THE EFFECTS OF SOCIAL DRINKING IN OLDER AGE ON COGNITION AND BRAIN HEALTH

BY

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DEDICATION

Without family, my journey is in vain.

To my father, Nasser - my guiding star
To my mother, Mona - my trailblazer
&
To my brother, Zeyaad – my best friend
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<tr>
<td>AAL</td>
<td>Automated anatomical labeling</td>
</tr>
<tr>
<td>ACC</td>
<td>Anterior cingulate cortex</td>
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<td>ATN</td>
<td>Attention network</td>
</tr>
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<td>AUDIT</td>
<td>Alcohol use disorders identification test</td>
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<tr>
<td>BAC</td>
<td>Blood alcohol content</td>
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<td>BMI</td>
<td>Body mass index</td>
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<tr>
<td>BOLD</td>
<td>Blood-oxygen-level dependent</td>
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<tr>
<td>BRC</td>
<td>Brain reserve capacity</td>
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<tr>
<td>CDF</td>
<td>Cumulative distribution function</td>
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<tr>
<td>CES-D</td>
<td>Center for epidemiological studies depression scale</td>
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<tr>
<td>CR</td>
<td>Cognitive reserve</td>
</tr>
<tr>
<td>CSF</td>
<td>Cerebral spinal fluid</td>
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<tr>
<td>CT</td>
<td>Computed tomography</td>
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<tr>
<td>CV</td>
<td>Coefficient of variation</td>
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<tr>
<td>DLPFC</td>
<td>Dorsal lateral prefrontal cortex</td>
</tr>
<tr>
<td>DMANCOVA</td>
<td>Double multivariate analyses of covariance</td>
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<td>DMN</td>
<td>Default mode network</td>
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<tr>
<td>DW-MRI</td>
<td>Diffusion-weighted magnetic resonance imaging</td>
</tr>
<tr>
<td>$E_{\text{glob}}$</td>
<td>Global efficiency</td>
</tr>
<tr>
<td>$E_{\text{koc}}$</td>
<td>Local efficiency</td>
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<tr>
<td>FA</td>
<td>Fractional anisotropy</td>
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<tr>
<td>fMRI</td>
<td>Functional magnetic resonance imaging</td>
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GM: Gray matter
HAROLD: Hemispheric asymmetry reduction model
ICA: Independent component analysis
K: Degree
LOD: Light older drinkers
MANCOVA: Multivariate analyses of covariance
MNI: Montréal neurological institute
MOD: Moderate older drinkers
3MSE: Modified mini mental state exam
N: Node
PCC: Posterior cingulate cortex
PCun: Precuneus
POMS: Profile of moods survey
Q: Modularity
ROI: Region of interest
RSN: Resting state network
SI: Scaled inclusivity
SPM: Statistical parametric mapping
STAC: Scaffolding theory of aging and cognition
SCID: Structured interview for DSM disorders
TBV: Total brain volume
TGMV: Total gray matter volume
TIV: Total intracranial volume
TLFB: Time line follow back
VBM: Voxel-based morphometry
WM: White matter
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ABSTRACT
Recent census data has found that roughly 40% of adults 65 years and older not only consume alcohol but also drink more of it than previous generations. Older drinkers are more sensitive than younger counterparts to the psychoactive effects of alcohol due to natural biological changes that occur with aging, and this may leave them vulnerable to even moderate amounts of alcohol consumption. The focus of this dissertation is on non-problem social alcohol consumption (7-21 drinks per week) in older age (≥ 65 years old), and the overarching goal was to determine whether or not it is associated with exacerbated age-related cognitive decline and brain changes.

Sixty-three individuals that consumed either light (≤ 2 drinks per week) or moderate amounts of alcohol (7-21 drinks per week) participated in this research. To address the effect of social alcohol consumption on cognition, a collection of validated tests commonly used in aging as well as substance use literature were used to evaluate attention, working memory, short-term memory, processing speed, planning, rule learning, and impulse control. Magnetic resonance imaging data was collected at rest and during working memory performance to address effects on measures of brain structure and function. Measures of brain structure included volume and white matter integrity. Functional brain networks were generated to collect measures of network structure, including connectivity and efficiency. An analysis of functional community structure was also conducted.

No evidence was found to support the idea that social alcohol consumption in older adults exacerbated age-related cognitive decline. In fact, moderate older drinkers tended to outperform light older drinkers in attention, short-term memory and rule learning tasks. Despite performing similarly to light older drinkers on a working-memory...
task and showing no difference in brain structure, older moderate drinkers showed greater variability in the way attention-related brain regions functionally connected with the rest of the brain. Overall, findings showed that non-problem social alcohol consumption in older age had little to no effect on age-related cognitive decline or brain changes. Future research will help to address whether or not functional differences are a sign of accelerated brain aging or neural compensation that serves to help improve performance in certain cognitive domains.
CHAPTER I

INTRODUCTION
Alcohol is widely used in the United States and it directly causes both acute and long-lasting detrimental changes in behavior as well as brain function. The central nervous system is in a continuous state of change due to developmental and maturation processes that occur from conception to birth and into older age. Together, these facts make it imperative for researchers to work towards an understanding of how alcohol affects the normal function of the central nervous system at any age. Unfortunately, research studies specifically designed to evaluate alcohol consumption in older adults is particularly lacking.

The studies described in this dissertation were designed to evaluate the effect of long-term social alcohol consumption on aspects of brain health in older adults. Social alcohol consumption included drinking patterns considered to be acceptable by society at large and fell within social norms. Social alcohol consumption was considered to be non-problematic. It did not include heavy drinking (≥5 drinks per day), binge drinking (≥4 drinks in less than 2 hours), alcoholism or other problematic patterns of alcohol consumption. The studies in this dissertation focused on long-term consumption (≥ 3 years) of light (1-2 drinks per week) to moderate (1-3 drinks per day) amounts of alcohol in adults aged 65 years and older. The first section of the Introduction provides a review of the existing literature on alcohol and the aging brain. The second section describes the molecular structure and pharmacological action of ethanol on the brain. The third section details available literature on the effect of long-term heavy alcohol exposure on cognition. The fourth and fifth sections detail available literature on the effect of long-term heavy alcohol exposure on brain structure and function, respectively. The final section of the Introduction will outline the three experiments designed and conducted to
address hypotheses on the effect of social alcohol consumption on cognition and brain health in older adults.

1.1 Alcohol and the Aging Brain

Chronological aging is associated with a variety of biological changes that increase the sensitivity of older adults to alcohol exposure. Increases in the proportion of fat to water and decreases in the rate of liver metabolism expose older adults to higher blood alcohol content (BAC) levels relative to younger adults with similar overall body mass (Vestal et al., 1977). An increased sensitivity to alcohol exposure could exacerbate age-related declines in cognition and brain health. Understanding whether or not these vulnerabilities result in negative outcomes is important because the number of older adults who drink as they age is poised to increase as alcohol consumption becomes more socially acceptable and the percentage of aging individuals sharply increases in the next 20 years (USCB, 2012, 2014). The most recent National Survey on Drug Use and Health conducted in 2012 found that approximately 40% of the estimated 43 million older adults in the US consumed at least one alcoholic drink within the last month. In fact, data have shown that the overwhelming majority of older drinkers in America are light (≤ 3 drinks per week) to moderate (7 – 14 drinks per week) consumers of alcohol, and not considered heavy or binge drinkers (NIAAA, 1998, 2006; SAMHSA, 2013).

The negative consequences of long-term heavy alcohol exposure to cognitive health are well-established findings in alcohol research, and the populations studied range from adolescents to older adults (Health, Human, & Alcohol, 2000; Mukherjee, 2013). However, an understanding of the effects of long-term social alcohol use on cognition in older adults is underdeveloped and the ramifications of this popular pattern of
consumption are unclear (Panza et al., 2009; Panza et al., 2012; Solfrizzi et al., 2007). The first study to detail the effects of long-term moderate alcohol consumption on cognitive health in older adults was published nearly 30 years ago (Goodwin et al., 1987). These and subsequent studies (Kaarin J. Anstey, Mack, & Cherbuin, 2009; Hendrie, Gao, Hall, Hui, & Unverzagt, 1996; Herbert et al., 1993) have been epidemiologic in nature and dominated by analyses that use secondary outcome measures from large-scale clinical trials, like the Framingham Heart Study (Elias, Elias, D'Agostino, Silbershatz, & Wolf, 1999), the Seattle Longitudinal Study (Zanjani, Downer, Kruger, Willis, & Schaie, 2013) and the Women’s Health Initiative (Espeland et al., 2006; Espeland et al., 2005). These studies benefited from large sample sizes and longitudinal queries have been able to explore causal relationships between moderate levels of alcohol consumption and cognition (Edelstein, Kritz-Silverstein, & Barrett-Connor, 1998; Virtaa et al., 2010). While highly valuable, these studies were not specifically designed to measure the effect of moderate alcohol consumption on age-related cognitive decline as the primary outcome. This fact may help to explain the variable findings in literature. To help illustrate this variability are studies that show a negative effect (Dufouil et al., 2000; Zhou et al., 2003), a positive effect (Arntzen, Schirmer, Wilsgaard, & Mathiesen, 2010; Zanjani et al., 2013), and no consistent effect of moderate alcohol consumption on cognition in older adults (Almeida, Hankey, Yeap, Golledge, & Flicker, 2014; Sabia et al., 2014). Consequently, there has been little to no consensus on this matter and the effect of moderate alcohol consumption on cognitive health in older age is still debated.

Age-related structural brain changes, which include gray matter atrophy and decreased white matter integrity (Bozzali, Cercignani, & Caltagirone, 2008; Eyler,
Sherzai, Kaup, & Jeste, 2011; Park & Reuter-Lorenz, 2009), are similar to those that are seen as a consequence of long-term heavy drinking (Monnig, Tonigan, Yeo, Thoma, & McCrady, 2013; Margaret Rosenbloom, Edith V. Sullivan, & Adolf Pfefferbaum, 2003; Natalie M. Zahr, Kaufman, & Harper, 2011). Queries related to the brain have also been extensions of unrelated clinical trials and there is currently little consensus as to whether or not long-term social drinking exacerbates age-related structural brain changes. While multiple studies have shown that long term-moderate alcohol consumption in older age is associated with decreased brain volume (Ding et al., 2004; Kapogiannis et al., 2012; Mukamal, Longstreth, Mittleman, Crum, & Siscovick, 2001; Taki et al., 2006), the most recent studies have actually shown increased brain volume in moderate alcohol consumers (Downer, Jiang, Zanjani, & Fardo, 2014; Gu et al., 2014). In addition to these studies are those that have reported no relationship between social drinking in older age and measures of brain volume (Cherbuin et al., 2008; de Bruin et al., 2005; Preti et al., 2014). Findings related to white matter integrity are similarly inconclusive (K. J. Anstey et al., 2006; de Bruin et al., 2005; A. Pfefferbaum, Rosenbloom, Deshmukh, & Sullivan, 2001; Preti et al., 2014; Sachdev, Chen, Wen, Anstey, & Anstry, 2008; Sasaki et al., 2009).

The ramifications of long-term social alcohol consumption in older adults on brain function have yet to be addressed in literature. However, studies have established that age-related changes to brain function parallel those demonstrated by heavy alcohol drinkers. A common theme is the sensitivity of frontal lobe brain regions to changes in functional activity. It is important to note, however, that both fields of research have documented differences in functional activity across all lobes of the brain. These studies
show that the effect of alcohol and aging on brain function is widespread, and difficult to isolate. They also point out that a key component to understanding the interactive effect of alcohol and aging on the brain involves not only knowing where these changes occur but also understanding how these changes relate to each other.

1.2 The widespread action of ethanol on the brain

Alcohol is a small and highly-soluble molecule that is passively diffused in and out of cells. Since the diffusion of alcohol resembles that of water it can readily pass the blood brain barrier to act on the brain. Contrary to many drugs that have a single site of action, alcohol is capable of producing a wide spectrum of brain effects by interacting with multiple targets. The most predominant effect of alcohol on the central nervous system is to reduce overall neural activity in the brain. This effect is due to alcohol acting by way of allostERIC modulation or direct interaction with several different cell-surface receptors (Diamond & Gordon, 1997; Moonat, Starkman, Sakharkar, & Pandey, 2010). For example, alcohol acts to reduce the excitatory actions of the neurotransmitter glutamate at the ligand-gated N-methyl-D-aspartate (NMDA) ion channel receptors. Alcohol also acts to enhance the inhibitory actions of the neurotransmitters gamma-aminobutyric acid (GABA) and glycine at GABA_A and glycine ligand-gated ion channel receptors. In addition to interacting directly with these synaptic receptors to alter neurotransmitter activity, alcohol can indirectly influence neuronal communication in the brain by altering the production of intracellular messenger molecules via G-protein receptors. Interactions between alcohol and G-protein receptors ultimately lead to changes in the distribution of protein kinases within neurons, which then act to phosphorylate (i.e. activate) a variety of proteins that lead to changes in cell function. For example, alcohol can alter postsynaptic
response efficacy and duration to neurotransmitters by virtue of interacting with G proteins that result in downstream changes in the number of surface receptors and/or neurotransmitter transporters. Finally, the ability of alcohol to directly and indirectly affect the function of key neuronal proteins allows it to produce wide ranging changes to neuronal communication and ultimately influence the workings of the entire brain and thus human behavior.

