects of early adolescent alcohol use. Further, it is the first study to examine the effect of age of weekly drinking onset on neurocognition. Importantly, only one other study has examined the relationship between age of alcohol use onset on functional connectivity (Weissman et al., 2015), and few have examined onset age as a continuous quantity. It has been suggested that cognitive development continues until 30 years of age (Craik & Bialystok, 2006; Sowell et al., 2003). Behaviorally and neuroanatomically, executive functions such as impulsivity, inhibition, problem solving, and decision making continue to develop until 20-29 years old (De Luca et al., 2003). Different areas of the brain follow different trajectories of neural development and pruning processes (Giedd et al., 1999; Østby et al., 2009; Somerville, 2016). Thus, grouping individuals with AFDOs under 25 (Joos et al., 2013) together likely overlooks a range of neuro-developments that occur within this time.

An important, yet unexpected, finding of this study concerned drinking duration, which acted as a suppressor variable (Darlington, 1968) in predicting AFDO. By

definition, a suppressor variable is neither a mediator nor moderator (MacKinnon, Krull, & Lockwood, 2000), but an independent variable having no significant correlation with the dependent variable (i.e., follow-up neuropsychological functioning). However, its inclusion in the model enhances the association between the predictor of interest (i.e., AFDO) and dependent variable, evidenced by an increase in regression coefficient magnitude (Conger, 1974). Although drinking duration was not significantly associated with outcome psychomotor speed and visual attention, it was negatively correlated with AFDO (r = -.37). Sensitivity analyses suggested little concern for multicollinearity between predictors in regression models (AFDO Variance Inflation Factor = 1.16; tolerance= 0.86). Evidence suggests that neither AFDO nor duration alone is an accurate predictor of outcome cognitive performance in adolescents and young adults. Rather, it is the *interplay* between these indices that warrants significance. It is possible that the mechanism by which AFDO influences cognition is through the number of years drinking behavior has been engaged in (Weissman et al., 2015). Individuals who begin drinking at the same age but engages in different trajectories of drinking may show differential patterns of cognitive performances in later life. One may speculate that youth who began drinking earlier are more likely to have longer drinking durations between age of onset and adulthood. This, in turn, allowed for greater alcohol-related neurotoxicity and exposure over an extended period of time, reflected in neuropsychological functioning and neural imaging differences at follow-up.

Caution should be used in the interpretation of the current results within the context of correlation versus causation. John Stuart Mill (1884) posited three necessary criteria in order to suggest causal inference. First, the effect must temporally follow the

cause; second, the cause and effect must be associated with each other; and third, other possible alternatives that may account for the relationship has been sufficiently ruled out or accounted for. To examine the results of the current study in this context, each criterion is assessed in turn. The longitudinal design of this study increased the accuracy with which AFDO and AWDO were assessed. Further, outcome neuropsychological performances were examined 4.7 years after the onset of first drinking and 3.1 years after onset of weekly drinking. Temporal order between age of onset and neuropsychological outcome has been established, and thus satisfies criterion one. Results of hierarchical regression analyses suggest that, at $p<.05$, the age of onset is significantly related to outcome neuropsychological performance, satisfying criterion two. In an attempt to control for extraneous factors that may influence either the dependent or independent variables of interest (i.e., criterion three), eight potential covariates were examined. Results were only considered statistically significant if AFDO or AWDO were significant predictors of neuropsychological functioning *above and beyond* baseline functioning, marijuana use, alcohol use and duration, familial factors (e.g., SES, family history of SUD), and externalizing symptomology. Some factors that may account for neuropsychological performance that were not examined included motivation (i.e., during laboratory sessions) and quality of education and school systems. The neurocognitive effects of AWDO and AFDO are unlikely independent of tobacco and marijuana, commonly used among US adolescents (Johnston et al., 2017). Further, initiation of alcohol (17.6 years), cigarettes (17.9 years) and marijuana (19.0 years) occur at around the same age (Lipari et al., 2016). To account for this, analyses controlled for use of tobacco and marijuana, and the rate of other substance use in this sample was minimal

(<2.7% in the past year). However, the unique effects of AFDO and AWDO on neurocognition can only be arrived at statistically in the current study, given the high co-occurring rate of youth who have tried alcohol, tobacco, and marijuana at least once. To better control for other substance use, future studies should examine the age of alcohol use onset in participants with no comorbid use of any other substances. Overall, based on Mill's criteria for causal inference, the current study met two of three proposed criteria. Additional studies are needed to explore this important question, in an animal model with a randomized design in which all extraneous factors inherent in human studies can be controlled.