1.3 The effect of long-term heavy alcohol consumption on cognition

Long-term heavy exposure to alcohol has unequivocally been shown to have adverse effects on cognitive health, with the degree of dysfunction generally following a continuum that is dependent upon the duration and amount of alcohol consumed (Butterworth, 1995; A. Pfefferbaum, Lim, Desmond, & Sullivan, 1996). At one end of the continuum is Korsakoff’s amnestic syndrome, which is common to alcoholics with extremely heavy alcohol consumption patterns (≥ 10 drinks per day) over long periods of time. Korsakoff’s amnestic syndrome is primarily characterized by anterograde amnesia, a cognitive disorder that renders an individual unable to retain new information (Eckardt et al., 1981). Heavy drinkers, who do not necessarily exhibit symptoms of Korsakoff’s amnestic syndrome, also present with deficits in cognitive health. Deficits commonly include general dysfunction in visuospatial and perceptual motor functioning and impairments in many higher order mental processes, like working memory, problem solving, inhibition and emotional control (M. Oscar-Berman & Marinkovic, 2003; Marlene Oscar-Berman & Marinković, 2007; Sullivan, Rosenbloom, Lim, & Pfefferbaum, 2000). In many cases cognitive health can partially recover with extended abstinence (e.g. ≥ 5 years); however, deficits in visuospatial and perceptual motor
functioning appear to be the most long-lasting (Di Sclafani et al., 1995; Peters, Peters, Warner, Beckett, & Bulpitt, 2008; Thomas & Rockwood, 2001).

1.4 The effect of long-term heavy alcohol consumption on brain structure

The first in vivo studies to characterize brain abnormalities associated with alcohol exposure were in alcoholics and used computerized tomography (CT). These studies showed that extremely heavy alcohol use was associated with global reductions in gray matter (GM) volume and enlarged ventricles relative to controls (Carlen, Wortzman, Holgate, Wilkinson, & Rankin, 1978; Jernigan et al., 1982; Kubota et al., 2001; A. Pfefferbaum, Rosenbloom, Crusan, & Jernigan, 1988). Studies that followed went on to show decreased cerebellar tissue volume (Haubek & Lee, 1979) and increased cerebral spinal fluid (CSF) volume in the intracranial zones of the cerebrum (Ishii, 1983; Jernigan et al., 1982; Mutzell, 1992). Quantitative and more sophisticated image analysis techniques, like voxel-based morphometry (VBM), have since been developed and used to measure brain volume deficits associated with alcohol exposure. Much like early research utilizing CT, initial studies utilizing VBM also focused on alcoholics. VBM studies have confirmed observations made with CT but have also helped to show that frontal lobe GM volume is particularly vulnerable and exhibits the greatest atrophy as a consequence of heavy alcohol use (A. Pfefferbaum et al., 1992; A. Pfefferbaum, Sullivan, Mathalon, & Lim, 1997; A. Pfefferbaum, Sullivan, Rosenbloom, Mathalon, & Lim, 1998). Research has also explored the effect of heavy alcohol consumption on the structural integrity of white matter (WM) fibers using diffusion-weighted magnetic resonance imaging (DW-MRI), and shown the degradation of fiber tracts in the centrum semiovale, and the genu and splenium of the corpus callosum (A. Pfefferbaum et al.,
2000; M. Rosenbloom, E. V. Sullivan, & A. Pfefferbaum, 2003). Much like the findings in brain volume, DW-MRI has helped to show that frontal lobe WM microstructure is also particularly vulnerable to deterioration as a consequence of heavy alcohol use (Adolf Pfefferbaum, Rosenbloom, Rohlfing, & Sullivan, 2009). In fact, experts have reached consensus that WM atrophy is a hallmark injury of alcohol use disorders and deficits have generally been observed before losses in gray matter (Kril & Halliday, 1999; M. Oscar-Berman & Marinkovic, 2007; A. Pfefferbaum & Sullivan, 2005).

1.5 The effect of long-term heavy alcohol consumption on brain function

WM fibers make up the structural network connecting subcortical and cortical brain regions and enable neural communication throughout the brain. Efficient communication among brain regions is directly related to the integrity of WM fibers and long-term exposure to heavy amounts of alcohol is therefore capable of disrupting features of brain function. Functional magnetic resonance imaging (fMRI) can be used to non-invasively collect what is known as the blood-oxygen-level-dependent (BOLD) signal. The BOLD signal represents an indirect measure of brain activity over time. It is collected at the resolution of voxels, which represent small cubes of tissue in a 3D image of the brain. The goal of traditional fMRI experiments has been to ascribe function to brain regions, and characterize differences in activation patterns between experimental and control groups. As it relates to long-term alcohol use, literature has focused on the difference in brain activation patterns between alcoholics and controls. Important to the work of this dissertation are studies that used paradigms designed to measure working memory (Desmond et al., 2003; A. Pfefferbaum, Desmond, et al., 2001; Tapert et al., 2001). A common finding to these studies is that alcoholics showed altered activation patterns in
attention-related brain regions. Regions include the dorsal lateral prefrontal cortex (DLPFC) and the parietal cortex, which are collectively referred to as the attention network (ATN) in this dissertation. Altogether, studies support that altered activation patterns are not only localized but also distributed across multiple, non-contiguous brain regions.

More recent analytical techniques have taken an alternative approach to the study of brain function by stressing the importance of connectivity (i.e. interactions) among brain regions. There are three predominant ways to measure functional connectivity using the BOLD signal, which include seed-based correlation analysis, independent component analysis (ICA) and graph theory. In seed-based correlation analyses (Biswal, Yetkin, Haughton, & Hyde, 1995), a region of interest (ROI), or seed, is chosen by the researcher. An ROI can be a single voxel within the brain; however, it is generally a collection of voxels that were previously identified in an fMRI activation study or an atlas-defined brain region. The BOLD signal from the ROI is then extracted and tested for correlation with the BOLD signal extracted from the rest of the voxels (or pre-defined brain regions) in the brain (Fox & Raichle, 2007). Regions with BOLD signals that show a high degree of positive correlation with the seed are considered functionally connected. In ICA, a BOLD time course is decomposed into statistically independent (i.e. isolated) components of activation and their corresponding spatial maps (Beckmann, DeLuca, Devlin, & Smith, 2005). These two methods come with their pros and cons. ICA can be preferred because it does not require a seed and is considered model-free. However, seed-based correlation analyses use the same seed across all subjects in a group, which can be preferred because it simplifies statistical issues and makes group comparisons easier. One
reason group comparisons are difficult when using ICA is the variation in the number of components recovered across subjects in a group. Also, distinguishing components that represent noise from those that represent “true” functional sub-networks is determined by the researcher and as a result considered a subjective process. In both cases, however, changes in the correlation structure are not considered in the context of an integrated whole-brain system. In seed-based correlation analyses only a subset of correlations within the brain are considered and as a result this excludes a great deal of available information. ICA components may collectively represent the entire brain, however, each one is entirely independent from each of the others and this does not allow for communication between components. The recent application of graph theory principles to brain data has helped address this weakness, and a field of network science in functional neuroimaging research has emerged as a result (Lang, Tome, Keck, Gorriz-Saez, & Puntonet, 2012). This research is built on understanding brain function in terms of relationships across the entire brain, and not relative to a seed or a component (Telesford, Simpson, Burdette, Hayasaka, & Laurienti, 2011). Assessments of global and local connectivity can be conducted and enable researchers to measure both integration and segregation in the brain (Rubinov & Sporns, 2010). Network science therefore lends itself well to pharmacological neuroimaging research in older adults and was used in this dissertation as a means of capturing both distributed and localized brain changes that are known to occur as a result both alcohol consumption and aging (Brier et al., 2014; Dennis & Thompson, 2014; N. M. Zahr, 2013).

Networks are made up of a collection of nodes (i.e. things) and the edges (i.e. relationships) between them. In this dissertation, functional brain networks are
represented by image voxels and the relationships between *all voxel pairs* were quantified by calculating the correlation between the BOLD signal time courses. Once a functional brain network is constructed a number of measures can be calculated to describe its structural properties (Bullmore & Sporns, 2009). Common measures include the *clustering coefficient*, which measures the formation of cliques around a particular node and serves as a general measure of integrative capacity. The concept of *path length* is also widely used. It is the average distance between all node-to-node connections in a network and serves as a general measure of distributive capacity (Watts & Strogatz, 1998). This dissertation focused on *modularity*, which is a network measure of community structure (Newman, 2006; Newman & Girvan, 2004). Modularity can be used to assess connectivity throughout the brain and detect communities, or modules, that are more interconnected with each other than with the rest of the brain network. It is a particularly powerful measure because it captures both integration (within-community connections) and segregation (between-community connections). Like ICA components, modules can be thought of as functional sub-networks that are often made up of non-contiguous brain regions. Unlike ICA components, modules are not statistically independent (i.e. isolated) from each other. Importantly, modules exhibit inter-connectivity and therefore allow for the exchange of information across an entire network.

The number of modules in subject’s functional brain network varies slightly across individuals despite similar overall community organization. Therefore, a major challenge in examining community structure has been how to summarize the consistency of modules across subjects and conduct statistical group-comparisons. A common solution has been to assess the community structure of a summary network produced by
averaging sets of pairwise correlations across individuals in a group. This has proven to be a useful data reduction strategy and has been used in previous research (Brier et al., 2012; Meunier, Achard, Morcom, & Bullmore, 2009; Power et al., 2011; Rubinov & Sporns, 2011; Zuo et al., 2011). However, more recent research using a combination of real and simulated networks has shown that average networks do not accurately capture the characteristics of the individual networks used to make the average (Simpson, Moussa et al. 2012). For example, averaging may adequately capture the connection strength between nodes A and B, but it does not consider how node A or B are connected to other nodes in the network. Recently, a method called scaled inclusivity (SI) has been developed to address this weakness (Steen, Hayasaka, Joyce, & Laurienti, 2011). However, the application of SI to human functional neuroimaging data has yet to be conducted and whether or not it more accurately summarizes community structure across a group of individuals remains unclear.

1.6 Dissertation outline

The focus of this dissertation is on social levels of alcohol consumption in older adults and its influence on cognitive health and brain function. Chapter II details the first experiment, which examined network community structure at the group-level without utilizing methodology based on averaging. Addressing this challenge was necessary in order to conduct the analyses in Chapter IV. The goals of the study were to demonstrate the feasibility of using SI on voxel-based functional neuroimaging data to quantify inter-subject community consistency, and to demonstrate its advantages over methods based on averaging.
Chapter III details an experiment designed to determine whether or not long-term moderate alcohol consumption in older age was associated with exacerbated age-related cognitive decline. To do this, validated cognitive tests common to aging and substance use literature were used to evaluate attention, working memory, short-term memory, processing speed, planning, rule learning, and impulse control in both younger and older adult drinkers. The first hypothesis was that younger drinkers would outperform older drinkers in all the cognitive domains tested. Given an increased sensitivity to the effects of alcohol exposure in older age, the second hypothesis was that long-term moderate older drinkers would exhibit exacerbated age-related declines in cognitive ability relative to light older drinkers.

Chapter IV details an experiment designed to determine whether or not long-term moderate alcohol consumption in older age was associated with exacerbated age-related changes to brain health. Brain volume and white matter integrity were assessed. Also, functional brain networks were generated and community structure at rest and during a working memory task was examined. Comparisons between younger and older adults were made to establish age-related differences. Once this was done, comparisons were made between moderate and light older drinkers. The first hypothesis was that older adults would demonstrate age-related declines in brain volume and white matter integrity as well as age-related changes to functional brain network structure. The second hypothesis was that long-term moderate older drinkers would exhibit exacerbated age-related changes to brain health.

Chapter V concludes the dissertation with a summary of the findings and a discussion on how the results fit into our current understanding of alcohol use and the
aging brain. The discussion also addresses what the findings have added to literature and suggests potential avenues for future research.
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CHAPTER II

CONSISTENCY OF NETWORK MODULES IN RESTING STATE fMRI CONNECTOME DATA

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Abstract

At rest, spontaneous brain activity measured by fMRI is summarized by a number of distinct resting state networks (RSNs) following similar temporal time courses. Such networks have been consistently identified across subjects using ICA (independent component analysis). Moreover, graph theory-based network analyses have also been applied to resting-state fMRI data, identifying similar RSNs, although typically at a coarser spatial resolution. In this work, we examined resting-state fMRI networks from 194 subjects at a voxel-level resolution, and examined the consistency of RSNs across subjects using a metric called scaled inclusivity (SI), which summarizes consistency of modular partitions across networks. Our SI analyses indicated that some RSNs are robust across subjects, comparable to the corresponding RSNs identified by ICA. We also found that some commonly reported RSNs are less consistent across subjects. This is the first direct comparison of RSNs between ICAs and graph-based network analyses at a comparable resolution.
2.1 Introduction

In a typical fMRI data set acquired during resting-state, BOLD (blood-oxygen level-dependent) signals often exhibit strong correlations between distant brain areas despite a lack of external stimuli or a cognitive engagement (Biswal, Yetkin et al. 1995, Greicius, Krasnow et al. 2003, Fox, Corbetta et al. 2006). Such elevated correlation, known as functional connectivity, has been identified in the motor cortex (Biswal, Yetkin et al. 1995), the dorsal and ventral pathways (Fox, Corbetta et al. 2006), and the default mode network (Raichle and Snyder 2007), to name a few. One way to find such networks following similar time courses is an ICA (independent component analysis). Without an explicit model, an ICA is able to separate time course data into a collection of independent signals, or components, with each component representing a network following a similar temporal pattern. For example, Damoiseaux et al. (Damoiseaux, Rombouts et al. 2006) examined resting-state fMRI data using ICA and discovered 10 networks that consistently occurred in multiple subjects. Similarly, De Luca et al. (De Luca, Beckmann et al. 2006) identified 5 distinct resting-state networks (RSNs) in BOLD fMRI data. More recently, Doucet et al. (Doucet, Naveau et al. 2011) examined the hierarchical structure of 23 RSNs found by ICA and identified 5 major modules among those RSNs.

Another approach to finding temporally correlated areas in resting-fMRI data is a graph theory-based approach. In such an approach, a functional connectivity network can be constructed based on a strong temporal correlation between brain areas (Bullmore and Sporns 2009). In particular, various brain areas, represented as network nodes, are considered connected to each other if the correlation between them is strong. These
strong correlations among nodes are represented by edges connecting the nodes. In the resulting network, some subsets of nodes may be highly interconnected among themselves, effectively forming communities of nodes. Such communities of nodes, also known as modules, have been identified in a number of brain network studies of resting-state fMRI (He, Wang et al. 2009, Meunier, Achard et al. 2009, Meunier, Lambiotte et al. 2009, Power, Cohen et al. 2011, Rubinov and Sporns 2011). Such modules represent areas of high temporal coherence in the brain, and some of the modules coincide with the RSNs discovered by ICA. For example, a module corresponding to the default mode network has been reported by multiple studies (He, Wang et al. 2009, Meunier, Lambiotte et al. 2009, Power, Cohen et al. 2011) whereas a module covering the motor network was also found in some studies (Meunier, Achard et al. 2009, Meunier, Lambiotte et al. 2009, Power, Cohen et al. 2011, Rubinov and Sporns 2011). It is fascinating that both approaches identify similar building blocks of the functional brain connectivity, but comparing the network modules directly to RSNs from ICA is challenging due to the difference in their spatial resolutions. While RSNs from ICA have a voxel-level resolution, most whole-brain networks are typically much coarser and consist of only a few hundred nodes.

Even though both ICA and graph theory-based network approach can find similar organization structure in the brain, a network approach offers two advantages. First, a network approach can be used to assess similarity or differences in overall network structure quantitatively. Recent advances in network science provide methods to examine how network modules change over time (Mucha, Richardson et al. 2010, Steen, Hayasaka et al. 2011). Such techniques have been applied to fMRI data to examine dynamic
reconfiguration of brain network organization (Bassett, Wymbs et al. 2011). Secondly, a network approach can examine how different modules are connected to and interact with each other. Although network modules tend to form cliques of their own, such modules are also connected to other modules, allowing exchange of information and forming the network as a whole. This is in contrast to ICA, in which each component is independent and isolated from the other components. Therefore, when functional brain networks are constructed at the voxel-level, a resolution similar to ICA, a network based approach offers distinct advantages over ICA in understanding the overall organization of the brain network.

A major challenge in examining network module organization is to summarize the consistency of modules across subjects. This is particularly a concern since each subject’s network structure varies slightly from other subjects even though the overall organization appears similar. One possible solution is to generate a group network summarizing the consistent network connectivity observed in a large number of subjects. Examining the modular organization of the resulting group network may enable evaluation of consistent network modules. The notion of an “average” network sounds very appealing in such a scenario. In fact, several functional network studies have generated a group network by simply averaging the correlation coefficients between the same set of nodes across subjects (Meunier, Achard et al. 2009, Power, Cohen et al. 2011, Rubinov and Sporns 2011, Zuo, Ehmke et al. 2011). Another study has examined whether or not the correlation coefficient between each voxel pair significantly differs from zero (He, Wang et al. 2009). Although averaging correlation matrices across subjects can represent the connectivity between two nodes as an element in the averaged matrix, such an approach
may not accurately summarize the consistent network structure. In other words, such an approach may adequately capture the connection strength between nodes A and B, but this method does not consider how node A is connected to other nodes in the network.

In this work, we attempt to examine modular organization of the resting-state brain network and compare the results to that of the RSNs identified by ICA. To do so, we constructed functional brain networks with fMRI voxels as network nodes (Hayasaka and Laurienti 2010), and thus the resulting network resolution is comparable to that of previous ICA studies. We then examined network modules in these voxel-based networks for consistency across subjects, and whether consistent modules are comparable to the RSNs found by ICA studies. To do so, we employed scaled inclusivity (SI), a metric quantifying consistency of modules across multiple networks of a similar type (Steen, Hayasaka et al. 2011). Our hypothesis is that, if RSNs are stable across subjects, our approach should be able to identify such RSNs as network modules associated with high SI. Since SI can be calculated at the nodal level, the consistency of the resulting modules can be assessed at the voxel-level. Moreover this allows us to compare the consistency of modules to the variability of the corresponding RSNs observed in an ICA study (Damoiseaux, Rombouts et al. 2006).
2.2 Methods

2.2.1 Data

Data used in this work is publicly available as part of the 1,000 functional connectome project (http://fcon_1000.projects.nitrc.org/), a collection of resting-state fMRI data sets from a number of laboratories around the world. From all the data sets available, 4 data sets from 4 different sites were chosen, all consisting of young to middle aged subjects (ages 20-42 years old). Namely, Leipzig data (n=37, male/female=16/21), Baltimore data (n=23, m/f=8/15), Oulu data (n=103, m/f=37/66), and St. Louis data (n=31, m/f=14/17). BOLD fMRI data in total of n=194 subjects (m/f=75/125) were included in our analysis, and all the images were acquired during resting-state with eyes open with a fixation cross.

2.2.2 Network Formation

The resting-state fMRI time series data from each subject was realigned to the accompanying T1-weighted structural image and spatially normalized to the MNI (Montréal Neurological Institute) template by the FSL software package (FMRIB; Oxford, UK), and any non-brain voxels were removed from the fMRI data. The normalized fMRI data was masked so that only the gray matter voxels corresponding to the areas specified by the AAL (Automated Anatomical Labeling) atlas (Tzourio-Mazoyer, Landeau et al. 2002) were included in the subsequent analyses. A band-pass filter (0.009-0.08 Hz) was applied to the masked time series data to filter out any physiological noises and low-frequency drift (Fox, Snyder et al. 2005, van den Heuvel, Stam et al. 2008, Hayasaka and Laurienti 2010). From the filtered data, confounding signals were regressed out, including 6 rigid-body transformation parameters generated...
during the realignment process and 3 global mean time courses (whole-brain, white matter, and ventricles) (Fox, Snyder et al. 2005, van den Heuvel, Stam et al. 2008, Hayasaka and Laurienti 2010). Then a cross-correlation matrix was calculated, correlating each voxel’s time course to all other voxels in the data set. The resulting correlation matrix was thresholded, yielding a binary adjacency matrix describing a network with each voxel as a node. In the adjacency matrix, 0 or 1 indicated the absence or presence of an edge between two nodes, respectively. The threshold was determined in a way that the number of nodes $N$ and the average degree $K$ followed the relationship $N=K^{2.5}$. This thresholding method was used in order to match the edge density across subjects (Hayasaka and Laurienti 2010). The resulting network had the edge density comparable to other types of self-organized networks of similar sizes (Laurienti, Joyce et al. 2011). $N$ and $K$ varied among subjects; the averages of $N$ and $K$ were 20,743 (range=17,255-21,813) and 55.5 (range=53.2-65.5), respectively.

2.2.3 Module Identification

In a network, the modular organization of nodes can be identified by finding densely connected groups of nodes that are only sparsely connected to other groups of nodes (Newman 2006). Thus a network can be partitioned into such groups of nodes, or modules, based on connectivity patterns. There are a number of community detection algorithms, calculating a metric known as modularity $Q$, a quality function describing optimal modular parcellation (Newman 2006). Finding the optimal community structure, or maximizing $Q$, is an NP-hard problem (Newman and Girvan 2004). Thus most algorithms only find an approximate modular partition of a network, and such algorithms often produce different solutions for each run. In this work, we used an algorithm called
Qcut (Ruan and Zhang 2008) to find modular organization in each subject’s brain network. Since Qcut is an algorithm producing different solutions in each run, it was run 10 times for each subject’s network, and the solution producing the highest Q was selected as the representative modular partition for that subject. The number of modules varied across subjects, with 14.5 modules in each subject’s network on average (range=6-29).

2.2.4 Global Scaled Inclusivity

Scaled inclusivity (SI) was developed as a metric to evaluate consistency of the modular organization across multiple realizations of similar networks. It is calculated by measuring the overlap of modules across multiple networks while penalizing for disjunction of modules. For example, a node V is part of module A in subject i and module B subject j. Then SI for node V, denoted as SI\textsubscript{V}, is calculated as

$$SI_V = \frac{|S_A \cap S_B|}{|S_A|} \frac{|S_A \cap S_B|}{|S_B|}$$  

(1)

where S\textsc{A} and S\textsc{B} denote sets of nodes in modules A and B, respectively, and || denotes the cardinality of a set (Steen, Hayasaka et al. 2011). Figure 2.1 shows a schematic of how SI can be calculated across different subjects. Although the overall modular organization is similar across subjects, modules slightly vary from subject to subject (Figure 2.1a). To assess the similarity between two modules from two different subjects, SI can be calculated based on (1) (Figure 2.1b). If the two modules A and B consist of the identical set of nodes, then SI\textsubscript{V}=1. As the overlap between S\textsc{A} and S\textsc{B} diminishes, the numerator of (1) decreases, leading to SI\textsubscript{V}<1. Or, if either S\textsc{A} or S\textsc{B} is larger than the other, then the denominator of (1) increases, resulting in SI\textsubscript{V}<1.
Although the modular organization appears similar across subjects, modules slightly vary from subject to subject (a). Different colors denote nodes belonging to different modules. Among the subjects, one subject is chosen as the referent subject, and any overlap between that subject’s modules and any other modules from the other subjects are determined (b). This process results in maps of overlapping nodes between modules, along with SI values summarizing the fidelity of the overlaps. A weighted sum of the overlap maps, with the SI values as the weights, is calculated, yielding a subject-specific SI map (c). A weighted average of the subject-specific SI maps, with the Jaccard indices as weights, is then calculated, resulting in the global SI map summarizing the consistency of the modular organization across subjects at the nodal level (d).
SI can be calculated between all modules in a particular subject, or the referent subject, against modules from all the other subjects (Steen, Hayasaka et al. 2011). If there is any overlap between the referent subject’s module and a module from another subject, then SI is calculated between the modules and the overlapping nodes are identified (Figure 2.1c). This process results in maps of overlapping nodes between the referent subject’s modules and the other subjects’ module, with the corresponding SI values (Figure 2.1c). A weighted sum of these maps is calculated, using SI as the weight, and the result is a subject-specific SI map. The subject-specific SI map shows the consistency of the referent subject’s modules when compared to the modular organization of all the other subjects (Figure 2.1c). In the subject-specific SI map, each node’s SI value reflects how consistently that particular node falls into the same module across subjects. Although a subject specific SI map can summarize the consistency of the modular organization across subjects, it is highly influenced by the choice of the referent subject (Steen, Hayasaka et al. 2011), as can be seen in Figure 2.1d. In order to avoid a potential bias caused by selection of a particular referent subject, subject-specific SI maps from all the subjects are summarized as a weighted average, with the Jaccard index for each subject as the weight. The Jaccard index summarizes the similarity in modular partitions between two subjects as a single number, ranging from 0 (dissimilar) to 1 (identical) (Ruan and Zhang 2008). The Jaccard indices are calculated between each subject against all the other subjects, and the resulting indices are averaged. The average Jaccard index for each subject describes how similar that subject’s modular partition is to all the other subjects’. The average Jaccard indices are appropriately scaled during the weighted
averaging process. The resulting weighted average map is the global SI map, demonstrating the consistency of modules at each node (Figure 2.1d).

The group SI image is scaled between 0 and n-1; if SI=n-1 at a particular node, that means that node is in the same module with exactly the same set of nodes in all the subjects. Needless to say, such an occurrence is very rare in the brain network. Details on the calculation of the global SI are found in Steen et al. (Steen, Hayasaka et al. 2011). In order to calculate SI across subjects, it is imperative that all the subjects’ networks have the same set of nodes. Since some subjects’ networks had fewer nodes than that of the others, artificial isolated nodes were also included to match the number of nodes. These artificial nodes were treated as a single dummy module during the calculation of SI, and later eliminated from the group SI image.

2.2.5 Module-Specific Scaled Inclusivity

As described above, the global SI image is calculated based on multiple subject-specific SI images (Figure 2.1). Consequently, at a particular node location, it is possible to determine the subject yielding the highest SI value, referred as the representative subject (Figure 2.2a). The highest SI value at that particular node location indicates that the module from the representative subject is considered most consistent across subjects. Once the representative subject is identified, its modular organization is examined and the module containing the node of interest is identified (Figure 2.2a). That module is considered as the representative module yielding the highest SI at that particular node location.