An important limitation of this study is that the interpretation of results should not be extrapolated to ages of onset earlier or later than those in the study, or pattern of drinking beyond those observed here. For example, although there is a range of age of onset and follow-up age in the current sample, the results of this study are limited by their upper and lower limits. AFDO ranged from 10 to 22 years and AWDO from 14 to 23 years, thus, it is unclear if and how the findings may apply to ages of onset outside this range. It is possible that once adolescents reach adulthood and full neural maturation, alcohol initiation may no longer exhibit effects in the same direction or pattern. Likewise, drinking duration played an important suppressor role in modeling the effects of AFDO on neuropsychological performance. It is unclear how this relationship may evolve as drinking duration becomes longer. Another limitation is that the sample is comprised largely of middle-class Caucasian youth, consistent with the surrounding geographic area. Caution is advised in the application of results to minority ethnicities.

Strengths of this study aided in the interpretation and bolster the robustness of the

results. Importantly, participants were followed each year to assess past year and recent substance use. Data on age of onset were not obtained through error-prone retrospective recall in adults, but calculated by trained psychometrists as youth transitioned into alcohol use while enrolled in the study. Secondly, neurocognitive functioning was assessed at baseline, when youth have had no or minimal experience with alcohol. This allowed for the examination of the effects of alcohol on neurocognition, *controlling for each individual's premorbid cognitive functioning.* Baseline neuropsychological functioning has previously been shown to be the most consistent predictor of performance after alcohol use initiation (Nguyen-Louie et al., 2015; Tapert et al., 2002), accounting for 30-55% of variance in follow-up performance. Thus, cross-sectionally examining this phenomenon without considering pre-drinking cognitive functioning may lead to inaccurate attributions and overestimation of effect sizes when examining the effects of alcohol. Importantly, this study also accounted for baseline cdFC in the same regions, thereby reducing possibly confounding effects of baseline neurological patterns.

The presented findings may have important implications for public safety and policies related to alcohol use. Currently, the legal age of drinking in the United States is 21 years of age. However, the adolescent brain does not reach full maturity until around age 25, or later for some processes in some individuals (Østby et al., 2009). Alcohol initiation at a younger age may disrupt the normal neurodevelopmental trajectory, resulting in immature brain function and deviations in neurocognition. Results suggest that there are no cut-offs for which alcohol use initiation is not deleterious to neurocognition between 10-23 years old. The legal drinking age of 21 marks a developmental and social, but not neurodevelopmental, transition into adulthood, thus it

may not be a “safe” drinking age with regards to neurotoxicity. Another important implication of this study is the possibility of utilizing these and future results in individualized and targeted treatment for AUD. Currently, drinkers undergo similar treatments regardless of age of onset and developmental stage. As neurocognitive performance changes linearly with age of onset, treatment may be individualized based on the age the individual began drinking to increase efficacy. For example, current diagnostic criteria for AUD (American Psychiatric Association, 2013) takes into account recent use patterns, physiological and psychological dependence, disruptions to everyday functioning, and a general history of frequency and quantity of use, but not age of onset. Clinical interviews may help guide treatment such that individuals with earlier ages of onset may receive a greater level of care, as early onset has been found to be correlated with greater psychosocial difficulties and based on the current results, poorer psychomotor speed, attention, and cognitive inhibition.

The literature has described in detail the structural, functional, and behavioral development of the brain from early childhood to adulthood, and evidence suggests that alcohol negatively impacts the adolescent brain. However, few studies have examined how these two processes –brain development and alcohol use initiation – interact. The current results suggest that alcohol impacts higher-order cognitive abilities and underlying brain regions by affecting the temporally linked functioning of important brain areas. Importantly, this study provides preliminary evidence that the cdFC between areas important for emotional and social cognition are particularly vulnerable to early ages of heavy drinking.

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TABLES

Table 1. Study design and achieved power

		Predictor: Age of Onset	
		First Drinking Onset age: 10-22 years Follow-up age: 18-25 years	**Weekly Drinking** Onset age: 14-23 years Follow-up age: 18-26 years
Outcome: Neurocognition	**NP**	Influence of AFDO on NP performance $N = 215$ $1 - \beta = 0.99$	Influence of AWDO on NP performance $N = 127$ $1 - \beta = 0.99$
	fcMRI	No post-hoc power analyses conducted.	Influence of AWDO on context-dependent fcMRI $N = 73$ $1 - \beta = 0.86$

Post-hoc power achieved based on f=0.40, $\alpha = 0.05$, total sample size (n), and final number of predictors in regression models.

AFDO = age of first drinking onset; AWDO = age of weekly drinking onset; NP = neuropsychological; fcMRI = functional connectivity

Table 2. Principal component analysis loading structure of follow-up neuropsychological test raw scores (N=215)

Item	Factor						Factor Label
	1	2	3	4	5	6	
CVLT-II Long Delayed Cued Recall	**.93**						Verbal Learning & Memory
CVLT-II Long Delayed Free Recall	**.91**						
CVLT-II Short Delayed Cued Recall	**.91**						
CVLT-II Short Delayed Cued Recall	**.88**						
CVLT-II List A Trial 1-5	**.85**						
CVLT-II List A Trial 5	**.82**						
CVLT-II List A Trial 1	**.49**				.35	.34	
D-KEFS CWI Discrepancy Score [a]		**.79**					Cognitive Inhibition
D-KEFS CWI Inhibition/Switching [b]		**.77**			.42		
D-KEFS CWI Inhibition [b]		**.72**			.40		
D-KEFS TMT Letter-Number Switching [b]		**.52**	.43	.35			
WAIS-IV Coding		.46	**.44**				Psychomotor Speed
D-KEFS TMT Visual Scanning [b]			**.74**				
Digit Vigilance Test [b]			**.70**				
D-KEFS TMT Number Sequencing [b]		.31	**.68**				
D-KEFS TMT Motor Speed [b]			**.63**				
D-KEFS TMT Letter Sequencing [b]		.33	**.51**				
WAIS-III Digits Backwards				**.73**			Working Memory
WAIS-III Digits Forward				**.72**			
WAIS-III Arithmetic				**.70**			
CVLT-II List B	.37			**.38**			
D-KEFS CWI Word Reading [b]					**.83**		Visual Attention
D-KEFS CWI Color Naming [b]		.32			**.74**		

Table 2. Principal component analysis loading structure of follow-up neuropsychological test raw scores (N=215), Continued

Item	Factor						Factor Label
	1	2	3	4	5	6	
Rey-Osterrieth Complex Figures Copy Accuracy						**.80**	Visuospatial Ability
Rey-Osterrieth Complex Figures Delay Accuracy						**.79**	
WASI Block Design	.40					**.50**	

Rotation method: Varimax with Kaiser normalization. All factor loadings <0.300 are omitted for clarity.

Identical structure, with similar coefficients, was obtained with baseline neuropsychological test score, and among youth who transitioned into weekly drinking at baseline and follow-up (N = 125).

[a] Discrepancy score was calculated as the difference in raw scores (time to completion) between D-KEFS Color Word Interference conditions 4 (Inhibition) and 1 (Color Naming).
[b] Time to completion; multiplied by -1: low values reflect worst/slower performance

CVLT-II = California Verbal Learning Test II; D-KEFS = Delis-Kaplan Executive Function System; WAIS = Wechsler Adult Intelligence Scale; WASI = Wechsler Abbreviated Scale of Intelligence; CWI = Color Word Interference; TMT = Trail Making Test.