Once the representative module is identified in the representative subject’s network, then it is possible to evaluate SI between that particular module and modules...
For a particular node of interest, the most representative subject with the highest SI is determined from subject-specific SI maps (a). Then the modular organization of the representative subject’s network is examined, and the module containing the node of interest is identified as the representative module. Next, modules with any overlap with the representative module are identified, and the corresponding SI values are calculated (b). A weighted sum of the overlapping modules is calculated with the SI values as weights, summing modules centered around the representative module. The resulting module-specific SI shows the consistency of the representative module across subjects.
from all the other subjects. Modules with any overlap with the representative module are recorded, along with the corresponding SI value (Figure 2.2b). All nodes in the overlapping modules, not just overlapping nodes, are recorded during this process; this is in contrast to the global SI calculation (Figure 2.1d) in which only the overlapping nodes are recorded. Finally a weighted sum of the modules is calculated, with SI values as weights, resulting in the module-specific SI map (Figure 2.2b). Such a module-specific SI map shows the consistency of the representative module across subjects. This is because a module-specific SI map summarizes any modules centered around the representative module by summing them together. Although nodes belonging to the representative module may have high SI values, nodes outside the representative module can also have high SI values if those nodes are consistently part of the same module across subjects (Steen, Hayasaka et al. 2011). A module-specific SI image has the same range as the global SI image, from 0 to n-1. As in the global SI image, SI=n-1 means all the subjects had exactly the same module comprising exactly the same set of nodes.

2.2.6 Average Network

In brain network analyses involving networks from multiple subjects, it is a common practice to generate an average network in order to summarize the common network characteristics present among the study subjects (He, Wang et al. 2009, Meunier, Achard et al. 2009, Power, Cohen et al. 2011, Zuo, Ehmke et al. 2011). However, it is not clear if such an average network truly captures the characteristics of individual networks it aims to represent. In particular, it is not clear whether the modular organization of the network is preserved in an average network. Thus, in order to examine whether an average network has similar characteristics as individual networks, we generated an average
network for the data we used in this study. This was done by averaging the correlation matrices from all the subjects, element by element. Since the number of voxels differed across subjects as described above, for each element in the correlation matrix, some subjects may have a valid correlation coefficient for the corresponding node-pair whereas the other subjects may not have a valid correlation coefficient because either node in the node-pair is missing. Thus, in the calculation of the average correlation matrix, the denominator was adjusted for the number of all valid correlation coefficients at each element of the matrix. The resulting correlation matrix was thresholded in the same way as described above, producing an adjacency matrix based on the average correlation. The modular organization of this average network was examined by the Qcut algorithm as described above.
2.3 Results

The data used in this work were part of the 1,000 functional connectome project (http://fcon_1000.projects.nitrc.org/), a collection of resting-state fMRI data sets from a number of laboratories around the world. Of all the data sets available, 4 data sets from 4 different sites (Baltimore, Leipzig, Oulu, and St. Louis), consisting of n=194 subjects in total, were selected because (i) these data sets consisted of young to middle-aged subjects (20-42 years old) and (ii) these data sets were acquired while subjects’ eyes were open and fixated on cross. The original resting-state fMRI data were processed using the same preprocessing pipeline available in our laboratory (see Methods). Networks were formed by calculating a correlation coefficient for every voxel pair then by thresholding the resulting correlation matrix to identify strong correlations. The threshold was adjusted for each subject in a way that the density of connections was comparable across subjects (see Methods). Each voxel was treated as a node in the resulting network. Each subject’s network consisted of an average of 20,743 nodes. Modules in each subject’s network were identified by the Qcut algorithm (Ruan and Zhang 2008). The algorithm identified sets of nodes that were highly interconnected among themselves and designated them as distinct modules. Each node in the network can only be part of one module at a time.

After modules were identified in all the subjects, the consistency of modules across subjects was assessed using SI. In brief, SI summarizes the overlap of nodes in modules across different subjects while penalizing any disjunction between modules (see Methods). SI is calculated at each node, forming an SI image summarizing across-subject consistency of the modular structure. More specifically, each SI value measures how consistently a particular node falls into a particular module. A high SI value indicates that
the voxel is located in the same module across subjects, while a low SI value signifies
that the voxel is likely part of different modules in different subjects. Theoretically, SI
ranges from 0 to n-1 (n-1=193 in this study) (Steen, Hayasaka et al. 2011). However, in
practice the SI values are considerably lower than the possible maximum value of n-1 due
to disjunction between modules across subjects. Figure 2.3 shows the SI image generated
from all the subjects’ modular organization, thresholded at SI>15. This threshold was
maintained throughout the manuscript to facilitate comparison between modular
organizations. The areas of high SI correspond to areas that were consistently part of the
same modules across subjects. These areas include the occipital lobe, precuneus,
posterior cingulate cortex, pre- and post-central gyri, medial frontal gyri and the
components of basal ganglia.

During the calculation of the global SI map shown in Figure 2.3, we were able to
determine which subject’s module was the most representative at a particular node
(Steen, Hayasaka et al. 2011). This representative module resulted in the largest SI value
at that particular voxel location among all the subjects’ modules. To further examine high
SI areas, the most representative modules that correspond to the brain regions in Figure 1
were identified. These representative modules were then used to summarize consistency
among subjects and SI was calculated with respect to these modules. The resulting
images are module-specific SI images and summarize group consistency at a voxel-level.
Module-specific SI images are analogous to coefficient of variation (CV) images, which
are used in ICA analyses to summarize consistency of RSNs at the voxel-level
(Damoiseaux, Rombouts et al. 2006).
Figure 2.3: Consistency of whole-brain functional modular organization across subjects

Global scaled inclusivity (SI) shows that several brain regions are consistently partitioned into the same modules across individuals. These areas include portions of the following cortices: visual, motor/sensory, precuneus/posterior cingulate, basal ganglia, and frontal.
The visual module covers the entire span of visual cortex and includes both primary and secondary cortices (Figure 2.4). This module is comparable to ICA components like components A and E that were found in Damoiseaux et al. (Damoiseaux, Rombouts et al. 2006), RSN1 in De Luca et al. (De Luca, Beckmann et al. 2006), and module M2b in Doucet et al. (Doucet, Naveau et al. 2011). The corresponding module has also been reported in previous functional brain network analyses, including Module II of He et al. (He, Wang et al. 2009), Module 4 of Rubinov and Sporns (Rubinov and Sporns 2011), and the posterior module of Meunier et al. (Meunier, Achard et al. 2009). Thus, this module is highly consistent among individuals and easily identifiable by both ICA and network methodologies. Moreover, the secondary cortices of the occipital lobe exhibited high SI values (Figure 2.4c), which is comparable to the reduced variability observed in visual components found by a previous ICA study (Damoiseaux, Rombouts et al. 2006).

The sensory/motor module (Figure 2.4) is analogous to the motor network identified by the seed-based correlation method (Biswal, Yetkin et al. 1995). The most consistent regions within this module include the pre- and post-central gyri. On the other hand, the supplementary somatosensory area (S2), surrounding auditory cortex and portions of the posterior insula show reduced consistency across subjects. This module roughly corresponds to component F in Damoiseaux et al. (Damoiseaux, Rombouts et al. 2006), RSN3 in De Luca et al. (De Luca, Beckmann et al. 2006), and module M2a in Doucet et al. (Doucet, Naveau et al. 2011). Similar to the results reported by Damoiseaux et al. (Damoiseaux, Rombouts et al. 2006), the consistency of this module was lower than that observed for both DMN and visual modules (Figure 2.4). Module I of He et al. (He,
Row 1: Four functional modules were found to be highly consistent across subjects. These modules include the visual (yellow), sensory/motor (orange) and basal ganglia (red) cortices as well as the default mode network (precuneus/posterior cingulate, inferior parietal lobes, and medial frontal gyrus; maroon). Overlap among these modules was present but minimal (white). Rows 2-5: Module-specific SI images for each of the four most consistent modules, namely the visual (row 2), sensory/motor (row 3), basal ganglia (row 4), and default mode (row 5) modules. Note that the visual, sensory/motor and basal ganglia all show higher consistency across subjects than the default mode module. Among the default mode areas, the precuneus and posterior cingulate cortex show the greatest consistency across subjects.
Wang et al. 2009) and Module 1 of Rubinov and Sporns (Rubinov and Sporns 2011) demonstrate similarities with our sensory/motor module. Interestingly, these previously reported modules also include portions of the insula and auditory cortices. These findings are not only consistent with ours but also to previous reports of the ICA results.

The basal ganglia module (Figure 2.4) consisted of the caudate, globus pallidus, putamen, and thalamus. It also extended into the medial temporal lobe, temporal pole, parahippocampal gyrus, hippocampus, amygdale and cerebellum. Interestingly, these brain regions have not been consistently classified into one component by ICA. While De Luca et al.’s RSN3 suggests some involvement of the hippocampus and thalamus (De Luca, Beckmann et al. 2006) within the motor component, other ICA studies did not find a component similar to this module (Damoiseaux, Rombouts et al. 2006, Doucet, Naveau et al. 2011). Studies that have identified components within the basal ganglia include of the work of Damoiseaux and colleagues (2008), where the thalamus, putamen and the insula defined one component. Findings also include components that consist of portions of the striatum [Luo, C. et al. (2011), Abou-Esleoud (2010); Kiviniemi et al. (2009)]. In addition to this, basal ganglia modules have been previously reported in studies that have used network methodologies. For example, Module V found by He et al. (He, Wang et al. 2009) and Module 3 by Rubinov and Sporns (Rubinov and Sporns 2011) contain all the regions of the basal ganglia. Variations of this have also been described in the central module of Meunier et al. (Meunier, Achard et al. 2009) and in the RSN3 of De Luca et al. (De Luca, Beckmann et al. 2006). Though these findings contain similar regions as our module, they extend further into the insular and motor cortices. Functional connectivity of the cerebellum with the rest of the basal ganglia proved unique in our results compared
to previous network module findings. Although global SI (Figure 2.3) values did not indicate high modular consistency of the cerebellum across subjects, the module-specific SI map shows that it is consistently part of the basal ganglia module across subjects.

The default mode network (DMN) (Raichle, MacLeod et al. 2001, Raichle and Snyder 2007) was also identified as a consistent module across subjects (Figure 2.4). This module included the precuneus (PCun), posterior cingulate cortex (PCC), inferior parietal cortex, superior medial frontal cortex, and anterior cingulate cortex (ACC). The PCC exhibited elevated SI values and was found to be the most consistent brain region of the DMN. In comparison, the SI values of the medial frontal gyri were attenuated, indicating this region to be less consistently found in the DMN module.

The intra-modular consistency of this module appeared comparable to the reduced variability of the DMN component found by an ICA (Damoiseaux, Rombouts et al. 2006). While this module covers the brain areas typically considered as part of the DMN, weaker SI in the frontal portion also suggests that the anterior and posterior portion of the DMN may not be as strongly coupled as the rest of the DMN. This may be because the connectivity pattern is slightly different between the anterior and the posterior portions of the DMN. Research supporting this hypothesis includes that of Andrews Hanna, J.R., et al. (2010) using temporal correlation analysis. In this study the authors determined that the DMN was composed of multiple components, including a medial core and a medial temporal lobe subsystem. Using ICA, Damoiseaux, J.S., et al. (2008) described two RSN components that together included the superior and middle frontal gyrus, the posterior cingulate, the middle temporal gyrus and the superior parietal cortices. Finally the work
of Greicius et al. note differences in the seed-based connectivity of the DMN when the seed was placed in either the PCC or the ventral ACC (Greicius, Krasnow et al. 2003). Among the modules shown in Figure 2.4, there were more than one choice for the most representative subject in the sensory/motor module and the default mode module. This can be seen in Figure 2.5 showing the image of the most representative subject by voxel locations. Within the motor / sensory strip and the precuneus, there were two subjects with the highest SI values. Even though either of these subjects could serve as the representative subject for these modules, the overall consistency of the entire module was still captured, as the module specific SI images appear strikingly similar even if different subjects were chosen as the representative subject (Figure 2.5).

The number of modules in Figure 2.3 seems surprisingly few, especially when compared to previous reports of ICA (Damoiseaux, Rombouts et al. 2006, Doucet, Naveau et al. 2011). Our results, however, do not indicate the absence of modules similar to previously found ICA components. Instead, some were only found to be less consistently organized across subjects (Figure 2.6). These modules do not necessarily include similar sets of nodes across subjects, and consequently do not exhibit high global SI values (Figure 2.3). Two of such modules are the ventral (superior parietal cortex as well as superior and medial frontal gyri) and dorsal (superior parietal cortex, superior and dorsal lateral frontal, and precentral gyri) attention networks identified by previous fMRI analyses (Fox, Corbetta et al. 2006). A previous ICA finding has combined these two systems into the same component (De Luca, Beckmann et al. 2006) while others have separated them into separate components for the left and right hemispheres (Damoiseaux, Rombouts et al. 2006, Doucet, Naveau et al. 2011). Here we present two distinct modules.
Of the four functional modules that were found to be highly consistent across subjects, two (motor/sensory cortices and the default mode) had multiple representative subjects that could have been chosen to calculate module-specific SI. Here we show that in each case the resulting module specific SI map is similar in the brain areas that are included as part of the overall module. For instance, images of the most representative subject by voxel location (top panel) show that two individuals are the most representative for the motor and sensory cortices, respectively. However, when each of these individuals was used to calculate module-specific SI it was found that the resulting module included both cortices.
Three resting state networks (RSNs) exhibited attenuated consistency across subjects, relative to those shown in Figure 2.4. Module-specific SI images are shown for the ventral attention network (superior parietal lobules, dorsal lateral prefrontal cortex and portions of the medial frontal gyrus, row 1), dorsal attention network (superior parietal lobules, intraparietal sulci, precentral and superior frontal gyri, row 2), and the cerebellum module (row 3).
corresponding to the separate ventral and dorsal attention systems which have also been found in previous network analyses (He, Wang et al. 2009, Power, Cohen et al. 2011). It is interesting to note that low SI values in our ventral and dorsal attention modules (Figure 2.6) are in contrast to the stability of corresponding components found using ICA (Damoiseaux, Rombouts et al. 2006).