Table 3. Standardized Cronbach's alpha for principle components analysis factor loadings at baseline and follow-up

Factor Label	**AFDO Sample (*N*=215)**		**AWDO Sample (*N*=127)**	
	Baseline	Follow-up	Baseline	Follow-up
Verbal Learning & Memory	.92	.94	.91	.94
Cognitive Inhibition	.81	.84	.77	.82
Psychomotor Speed	.73	.76	.66	.71
Working Memory	.53	.65	.47	.62
Visual Attention	.79	.80	.80	.86
Visuospatial Ability	.58	.60	.57	.60

AFDO=age of first drinking onset; participants who have transitioned into any alcohol use and have had at least one standard drink

AWDO=age of weekly drinking onset; participants who have transitioned into weekly drinking onset (i.e., drinks at least one standard drink at least once a week)

Table 4. Demographic characteristics at baseline and follow-up (*N*=215)

	M (SD) or % [Range]	
	Baseline	**Follow-up**
Age	13.6 (0.8)	20.2 (1.5)
Age first drank (*N* = 215)	-	16.1 (2.0) [10.0-22.8]
Age first drank weekly (*N* = 127)	-	18.4 (1.7) [14.00-23.2]
% Female	41.4%	-
% with family history of AUD [a]	27.9%	-
Lifetime conduct disorder	9.4%	-
Race		
Caucasian	67%	-
Latino/a	19%	-
Multiple races	8%	-
African American/Black	2%	-
Asian American	4%	-
Native Hawaiian/Pacific Islander	1%	-
Socioeconomic status	23.0 (14.1)	-
Tried alcohol (≥ 1 standard drink)	9.8%	100.0%
Tried tobacco	4.2%	67.1%
Tried marijuana	5.2%	75.6%
Tried other illicit drugs	0.0%	4.3%
Drank in the past year	8.8%	95.7%
Past year drinking days	0.4 (1.8)	65.4 (71.3)
Past year binge days [b]	0.0 (0.0)	31.7 (49.7)
Drinks per peak drinking occasion past 3-months	1.7 (1.1)	7.0 (4.6)

Table 4. Demographic characteristics at baseline and follow-up (*N*=215), Continued

	M (SD) or % [Range]	
	Baseline	**Baseline**
Days since last drink	119.5 (102.7)	87.9 (252.9)
	[30.0 – 365.0]	[2.0 – 1920.0]
Past year marijuana use days	0.6 (1.2)	56.1 (105.7)
Days since last tobacco use	397.8 (301.6)	245.9 (469.1)
	[60.0 – 998.0)	[1.0 – 2555.0]
Days since last marijuana use	223.9 (203.0)	153.0 (291.0)
	[14.0 – 730.0]	[2.0-1828.0]
Past year alcohol dependence	0.0%	8.6%
Past year drug use classification (including marijuana)		
Non-user	96.7%	40.0%
Infrequent user	3.26%	20.9%
Moderate user	-	24.6%
Drug abuse (DSM-IV)	-	7.6%
Drug dependent (DSM-IV)	-	9.5%
Full sustained remission	-	0.5%

[a] At least one first degree relative with an alcohol use disorder
[b] Consumed ≥5 drinks per occasion for men or ≥4 drinks per occasion for women
Socioeconomic status was assessed using the Hollingshead Index of Social Position score; AUD = alcohol use disorder

Table 5. Association between context-dependent functional connectivity and cognitive domain scores at follow-up (*N*=73).

	L parahippocampal gyrus to R superior frontal gyrus	L parahippocampal gyrus to R supramarginal gyrus	R posterior cingulate to R inferior frontal gyrus
Verbal Learning & Memory	-.11	-.14	-.19
Cognitive Disinhibition	**-.30***	-.03	-.13
Psychomotor Speed	**-.30***	-.01	-.11
Working Memory	**-.29***	-.22	-.05
Visual Attention	-.16	-.03	.02
Visuospatial Abilities	**-.31***	**-.29***	**-.26***

Bivariate correlations (Pearson's *r*) between regions with significant context-dependent functional connectivity and neuropsychological performance at follow-up. Context-dependent functional connectivity was assessed in response to high relative to low conditions (i.e., 6-2 dot contrast) of a visual working memory task.

Note: * uncorrected $p < .05$; No correlation was significant after correction for multiple comparisons at a false discovery rate of q=0.05.

R= right; L= left

Table 6. Regions of significant visual working memory BOLD response contrast associated with age of weekly drinking onset (*N*=73)

	Talairach coordinates (LPI center of mass)			
Anatomical Region	**x**	**y**	**z**	**Cluster size (# voxels)**
Whole-brain exploratory analyses				
R posterior cingulate	9	-61	13	83
R parahippocampal gyrus	15	-37	-6	47
R inferior parietal lobule	41	-30	47	40
R superior temporal gyrus	44	-23	4	32
R posterior middle temporal gyrus	34	-73	20	31
R anterior middle temporal gyrus	43	-58	13	29
L medial frontal gyrus	-7	34	40	67
L middle frontal gyrus	-39	7	40	25
L inferior frontal gyrus	-28	24	6	26
L middle occipital gyrus	-42	-70	5	47
L globus pallidus	-25	-20	4	43

Regions that showed significant changes in blood oxygen level dependent (BOLD) activation to visual working memory task 6-2 dot contrast alcohol in a linear regression model examining the relationship between age of weekly drinking onset and BOLD response (per-voxel $p<.01$, whole volume $\alpha = .01$). For all regions, higher age of weekly drinking onset predicted decreased activation. No significant relationship was found between BOLD response and age of first drinking onset.

L=left hemisphere, R=right hemisphere
ROI= region of interest
LPI = coordinate system in which left, posterior, and inferior regions are depicted as negative x, y, and z coordinates, respectively

FIGURES

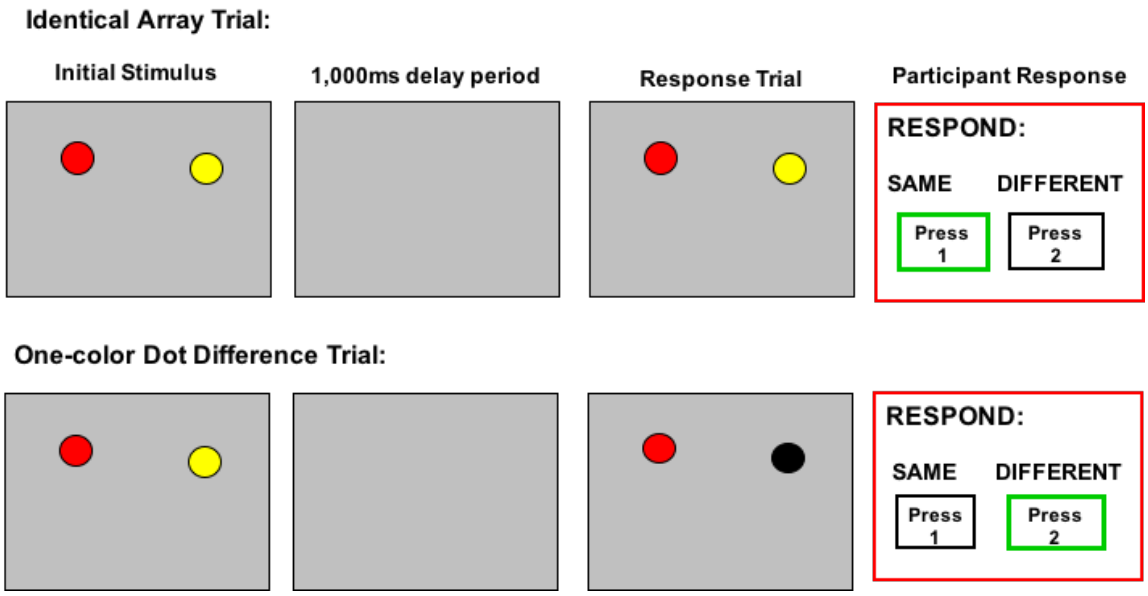


Figure 1. Example of Visual Working Memory task 2-dot condition

Task adapted from: Luck, S. J., & Vogel, E. K. (1997). The capacity of visual working memory for features and conjunctions. *Nature, 390*(6657), 279-281.