In addition to the ventral and dorsal attention modules, we present a module containing the cerebellum (Figure 2.6). Though the cerebellum was found to be consistently connected to the basal ganglia (Figure 2.4), many nodes within the cerebellum formed a unique module by themselves. However, reduced module-specific SI values indicate that this module demonstrates limited consistency across subjects. Thus, while the cerebellum may belong to the same module as the basal ganglia in some subjects, in another group of individuals the cerebellum belong to an isolated module as shown in Figure 2.6.

We used SI to assess the consistency of modules across subjects rather than calculating the average network, which has been used by some researchers to generate a “summary” network for a study population (He, Wang et al. 2009, Meunier, Achard et al. 2009, Power, Cohen et al. 2011, Rubinov and Sporns 2011, Zuo, Ehmke et al. 2011). An average network, which is produced by averaging correlation matrices across subjects, does not properly represent the characteristics of the individual networks (Simpson, Moussa et al. 2012). Rather, it produces a network whose key modular structure is altered from that of the individual networks. Figure 2.7 shows an example of such an alteration. In particular, we generated an average network by averaging the correlation matrices from all the subjects (n=194). This average correlation matrix was then thresholded
Figure 2.7: The modular structure of the average network

a) The modular structure of the average network, with each color indicating a distinct module. Note that the default mode network is split into two modules: b) anterior (medial frontal gyrus, green) and c) posterior (precuneus/posterior cingulate & inferior parietal lobes, red) modules. d) On the other hand, both anterior and posterior default mode regions appear consistent across subjects when analyzed using module-specific SI. e) Representative subjects from each of the four data sets confirm that both anterior and posterior portions of the DMN constitute one module at the individual level.
and modular organization was then detected on the resulting adjacency matrix. The modular organization of this average network is shown in Figure 2.7a, with each color denoting a network module. The data used in our analysis represent a subset of the subjects used by (Zuo, Ehmke et al. 2011) and show that modular organization is very similar to theirs. Most striking, however, is the modules associated with the default mode. Using an average network, we find that two distinct anterior (Figure 2.7b) and posterior (Figure 2.7c) modules exist. This is in stark contrast to the DMN module-specific SI image, which does not separate into anterior and posterior parts (Figure 2.7d). To add further confidence in this finding, DMN modules of the individuals of each data set were examined. We found that the anterior and posterior portions of the DMN were indeed commonly found as one module (Figure 2.7e).

A comparison between the other three SI modules shown in Figure 2.4 and the two shown in Figure 2.6 with those from the mean network are presented in Figure 2.8. Here we show the modules for the visual and motor/sensory cortices as well as the basal ganglia from the average network. These three modules comprise similar areas represented in the module specific SI images of the corresponding modules in Figure 2.4. In addition to previously mentioned differences (Figure 2.7b, c), we show that average modules corresponding to the ventral and dorsal attention brain regions are quite different than those found using module specific SI in Figure 2.6. For instance, averaging correlation matrices across individual subjects resulted in the separation of the left from the right dorsal lateral prefrontal cortex. Neither of these modules included the superior portions of the parietal lobules. Instead, these brain areas were identified as a separate module. Interestingly, this module included bilateral secondary sensory cortices.
Figure 2.8: Selected modules from average network

Shown here are the modules from the average network that correspond to the module-specific SI images shown in Figures 2.4 & 2.6. The modules from the average network that correspond to the motor/sensory cortices, the basal ganglia and the cerebellum were found to be similar with respect to their corresponding module-specific SI image. However, two distinctions were found in addition to those demonstrated in Figure 2.7. First, the average visual module includes only the area of the primary visual cortex. This is in contrast to the module-specific SI image for the visual cortex shown in Figure 2.4, which extends into secondary visual cortices. Second, the average network segregates the anterior from the posterior portions of the ventral and dorsal attention systems. In this case, the anterior portion consists of two modules, one for each of the bilateral dorsal lateral prefrontal cortices. Interestingly the posterior element of both ventral and dorsal attention systems (superior parietal lobules) is not separated into bilateral portions. It does, however, include secondary sensory cortices.
Averaging alters not only modular organization, but also other network characteristics (Simpson, Moussa et al. 2012). Figure 2.9 shows the distributions of node degree, or the number of edges per node, for all n=194 subjects (blue) as well as that of the average network (red). As it can be seen in Figure 2.9, the average network has far more low degree nodes than any of the subjects in the data set. However, the average network lacks medium degree nodes and thus its degree distribution drops faster than that of the other individual networks. Various network metrics are also altered in the average network. For example, the clustering coefficient and the path length, describing tight local interconnections and efficient global communication respectively (Watts and Strogatz 1998), are significantly different (p<0.0001, one-sample T-test) from that of the individual networks (Table 2.1). Taking all these observations together, we can conclude that the average network does not accurately represent characteristics of individual networks in the data.
Figure 2.9: Degree distributions of the average network and individual networks

The distribution of the number of connections at each node, or degree, is plotted for each of the 194 subjects (blue), as well as for the average network (red). The Y-axis is the complimentary cumulative distribution (i.e., 1 minus the cumulative distribution function (CDF)). The average network has more low degree nodes than any of the other individual networks. The degree distribution of the average network, however, drops dramatically for degrees greater than 10, suggesting that there are fewer medium degree nodes.
Table 2.1: Comparison of network characteristics between the average network and individual networks

<table>
<thead>
<tr>
<th></th>
<th>Clustering coefficient</th>
<th>Path length</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Average network</strong></td>
<td>0.457</td>
<td>7.64</td>
</tr>
<tr>
<td><strong>Mean (SD) of individual networks</strong></td>
<td>0.353 (0.031)</td>
<td>5.14 (0.52)</td>
</tr>
</tbody>
</table>


2.4 Discussion

In this work, consistency of modules in resting-state functional connectivity networks was examined at the voxel-level, a resolution comparable to that of group ICA. Module consistency across subjects (n=194) was assessed and the results were compared to ICA components and network modules previously reported by other studies. Modular consistency was assessed using SI, which quantifies inter-subject variability in modular organization. The use of SI also allowed us to examine inter-subject consistency of a particular module at the voxel-level. This showed what brain regions within a module were consistent in an analogous fashion to group ICA results (Damoiseaux, Rombouts et al. 2006). Our global SI data show that only a handful of brain areas were consistently organized in modules. These modules alone, however, were not found to constitute the entire network. Instead, we show that other network modules are less consistent across subjects; multiple examples are presented to convey this point.

Interestingly, despite the large number of nodes in our brain network data, the number of major modules did not change dramatically from the previously reported brain network modularity (He, Wang et al. 2009, Meunier, Achard et al. 2009, Meunier, Lambiotte et al. 2009, Power, Cohen et al. 2011, Rubinov and Sporns 2011, Wu, Taki et al. 2011). Increasing the network resolution (the number of nodes used to model the brain as a network) did not result in more modules. Power et al. (Power, Cohen et al. 2011) also discovered a similar number of modules despite differences in the network resolution. This is particularly interesting because Power et al. (Power, Cohen et al. 2011) cautioned against using network nodes that were not derived based on brain functional anatomy. Based on our finding and Power et al.’s finding, we conclude that modular
structure is robust and can be ascertained despite differences in the parcellation scheme of the brain. However, a voxel-based network is advantageous since the shape of each module can be determined at finer granularity. A voxel-based network also enables examination of intra-modular characteristics within a particular brain area.

Some RSNs, although reported in multiple studies, were not found to be consistent in our analysis. This may falsely suggest that there are only a handful of modules in the resting-state functional brain network. Other modules, however, exist and are found when modules from each subject’s network are examined carefully. A few examples of such network modules are shown in Figure 2.6, with somewhat attenuated SI values than the RSN modules reported in Figure 2.4. Thus, the global SI image needs to be interpreted carefully. It cannot be used to identify a “significant” module that exceeds a certain threshold, an approach commonly used in a typical fMRI analysis. It only enables assessment of modular consistency across subjects and does not eliminate the need to qualitatively evaluate network structure (Telesford, Simpson et al. 2011). In fact, the extension of the basal ganglia module into the cerebellum (Figure 2.4) could not have been observed if this module were not carefully examined.

The work of Kiviniemi et al. (2009) serves as a prime example of ICA of data similar in demographic characteristics and scanning protocol to the data in our analysis. These data, which were collected at Oulu University, identified several components that are similar to modules described in our study. The authors used peri-Sylvian, occipito-parietal, frontal and temporal signal sources to describe 42 RSN components. These results do bear similarity with our presented findings. For example, these authors described components consistent with the functional association of major cortical areas,
including the visual, sensory and motor cortices. In addition to this, they present a component similar to the dorsal attention module presented in Figure 2.6. However, modular analysis of consistent functional neighborhoods in the brain does in fact differ from the results of ICA. The most prominent dissimilarity is the number of components in relation to the number of modules. For instance, the visual module identified in our study corresponds to seven separate components found in Kiviniemi et al. (2009). Also, the ventral attention module described here is a functional neighborhood comprised of the DLPFC and the superior parietal lobules. Using ICA, however, the DLFPC was found to be an isolated component. Finally, these authors showed that, depending on the number of components, the anterior and posterior portions of the DMN are separated into distinct components.

When examining the consistent modular organization present in a group of subjects, one may be tempted to generate an average network and examine its modular organization. This approach seems intuitive and reasonable especially for those neuroimaging researchers who are accustomed to voxel-based analyses of neuroimaging data. The notion of average images may sound reasonable in fMRI analyses examining activation patterns through the averaging of multiple individual activation maps; hence one may believe that averaging connection strengths across subjects may also result in a network that summarizes the overall characteristics of the group. Although such an averaging process may be able to summarize the correlation between two particular nodes, it alters the characteristics of the network as a whole tremendously. Such altered characteristics include the modular organization (Figure 2.7), degree distribution (Figure 2.9), and network metrics (Table 2.1). Moussa et al. also demonstrated that average
metrics do not imply regional consistency (Moussa, Vechlekar et al. 2011). Since the average network does not necessarily represent the characteristics of the networks it aims to represent, an alternative approach should be considered in summarizing a collection of networks. For the modular organization in particular, selecting a representative subject, based on the Jaccard index, is a simple solution (Joyce, Laurienti et al., Meunier, Lambiotte et al. 2009). The SI-based approach, as used in this paper, is a more sophisticated way to examine consistency of modular organizations across subjects.

Several network science methods have been developed to compare the modular organization across multiple networks (Mucha, Richardson et al. 2010, Steen, Hayasaka et al. 2011), thus application of such methods in brain network data is more appropriate than simply averaging correlation matrices.

Our use of SI demonstrated consistency of the network modular structure quantitatively. However, there are some limitations associated with our approach. First, in the algorithm we used to identify modules (Ruan and Zhang 2008), each node can only be part of one module. However, it is plausible that some parts of the brain, in particular multi-modal areas, may be associated with multiple modules at once. In recent years, a number of algorithms have been proposed to analyze overlapping modules (Palla, Derenyi et al. 2005, Kovacs, Palotai et al. 2010, Lancichinetti, Radicchi et al. 2011) in which some nodes are assigned to multiple modules. Such an algorithm has been applied to an analysis of a 90-node structural brain network and overlap between modules has been outlined (Wu, Taki et al. 2011). However, interpretation of such overlapping modules is unclear. Moreover, since overlapping module algorithms tend to be computationally intensive, applying such methods to brain networks at the voxel-level
may pose a significant challenge. However, the evaluation of modular consistency across a group of individuals can identify multiple modular structures that contain a single brain region. This was observed with the cerebellum in our work. Another limitation of our approach is that the algorithm to identify modules is imprecise. Identifying the true modular structure of a network is an NP-hard problem (Newman and Girvan 2004). Most algorithms that find modular organization, including Qcut (Ruan and Zhang 2008), can yield only an approximation to the true solution and have some variability associated with each approximated solution. To overcome this problem, we ran Qcut 10 times for each subject’s network, and selected the most representative modular partition as the best solution (see Materials and Methods). Even then, the variability in the modular organization cannot be completely eliminated. However, we believe that, if the modular organization of the brain network is truly robust across subjects, our global SI image can identify nodes that belong to the same module despite some variability in modular partitions. Finally, some issues remain as inherent confounds. One example includes the effect of head movement correction on our analyses and their functional interpretation. For instance, the work of Van Dijk, K.R. et al., 2012 demonstrates the difficulty of controlling for head movement even after extensive correction. This confound has also been described in the work of Power, J.D. et al., 2012 and Satterthwaite, T.D. et al., 2012.