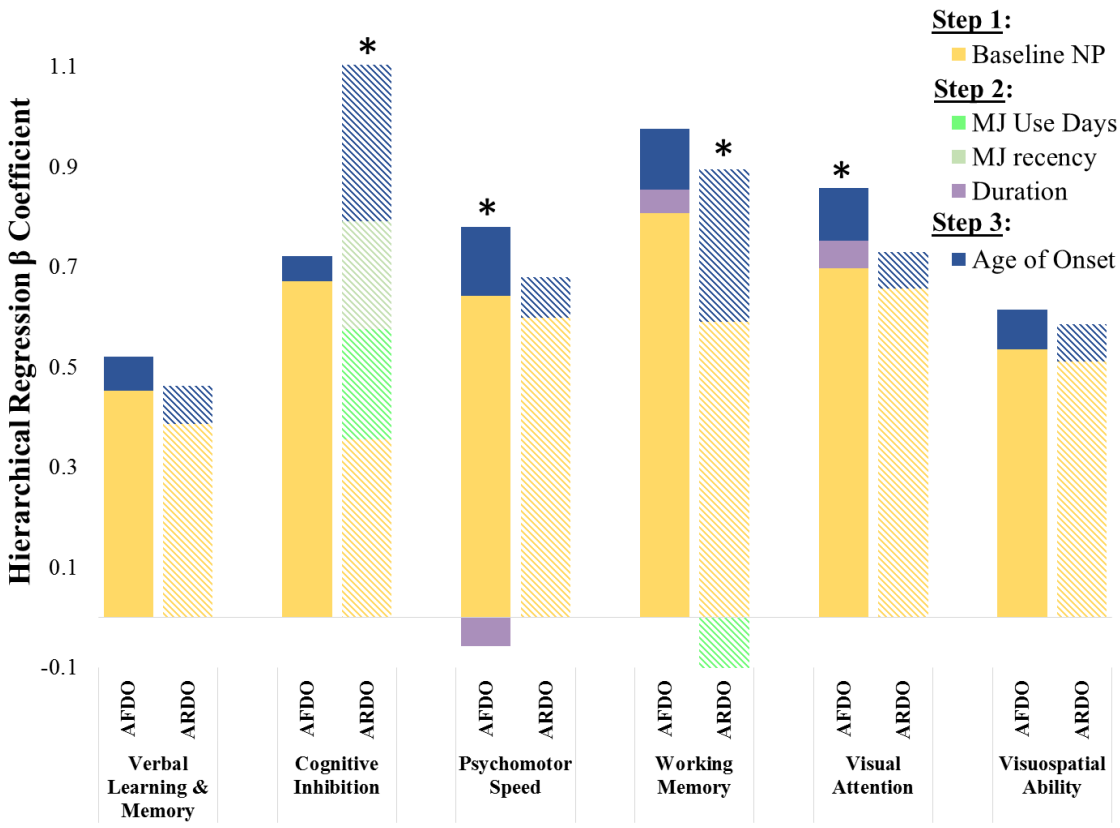


Figure 2. Results of hierarchical regression examining the effects of age of onset on neuropsychological performances in six cognitive domains.

Hierarchical regressions examined the effects of baseline (i.e., pre-drinking) performance in each neuropsychological domain at step 1, other covariates (i.e., follow-up age, substance use disorder familial density, socioeconomic status, externalizing symptoms, lifetime drinking duration, past year drinking and marijuana use days, number of days since last marijuana use) in step 2, and the predictor of interest (age of first drinking onset, *N*=215 or age of weekly drinking onset, *N*=127) in step 3. Positive regression coefficients indicate a positive relationship between age of onset with neuropsychological performance, such that higher ages of first or weekly drinking onset predicted better performance at follow-up 3-4 years after onset; negative regression coefficients indicate the opposite directionality.
AFDO = age of first drinking onset; AWDO = age of weekly drinking onset; MJ = marijuana; MJ recency = number of days prior to neuropsychological testing since last marijuana use occasion