In summary, we found that the functional brain network at resting-state consisted of several modules that are highly consistent across subjects. These modules were analogous to the RSNs found in previous ICA and network analyses, even at the voxel-level resolution. Consistency of these modules across multiple study sites, with different MRI scanners and imaging protocols, indicates robust yet consistent organization of the
functional connectivity network at rest. The methodology used in this work can be further extended to examine alterations in the modular structure of the brain network under various cognitive states or neurological conditions.
REFERENCES


CHAPTER III

LONG-TERM MODERATE ALCOHOL CONSUMPTION DOES NOT EXACERBATE AGE-RELATED COGNITIVE DECLINE IN HEALTHY, COMMUNITY- DWELLING OLDER ADULTS


The following chapter was published in 2014 in the journal *Frontiers in Aging Neuroscience, 6*(341)
DOI: 10.3389/fnagi.2014.00341
Abstract

Recent census data has found that roughly 40% of adults 65 years and older not only consume alcohol but also drink more of it than previous generations. Older drinkers are more vulnerable than younger counterparts to the psychoactive effects of alcohol due to natural biological changes that occur with aging. This study was specifically designed to measure the effect of long-term moderate alcohol consumption on cognitive health in older adult drinkers. An extensive battery of validated tests commonly used in aging and substance use literature was used to measure performance in specific cognitive domains, including working memory and attention. An age (young, old) * alcohol consumption (light, moderate) factorial study design was used to evaluate the main effects of age and alcohol consumption on cognitive performance. The focus of the study was then limited to light and moderate older drinkers, and whether or not long–term moderate alcohol consumption exacerbated age-related cognitive decline. No evidence was found to support the idea that long-term moderate alcohol consumption in older adults exacerbates age-related cognitive decline. Findings were specific to healthy community dwelling social drinkers in older age and they should not be generalized to individuals with other consumption patterns, like heavy drinkers, binge drinkers or ex-drinkers.
3.1 Introduction

Alcohol consumption among older adults is on the rise in the United States. To illustrate this point, the cumulative probability of exposure to alcohol before the age of 100 years old was confined to approximately 50% of the US population between the years of 1894 and 1937, and in 1974 it rose to 75% by the age of 30 years old (USDA and USDHHS 2010, Wang and Andrade 2013). The most recent National Survey on Drug Use and Health conducted in 2012 found that approximately 40% of the estimated 43 million older adults in the US consumed at least one alcoholic drink within the last month and that the majority of these individuals were neither heavy drinkers nor binge drinkers (SAMHSA 2013). In fact, findings from the National Longitudinal Alcohol Epidemiologic Survey (NLAES) (NIAAA 1998) and the National Epidemiologic Survey on Alcohol and Alcohol Related Conditions (NESARC) (Fryar, Hirsch et al. 2006, NIAAA 2006) show that the majority of older American drinkers consume light (≤ 3 drinks/week) to moderate (7–14 drinks/week) amounts of alcohol. Potential reasons for an overall increase in moderate alcohol consumption may stem from the belief that exposure to moderate levels of alcohol is associated with psychological (Peele and Brodsky 2000) and physiological (Marchi, Muniz et al. 2014) benefits as well as a lower risk of developing dementia syndromes (Panza, Capurso et al. 2009, Panza, Frisardi et al. 2012).

In today’s world, older adults enjoy longer lives and rely on their cognitive abilities for many years prior to the debilitating losses in brain function associated with dementia (Plassman, Langa et al. 2007, W.H.O. 2012). Older adults, however, are still subject to significant biological changes that occur with normal aging and that make them
particularly vulnerable to alcohol exposure. For example, increases in the proportion of fat to water and decreases in the rate of liver metabolism expose older adults to higher blood alcohol content (BAC) levels relative to young adults with similar overall body mass (Vestal, McGuire et al. 1977). Ethanol, which acts directly on the central nervous system, has psychoactive properties that are known to significantly affect behaviors like attention, working and short-term memory (Guillot, Fanning et al. 2010, Dry, Burns et al. 2012, Magrys and Olmstead 2014). These neurologic effects can be transient and reversible in the case of acute alcohol exposure (Gilbertson, Ceballos et al. 2009, Sklar, Gilbertson et al. 2012). On the other hand, problematic drinking habits like those practiced by older heavy drinkers and alcoholics have been firmly associated with severe cognitive deficits that can persist even after years of abstinence (Thomas and Rockwood 2001, Peters, Peters et al. 2008).

It is not clear, however, whether or not long-term moderate (i.e. social) drinking affects age–related cognitive decline. Research addressing this topic is primarily epidemiologic in nature and dominated by analyses that use secondary outcome measures from large-scale clinical trials, like the Framingham Heart Study (Elias, Elias et al. 1999), the Seattle Longitudinal Study (Zanjani, Downer et al. 2013) and the Women’s Health Initiative (Espeland, Gu et al. 2005, Espeland, Coker et al. 2006). These and similar trials collected summary measures related to alcohol consumption and overall cognitive health but were not specifically designed to measure the effect of moderate alcohol consumption on age-related cognitive decline as the primary outcome. See reviews for more detail (Solfrizzi, D’Introno et al. 2007, Peters, Peters et al. 2008, Panza, Capurso et al. 2009, Kim, Lee et al. 2012, Panza, Frisardi et al. 2012).
This study was specifically designed to determine the effect of long-term moderate alcohol consumption on age–related cognitive decline in healthy community dwelling adults. A collection of validated tests commonly used in aging as well as substance use literature was used to evaluate attention, working memory, short-term memory, processing speed, planning, rule learning, and impulse control. The first study hypothesis was that younger drinkers would outperform older drinkers in all the cognitive domains tested. Heavy alcohol use in older age has been linked to severe deficits in cognitive health (Moriyama, Mimura et al. 2006, Green, Garrick et al. 2010) and because of this it was thought that the effect of alcohol consumption level on cognition would follow a continuum. Therefore, the second study hypothesis was that light older drinkers would outperform moderate older drinkers on all the cognitive domains tested. At present, there is no curative treatment or therapeutic approach to reversing age-related declines in cognitive function. Understanding whether or not older adults are more vulnerable to such declines as a result of long-term moderate alcohol consumption will help a growing segment of the older American population make informed decisions about their cognitive health.
3.2 Methods

Our main study question focused on the effect of moderate alcohol consumption on cognitive function in older adults, and to best address this question we adopted an age (young, old) * alcohol consumption (light, moderate) factorial study design. All participants were residents of Winston-Salem, North Carolina, and were recruited via local advertisements (physical flyers and internet) and by word-of-mouth. The Institutional Review Board of Wake Forest School of Medicine approved the study (IRB # 19961) and all participants gave written informed consent.

3.2.1 Study Population

A total of 63 individuals were enrolled in the study, and of these individuals 22 were younger adults (24-35 years old) and 41 were older adults (65-80 years old). The final study groups were as follows: 11 light young, 11 moderate young, 20 light old and 21 moderate old drinkers. Census findings from the NLAES and the NESARC were used to help define light and moderate alcohol consumption criteria. Criteria were also defined such that light and moderate alcohol intake did not overlap. Light alcohol consumption was defined to be 1-8 drinks per month and did not exceed 2 drinks per week. Moderate alcohol consumption was defined as 7-21 drinks per week and did not exceed 3 drinks per day. Enrollment in the study was dependent on the self-report number of drinks per week as measured by the Time Line Follow Back (TLFB) questionnaire (Sobell and Sobell 1992). Daily alcohol intake over 3 months was measured and only adults who reported maintaining either a light or moderate alcohol consumption pattern for at least 3 years were included.
3.2.2 Exclusion Criteria

3.2.2.1 Alcohol and other substance use

Participants were excluded if they reported more than 1 binge in the last 3 months (≥5 drinks for men and ≥4 drinks for women in less than 2 hours) (NIAAA 2004). Disqualification from the study also included a > 0.00 alcohol reading as measured by an Intoxilyzer S – D5 breath alcohol screen (www.alcoholtest.com), or a positive test for illicit substance use as measured by an Alere iCassette 6 – panel drug screen at the start of any study visit (cocaine, THC, opiates, amphetamines, methamphetamines or benzodiazepines, www.alere.com). Use of illicit substances within the last 3 months was also grounds for disqualification. Subjects with a history of alcohol or drug abuse/dependence and/or current (within the last 6 months) Axis I disorders as determined by the Structured Interview for DSM Disorders (SCID) were also excluded (Fist, Spitzer et al. 2002). Individuals who consumed greater than 500 mg of caffeine per day were not included in this study so as to avoid the effects of excessive caffeine exposure or caffeine withdrawal on cognitive performance. Also, individuals who smoked ≤ 30 cigarettes (i.e. individuals defined by the World Health Organization as nonsmokers – heavy smokers) were allowed to participate in the study so that during recruitment any potential confounding difference in cigarette smoking between light and moderate drinkers could be avoided.

3.2.2.2 Cognitive

Participants at high risk for dementia as measured by the Modified Mini Mental State Exam (3MSE score ≤ 80) (Jones, Schinka et al. 2002), those with active neurological dysfunction that may affect cognitive processing (i.e., schizophrenia, Alzheimer’s
disease, Parkinson’s disease, prior history of stroke, epilepsy, mental retardation and attention deficit-hyperactivity disorder) as well as those using antipsychotic and/or antiepileptic medications with known neurological/cognitive side effects were excluded. Individuals with previous brain surgery, serious CNS trauma as defined by a history of acquired sub- or epidural hematomas, or loss of consciousness for greater than 5 minutes were not included. Participants taking antidepressants were enrolled if they had been on stable treatment for more than 2 months and were not depressed according to the Center for Epidemiological Studies Depression Scale (CES-D) (Haringsma, Engels et al. 2004) or Profile of Moods Survey (POMS) (Shacham 1983).

3.2.2.3 Physical

Participants with a body mass index (BMI kg/m2) (Keys, Fidanza et al. 1972) of less than 18 (normal) or greater than 35 (moderately obese) were excluded from the study in order to help control for the interaction of weight and alcohol metabolism (Sayon-Orea, Martinez-Gonzalez et al. 2011). Adults with diabetes (insulin-dependent) were also excluded, and individuals with high blood pressure were only included if they had been on stable treatment for at least 1 year (Hillbom, Saloheimo et al. 2011). Other physical exclusions included visual acuity less than 20/40 (corrected), hearing loss, left-handed individuals, and positive pregnancy test results.

3.2.3 Procedure

Potential participants completed a phone screen with questions about their alcohol, drug and medication use. A modified version of the SHORT AUDIT-C (Babor, Higgins-Biddle et al. 2001) was administered as part of the phone screen. This modified version included Questions #1 and #2 of the original version but excluded Question #3. This
question was removed because it directly related to binge drinking, which was assessed elsewhere in the phone screen. The sum of Questions #1 and #2 were used as an initial measure of alcohol consumption. Participants with a score between 1 and 2 were conditionally recruited as light drinkers, and a score between 4 and 6 as moderate drinkers. See Figure 3.1 for additional scoring information. Participants were also asked how long they had maintained their particular drinking pattern and how long they had been exposed to alcohol. All participants were asked whether or not they would agree to submit to an alcohol and drug screen at the beginning of each study visit.

Individuals that met phone screen criteria were asked to come to the laboratory for formal screening. Participants were given time to record 3 months of alcohol consumption using the TLFB. A 12 oz. (beer), 5 oz. (wine) and a 1.5 oz. (hard liquor) glass were placed on the participant’s desk; they were told that the glasses represented standard drink sizes. Participants were asked to use these glasses as reference when filling out the TLFB. The following were also administered during the formal screening visit: mood (POMS) and depression questionnaires (CES-D), vision and hearing tests, medical history and Axis I disorder assessments (SCID), and a dementia screen (3MSE).