*p<.05

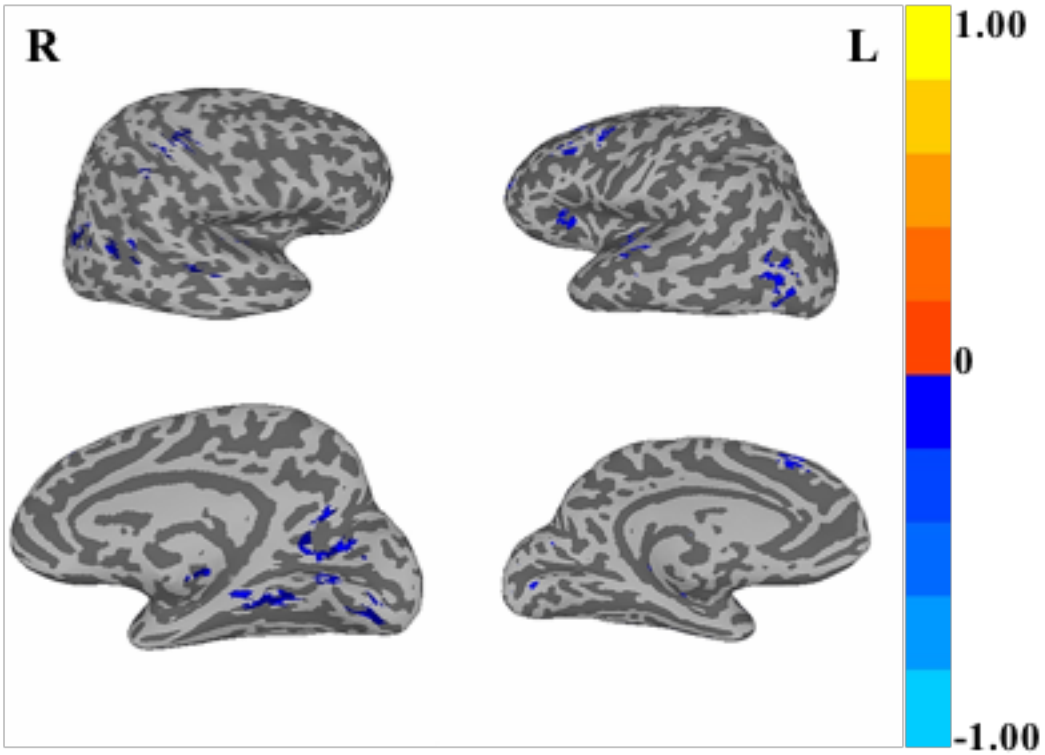


Figure 3. Age of drinking onset and BOLD activation in whole-brain analyses

Regions that showed significant associations between blood oxygen-level dependent (BOLD) contrast response to a visual working memory task 6-2 dot contrast and age of weekly drinking onset (AWDO; *N*= 73). All regions showed a negative relationship, such that higher AWDO predicted decreased activation. No significant relationship between age of first drinking onset and BOLD contrast response was found (*N*= 136).

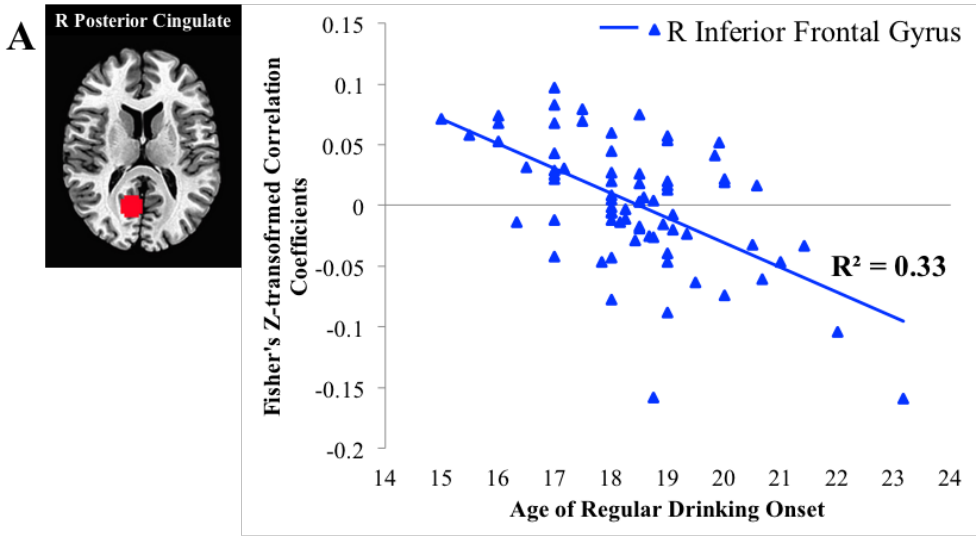


Figure 4. Relationship between age of weekly drinking onset and context-dependent functional connectivity in whole-brain analyses (*N*= 73)

Whole-brain analyses examining the relationship between age of weekly drinking onset (AWDO) and context-dependent functional connectivity (cdFC) in response to a visual working memory task 6-2 dot contrast showed five pairs of regions that showed a significant negative relationship between cdFC and AWDO. Higher AWDO predicted more negative cdFC three years after adolescents transitioned into weekly alcohol use. The right posterior cingulate, left globus pallidus, and left parahippocampal gyrus in A, B, and C, respectively, were spherical anatomical seed regions used in cdFC analyses. Scatter plots depict linear relationship between cdFC (i.e., Fisher's Z-transformed correlation coefficients) and AWDO. Results remained significant even after accounting for the effects of covariates: age, socioeconomic status, drinking duration, externalizing symptoms, tobacco and marijuana use, and binge drinking frequency.

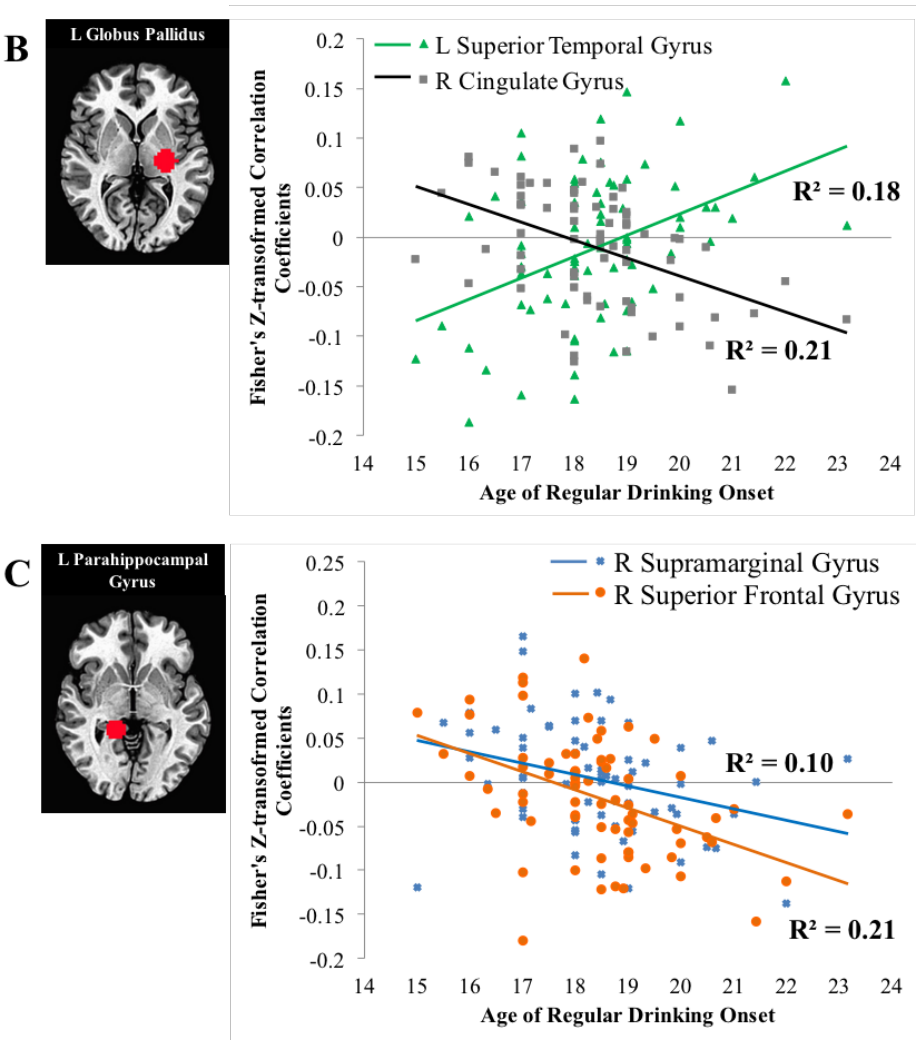


Figure 4. Relationship between age of weekly drinking onset and context-dependent functional connectivity in whole-brain analyses (*N*= 73), Continued