3.2.3.1 Testing Visit One

Participants that passed formal screening criteria were officially enrolled into the study and asked to return on a separate day for 2.5 hours of cognitive testing separated by two 15-minute breaks. The domains that were tested included attention, working memory, short-term memory, processing speed, planning, rule learning, and motor control. For a list of the tasks and behavioral measures used to assess performance see Table 3.1a.
Figure 3.1: Questions and scoring used to identify light and moderate drinkers during the phone screen

1. How often do you have a drink containing alcohol?
   - Never (0 points)
   - Monthly or less (1 point)
   - 2-4 times a month (2 points)
   - 2-3 times a week (3 points)
   - 4 or more times a week (4 points)

2. How many standard drinks containing alcohol do you have on a typical day?
   - 1 or 2 (0 points)
   - 3 or 4 (1 point)
   - 5 or 6 (2 points)
   - 7 to 8 (3 points)
   - 10 or more (4 points)

A modified version of the SHORT Alcohol Use Disorders Identifications Test – C was used as an initial measure of alcohol consumption. Participants with a total score between 1 and 2 were conditionally recruited as light drinkers, and a score between 4 and 6 as moderate drinkers.
Table 3.1a: Tasks and measures used to assess domain-specific cognition during Testing Visit One

<table>
<thead>
<tr>
<th>ATTNENTION</th>
<th>MEASURE</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eriksen Flanker Test</td>
<td>Incongruent – Congruent Percent Accuracy</td>
<td>(Eriksen and Eriksen 1974)</td>
</tr>
<tr>
<td></td>
<td>Incongruent – Congruent Reaction Time</td>
<td></td>
</tr>
<tr>
<td>WORKING MEMORY</td>
<td>MEASURE</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>1Back Test</td>
<td>Percent Accuracy</td>
<td>(Kirchner 1958)</td>
</tr>
<tr>
<td></td>
<td>Reaction Time</td>
<td></td>
</tr>
<tr>
<td>Delayed Match to Sample Test</td>
<td>Percent Accuracy</td>
<td>(Sahakian, Morris et al. 1988)</td>
</tr>
<tr>
<td></td>
<td>Reaction Time</td>
<td></td>
</tr>
<tr>
<td>SHORT – TERM MEMORY</td>
<td>MEASURE</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>Spatial Recognition Test</td>
<td>Percent Accuracy</td>
<td>(Owen, Downes et al. 1990)</td>
</tr>
<tr>
<td></td>
<td>Reaction Time</td>
<td></td>
</tr>
<tr>
<td>Pattern Recognition Test</td>
<td>Percent Accuracy</td>
<td>(Sahakian, Downes et al. 1990)</td>
</tr>
<tr>
<td></td>
<td>Reaction Time</td>
<td></td>
</tr>
<tr>
<td>Spatial Span Test</td>
<td>Maximum Span Recalled</td>
<td>(Milner 1971, Owen, Downes et al. 1990)</td>
</tr>
<tr>
<td>PROCESSING SPEED</td>
<td>MEASURE</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>Reaction Time Test</td>
<td>Reaction Time</td>
<td><a href="http://www.cambridgecognition.com">www.cambridgecognition.com</a></td>
</tr>
<tr>
<td>Symbol Digit Modality Test</td>
<td>Number Correct</td>
<td>(Smith 1968, Smith 1982)</td>
</tr>
<tr>
<td>PLANNING</td>
<td>MEASURE</td>
<td>REFERENCE</td>
</tr>
<tr>
<td>Stockings of Cambridge Test</td>
<td>Number Answered in Minimum Moves</td>
<td>(Robbins, James et al. 1998)</td>
</tr>
<tr>
<td>Trails Making Test</td>
<td>Trials B – Trials A Completion Time</td>
<td>(Reitan 1958, Reitan and Wolfson 1985)</td>
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<tr>
<td>RULE LEARNING</td>
<td>MEASURE</td>
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<td>Intra-Extra Dimensional Set Shift Test</td>
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<td>(Downes, Roberts et al. 1989)</td>
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<td>MOTOR CONTROL</td>
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</tr>
<tr>
<td>Simple Reaction Time Test</td>
<td>Movement Time</td>
<td><a href="http://www.cambridgecognition.com">www.cambridgecognition.com</a></td>
</tr>
</tbody>
</table>
3.2.3.2 Testing Visit Two

Measures of performance on cognitive tests are the primary outcomes of this study. However, approximately one year after beginning recruitment the study became affiliated with a larger NIAAA-funded project grant focused on interactions of stress and anxiety with alcohol consumption. It was at that time that measures of stress, anxiety, and impulsivity were added as secondary outcome measures and used to more thoroughly characterize older adult drinkers (Table 3.1b). Of the 13 light older drinkers that had already completed Testing Visit One, 10 returned to complete measures of stress, anxiety and impulsivity as part of Testing Visit Two. All 14 moderate older drinkers that already completed Testing Visit One were able to return and completed Testing Visit Two. The TLFB was re-administered upon their return to laboratory to ensure that light and moderate drinkers had not altered their drinking habits. No significant differences in the number of drinks per week were found in either light or moderate drinkers between Testing Visit One and Testing Visit Two (Light Old: t (9) = -1.33, p = 0.22; Moderate Old: t (13) = 1.45, p = 0.16). Individuals recruited after the addition of Testing Visit Two (7 light and 7 moderate older drinkers) completed the entire study within one month of enrollment.

3.2.4 Statistical Analysis

Multivariate analyses of covariance (MANCOVA) were used to assess the relationships between age (young, old) and alcohol consumption (light, moderate) with results from each cognitive test after controlling for four confounding variables: presence or absence of high blood pressure, BMI, total number of years consuming alcohol and the total number of years the individual maintained either a light or moderate alcohol consumption
Table 3.1b: Questionnaires and measures used to assess stress, anxiety and impulsivity during Testing Visit Two

<table>
<thead>
<tr>
<th>MEASURE</th>
<th>REFERENCE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STRESS</strong></td>
<td></td>
</tr>
<tr>
<td>Perceived Stress Scale</td>
<td>Total Score</td>
</tr>
<tr>
<td><strong>ANXIETY</strong></td>
<td></td>
</tr>
<tr>
<td>Geriatric Anxiety Scale</td>
<td>Total Score</td>
</tr>
<tr>
<td><strong>IMPULSIVITY</strong></td>
<td></td>
</tr>
<tr>
<td>Barrett Impulsivity Scale</td>
<td>Total Score</td>
</tr>
<tr>
<td>Lifetime History of Impulsive Behavior Interview</td>
<td>Total Score</td>
</tr>
<tr>
<td><strong>IMPULSE CONTROL</strong></td>
<td></td>
</tr>
<tr>
<td>Go No-Go Task</td>
<td><strong>Cue Dependent Response Inhibition</strong></td>
</tr>
<tr>
<td></td>
<td><strong>Cue Dependent Response Time</strong></td>
</tr>
</tbody>
</table>
pattern. Additionally, sex differences were assessed and the drinking and age groups were collapsed across sex if found to be non-significant. Tests of normality were performed for each set of dependent variables (given the covariates) and any non-normally distributed variables were transformed appropriately (log transformed in our cases). Co-linearity and outlier assessments were also performed to ensure model validity. Step-down tests of the least square means were performed employing Tukey’s adjustment for multiple comparisons if a significant main effect of alcohol, age or their interaction was found. All statistical analyses were performed using SAS software version 9.3.
3.3 Results

3.3.1 Demographics

Sample characteristics for both light and moderate older drinkers can be found in Table 3.2. Light older drinkers consumed 1.1 ± 0.7 drinks per week and moderate older drinkers consumed 11.8 ± 4.1 drinks per week. An expected significant difference in the number of drinks per week consumed by light and moderate older drinkers was observed (t (39) = -11.6, p < 0.0001). The two groups did not differ from each other in the total number of years they had maintained that consumption level (light: 21.0 ± 16.1 years, moderate: 16.1 ± 14.4 years; t (39) = 1.0, p = 0.31) or the total number of years they had been consuming alcohol (light: 46.3 ± 10.0 years, moderate: 43.4 ± 11.5 years; t (39) = 0.87, p = 0.39). There were no statistical differences between light and moderate older drinkers in sex (light: 12 male, 8 female, moderate: 10 male, 11 female; χ² = 0.63, p = 0.43), age (light: 71.1 ± 3.4 years old, moderate: 70.1 ± 4.2 years old; t (39) = 0.80, p = 0.43), BMI (light: 27.4 ± 3.8, moderate: 26.3 ± 2.5; t (39) = 1.12, p = 0.27) or years of education (light: 16.2 ± 3.0 years, moderate: 16.5 ± 2.1 years; t (39) = -0.40, p = 0.69). Older drinkers scored similarly on depression (CES-D, light: 4.5 ± 3.6, moderate: 4.3 ± 4.9; t (39) = 0.12, p = 0.90) and mood screens (POMS, light: -3.4 ± 11.0, moderate: -1.6 ± 13.8; t (39) = -0.46, p = 0.65). Older drinkers also performed similarly on the dementia screen (3MSE, light: 97.1 ± 3.4, moderate: 97.8 ± 3.0; t (39) = -0.71, p = 0.48). No significant difference in the proportion of people on a stable regimen of prescription medication was found (light: 16/20, moderate: 17/21, χ² = 0.01, p = 0.94). More specifically, no differences in the proportion of people on medication to treat high blood pressure (light: 7/20, moderate: 10/21, χ² = 1.33, p = 0.25), high cholesterol (light: 4/20, moderate: 3/21,
Table 3.2: Light and moderate older adult drinker sample characteristics

<table>
<thead>
<tr>
<th>Mean ± SD (Min - Max)</th>
<th>Sex</th>
<th>Age</th>
<th>BMI</th>
<th>Education</th>
<th>Drinks Week *</th>
<th>Pattern Maintenance</th>
<th>Lifetime Drinking</th>
</tr>
</thead>
<tbody>
<tr>
<td>OLDER ADULTS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light (n = 20)</td>
<td>12</td>
<td>8</td>
<td>71.1 ± 3.4 (66 - 75)</td>
<td>27.4 ± 3.8 (22 - 35)</td>
<td>16.2 ± 3.0 (12 - 25)</td>
<td>1.1 ± 0.7 (0.1 – 2.8)</td>
<td>21.0 ± 16.1 (3 - 54)</td>
</tr>
<tr>
<td>Moderate (n = 21)</td>
<td>10</td>
<td>11</td>
<td>70.1 ± 4.2 (63 -78)</td>
<td>26.3 ± 2.5 (23 - 31)</td>
<td>16.5 ± 2.1 (12 - 20)</td>
<td>11.8 ± 4.1 (7 - 19)</td>
<td>16.1 ± 14.4 (4 - 51)</td>
</tr>
</tbody>
</table>

Drinks per week were calculated using the self-report number of drinks in the past three months using the Time Line Follow Back Questionnaire. BMI = body mass index. BMI, whether or not an individual had high blood pressure, the number of years an individual maintained either a light or moderate drinking pattern, and the total number of years an individual drank alcohol were used as covariates during statistical analysis. Seven light and ten moderate older drinkers were on a stable medication regimen to treat high blood pressure. * p < 0.05 for null hypothesis of no difference between light and moderate older adult drinkers.
χ² = 0.24, p = 0.67), Type II diabetes (light: 2/20, moderate: 1/21, χ² = 0.42, p = 0.52) or depression were found (light: 1/20, moderate: 5/21, χ² = 2.9011, p = 0.09). Other commonly cited conditions that required prescription medication in both light and moderate older drinkers included hypothyroidism, arthritis, osteoporosis, and heartburn. In the light older drinker group, only one individual smoked (less than thirty cigarettes per day) and there were no ex-smokers. In the moderate older drinker group, no one actively smoked cigarettes; one individual was an ex-smoker.

For comparative purposes, sample characteristics for young adult drinkers can be found in Table 3.3. Light younger drinkers (27.2 ± 3.3 years old) consumed 1.6 ± 0.6 drinks per week and moderate younger drinkers (27.5 ± 3.7 years old) consumed 10.8 ± 2.6 drinks per week. These consumption patterns were statistically similar to the consumption patterns observed in light (t (29) = 1.89, p = 0.07) and moderate (t (30) = -0.70, p = 0.50) older adult drinker counterparts. The most notable medication taken by younger adult drinkers was birth control and none of the younger adult drinkers smoked cigarettes.

3.3.2 Cognitive Task Performance

3.3.2.1 Effects of Age

Age * alcohol consumption MANCOVA results are presented in Table 3.4. As expected, significant effects of age showed that younger adults outperformed older adults in several cognitive domains, including executive attention (F (54) = 7.25, p < 0.01), working-memory (F (52) = 7.29, p < 0.0001), short-term memory (F (50) = 4.58, p < 0.0001), processing speed (F (54) = 6.09, p = 0.01), and rule learning (F (52) = 9.73, p < 0.01). Younger adults trended towards faster movement times than older adults in the motor
Table 3.3: Light and moderate younger adult drinker sample characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sex</th>
<th>Age</th>
<th>BMI</th>
<th>Education</th>
<th>Drinks Week *</th>
<th>Pattern Maintenance</th>
<th>Lifetime Drinking</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>YOUNGER ADULTS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Light</td>
<td>5</td>
<td>6</td>
<td>27.2 ± 3.3 (24 – 35)</td>
<td>22.4 ± 3.5 (18 – 29)</td>
<td>19.4 ± 2.3 (15 – 22)</td>
<td>1.6 ± 0.6 (0.4 – 2)</td>
<td>4.6 ± 2.2 (3 – 11)</td>
</tr>
<tr>
<td>Moderate</td>
<td>5</td>
<td>6</td>
<td>27.5 ± 3.7 (24 – 35)</td>
<td>23.9 ± 3.5 (20 – 30)</td>
<td>19.1 ± 2.3 (16 – 24)</td>
<td>10.8 ± 2.6 (8 – 17)</td>
<td>5.3 ± 1.7 (3 – 9)</td>
</tr>
</tbody>
</table>

Drinks per week were calculated using the self-report number of drinks in the past three months using the Time Line Follow Back Questionnaire. BMI = body mass index. BMI, whether or not an individual had high blood pressure, the number of years an individual maintained either a light or moderate drinking pattern, and the total number of years an individual drank alcohol were used as covariates during statistical analysis. Neither light nor moderate younger drinkers were on a stable medication regiment to treat high blood pressure. * p < 0.05 for null hypothesis of no difference between light and moderate younger adult drinkers.
Table 3.4: Results of consumption level (low, moderate) * age group (young, old) MANCOVA analyses of cognitive performance

<table>
<thead>
<tr>
<th>Function</th>
<th>Age</th>
<th>Drink</th>
<th>Drink * Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXECUTIVE ATTENTION</td>
<td>$F (54) = 7.25$</td>
<td>$F (54) = 1.99$</td>
<td>$F (54) = 2.59$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; 0.01^*$</td>
<td>$p = 0.15$</td>
<td>$p = 0.08$</td>
</tr>
<tr>
<td>WORKING MEMORY</td>
<td>$F (52) = 7.29$</td>
<td>$F (52) = 2.54$</td>
<td>$F (52) = 1.84$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; 0.0001^*$</td>
<td>$p = 0.05^*$</td>
<td>$p = 0.14$</td>
</tr>
<tr>
<td>OTHER EXECUTIVE FUNCTIONS</td>
<td>$F (50) = 4.58$</td>
<td>$F (50) = 1.05$</td>
<td>$F (50) = 1.00$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; 0.0001^*$</td>
<td>$p = 0.40$</td>
<td>$p = 0.44$</td>
</tr>
<tr>
<td>SHORT-TERM MEMORY</td>
<td>$F (54) = 6.09$</td>
<td>$F (54) = 0.11$</td>
<td>$F (54) = 0.08$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; 0.01^*$</td>
<td>$p = 0.90$</td>
<td>$p = 0.93$</td>
</tr>
<tr>
<td>PROCESSING SPEED</td>
<td>$F (54) = 1.31$</td>
<td>$F (54) = 1.51$</td>
<td>$F (54) = 0.93$</td>
</tr>
<tr>
<td></td>
<td>$p = 0.28$</td>
<td>$p = 0.23$</td>
<td>$p = 0.40$</td>
</tr>
<tr>
<td>PLANNING</td>
<td>$F (52) = 9.73$</td>
<td>$F (52) = 0.92$</td>
<td>$F (52) = 4.50$</td>
</tr>
<tr>
<td></td>
<td>$p &lt; 0.01^*$</td>
<td>$p = 0.34$</td>
<td>$p = 0.04^*$</td>
</tr>
<tr>
<td>RULE LEARNING</td>
<td>$F (55) = 3.13$</td>
<td>$F (55) = 0.22$</td>
<td>$F (55) = 0.69$</td>
</tr>
<tr>
<td></td>
<td>$p = 0.08$</td>
<td>$p = 0.64$</td>
<td>$p = 0.41$</td>
</tr>
</tbody>
</table>

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control domain (F (55) = 3.13, p = 0.08) but did similarly to older adults in the planning domain (F (54) = 1.31, p = 0.28). See Table 3.5 for the estimated performance means and 95% confidence intervals for both younger and older drinkers.

3.3.2.2 Effects of Alcohol Consumption

A modest effect of alcohol consumption was found in the working memory domain (F (52) = 2.54, p = 0.05). No differences in 1Back Task percent accuracy were found (Light = 95.26%, 89.27 – 101.25%; Moderate = 92.66%, 86.75 – 98.58%; t (55) = 0.68, p = 0.50). However, moderate drinkers responded faster during the 1Back Task (Light = 861.09 ms, 807.83 – 914.35 ms; Moderate = 773.26 ms, 720.65 – 825.87 ms; t (55) = 2.57, p = 0.01). This finding was driven by a nearly significant difference between the reaction times of younger drinkers (Light Young = 844.19 ms, 717.83 – 970.55 ms; Moderate Young = 709.94 ms, 590.47 – 829.41 ms; t (55) = 2.44, p = 0.08) but not older drinkers (Light Old = 877.98 ms, 797.84 – 958.14 ms; Moderate Old = 836.58 ms, 762.57 – 910.58 ms; t (55) = 1.0, p = 0.75). Moderate drinkers performed better on the Delayed Match to Sample Task (Light = 79.15%, 75.29 – 83.02%; Moderate = 84.15%, 80.33 – 87.96%; t (55) = -2.02, p = 0.05). This finding was driven by a nearly significant difference between the percent accuracies of older adults (Light Old = 72.20%, 66.89 – 78.51%; Moderate Old = 80.31%, 74.94 – 85.67%; t (55) = -2.53, p = 0.07) but not younger adults (Light Young = 85.61%, 76.44 – 94.77%; Moderate Young = 87.99%, 79.33 – 96.66%; t (55) = -0.60, p = 0.93). No difference between light and moderate drinker Delayed Match to Sample Task reaction times was found (Light = 2,844.25 ms, 2,503.01 – 3,185.49 ms; Moderate = 3,014.53 ms, 2,677.48 – 3,351.59; t (55) = -0.78, p =
| Table 3.5: Cognitive test performance in younger and older adult drinkers |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                 | **YOUNGER DRINKERS**          | **OLDER DRINKERS**               |                                 |                                 |
|                                 | **Estimated Mean** | **95% CI** | **Estimated Mean** | **95% CI** |
| **ATTENTION**                   |                                 |                                 |                                 |                                 |
| Eriksen Flanker Test            | Incongruent – Congruent Percent Accuracy | 4.08 % | -9.80 – 17.95 % | -16.60 % | -24.81 – (- 8.39) %   |
|                                 | Incongruent – Congruent Reaction Time | 43.25 ms | 2.24 – 84.25 ms | 147.62 ms | 123.35 – 171.88 ms   |
| **WORKING MEMORY**              |                                 |                                 |                                 |                                 |
| 1Back Test                      | Percent Accuracy               | 98.31 % | 85.95 – 110.66 % | 89.61 % | 82.30 – 96.92 %   |
|                                 | Reaction Time                  | 777.07 ms | 667.20 – 886.93 ms | 857.28 ms | 729.26 – 922.30 ms |
| Delayed Match to Sample Test    | Percent Accuracy≈              | 86.80 % | 78.83 – 94.77 % | 76.50 % | 71.79 – 81.22 %   |
|                                 | Reaction Time*                 | 1,637.65 ms | 933.74 – 2,341.56 ms | 4,221.14 ms | 3,804.54 – 4,637.73 ms |
| **SHORT – TERM MEMORY**         |                                 |                                 |                                 |                                 |
| Spatial Recognition Test        | Percent Accuracy*              | 81.55 % | 70.02 – 94.98 % | 60.50 % | 55.28 – 66.22 %   |
|                                 | Reaction Time*                 | 1,504.97 ms | 1,205.32 – 1,879.11 ms | 2,600.83 ms | 2,280.58 – 2,966.06 ms |
| Pattern Recognition Test        | Percent Accuracy               | 93.30 % | 87.61 – 99.36 % | 91.37 % | 88.03 – 94.83 %   |
|                                 | Reaction Time*                 | 1,369.64 ms | 1,182.64 – 1,586.22 ms | 2,276.83 ms | 2,087.37 – 2,483.49 ms |
| Spatial Span Test               | Maximum Span Recalled*         | 6.59    | 5.60 – 7.75    | 5.23    | 4.75 – 5.76     |
| Hopkins Verbal Learning Test    | Retention                      | 96.82 % | 77.77 – 120.53 % | 95.17 % | 83.59 – 108.34 % |
| **PROCESSING SPEED**            |                                 |                                 |                                 |                                 |
| Reaction Time Test              | Reaction Time*                 | 269.24 ms | 233.84 – 304.64 ms | 323.19 ms | 302.24 – 344.14 ms |
| Symbol Digit Modality Test      | Number Correct*                | 60.06   | 52.87 – 67.25  | 41.96   | 37.70 – 46.21   |
| **PLANNING**                    |                                 |                                 |                                 |                                 |
| Stockings of Cambridge Test     | Number Answered in Minimum Moves≈ | 9.45    | 8.02 – 10.88   | 7.63    | 6.79 – 8.48     |
| Trails Making Test              | Trials B – Trials A Completion Time | 39.75 ms | 7.84 – 71.66 ms | 36.30 ms | 17.41 – 55.18 ms |
| **RULE LEARNING**               |                                 |                                 |                                 |                                 |
| Intra-Extra Dimensional Set Shift Test Total Number of Errors* | 10.02 | 6.62 – 15.17 | 22.18 | 17.36 – 28.35 |
| **MOTOR CONTROL**               |                                 |                                 |                                 |                                 |
| Simple Reaction Time Test*      | Movement Time                  | 363.62 ms | 302.50 – 437.10 ms | 499.91 ms | 448.32 – 557.44 ms |

Estimated performance means and 95% confidence intervals associated with each cognitive test collapsed across age. * denotes a statistically significant finding of p ≤ 0.05, and ≈ denotes a nearly significant finding of p ≈ 0.08.
0.44). See Table 3.6 for the estimated performance means and 95% confidence intervals for both light and moderate drinkers.

3.3.2.3 Interactive Effects of Age and Alcohol Consumption

A modest age * alcohol consumption interaction effect was found in the rule learning domain (F (52) = 4.50, p = 0.04). Further analysis showed that light old drinkers tended to make the most errors during the Intra-Extra Dimensional Set Shift Task. More specifically, light old drinkers (26.58 errors, 19.49 – 35.87 errors) were found to make significantly more errors than both light young (9.03 errors, 5.64 – 14.56 errors; t (55) = -3.12, p = 0.02) and moderate young drinkers (11.02 errors, 7.03 – 17.46 errors; t (55) = -2.65, p = 0.05). Although the number of errors did not significantly differ between older drinkers (t (55) = 2.28, p = 0.11), moderate old drinkers (18.54 errors, 14.01 – 24.53 errors) performed just as well as light young (t (55) = -2.17, p = 0.15) and moderate young drinkers (t (55) = -1.63, p = 0.37).

A nearly significant age * alcohol consumption interaction effect was found in the executive attention domain (F (54) = 2.59, p = 0.08). Light old drinkers tended to have the lowest percent accuracy on the Eriksen Flanker Task (Light Young = 10.51%, -5.45 – 26.46%; Moderate Young = -2.35%, -17.44 – 12.73%; Light Old = -19.98%, -30.10 – -9.86%; Moderate Old = -13.22%, -22.56 – -3.87%). In addition to this, light old drinkers tended to exhibit the slowest reaction times (Light Young = 43.75 ms, -3.41 – 90.91 ms; Moderate Young = 42.74 ms, -1.85 – 87.33 ms; Light Old = 165.31 ms, 135.40 – 195.22 ms; Moderate Old = 129.93 ms, 102.30 – 157.55 ms).

No significant age * alcohol consumption interaction effects were found in working memory (F (52) = 1.84, p = 0.14), short-term memory (F (50) = 1.00, p = 0.44),
Table 3.6: Cognitive test performance in light and moderate adult drinkers

<table>
<thead>
<tr>
<th></th>
<th>LIGHT DRINKERS</th>
<th>MODERATE DRINKERS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated Mean</td>
<td>95% CI</td>
</tr>
<tr>
<td>ATTENTION</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eriksen Flanker Test</td>
<td>Incongruent – Congruent Percent Accuracy</td>
<td>-4.74 %</td>
</tr>
<tr>
<td></td>
<td>Incongruent – Congruent Reaction Time</td>
<td>104.53 ms</td>
</tr>
<tr>
<td>WORKING MEMORY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1Back Test</td>
<td>Percent Accuracy</td>
<td>95.26 %</td>
</tr>
<tr>
<td></td>
<td>Reaction Time*</td>
<td>861.09 ms</td>
</tr>
<tr>
<td></td>
<td>Percent Accuracy*</td>
<td>79.15 %</td>
</tr>
<tr>
<td></td>
<td>Reaction Time</td>
<td>2,844.25 ms</td>
</tr>
<tr>
<td>SHORT – TERM MEMORY</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spatial Recognition Test</td>
<td>Percent Accuracy</td>
<td>71.58 %</td>
</tr>
<tr>
<td></td>
<td>Reaction Time</td>
<td>2,062.49 ms</td>
</tr>
<tr>
<td>Pattern Recognition Test</td>
<td>Percent Accuracy</td>
<td>91.87 %</td>
</tr>
<tr>
<td></td>
<td>Reaction Time</td>
<td>1,829.76 ms</td>
</tr>
<tr>
<td>Spatial Span Test</td>
<td>Maximum Span Recalled</td>
<td>5.78</td>
</tr>
<tr>
<td>Hopkins Verbal Learning Test</td>
<td>Retention</td>
<td>95.10 %</td>
</tr>
<tr>
<td>PROCESSING SPEED</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction Time Test</td>
<td>Reaction Time</td>
<td>293.09 ms</td>
</tr>
<tr>
<td>Symbol Digit Modality Test</td>
<td>Number Correct</td>
<td>49.99</td>
</tr>
<tr>
<td>PLANNING</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stockings of Cambridge Test</td>
<td>Number Answered in Minimum Moves</td>
<td>8.59</td>
</tr>
<tr>
<td>Trails Making Test</td>
<td>Trials B – Trials A Completion Time</td>
<td>41.85 ms</td>
</tr>
<tr>
<td>RULE LEARNING</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-Extra Dimensional Set Shift Test</td>
<td>Total Number of Errors</td>
<td>15.50</td>
</tr>
<tr>
<td>MOTOR CONTROL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple Reaction Time Test</td>
<td>Movement Time</td>
<td>425.37 ms</td>
</tr>
</tbody>
</table>

Estimated performance means and 95% confidence intervals associated with each cognitive test collapsed across consumption level. * denotes a statistically significant finding of p ≤ 0.05.
processing speed (F (54) = 0.08, p = 0.93), planning (F (54) = 0.93, p = 0.40) or motor control (F (55) = 0.69, p = 0.41) domains. See Table 3.7 for the estimated performance means and 95% confidence intervals for light and moderate older drinkers and Table 3.8 for light and moderate younger drinkers.

3.3.3 Stress, Anxiety and Impulsivity

Light and moderate older drinkers did not differ from each other in measures known to influence cognition and overall alcohol consumption. Neither perceived stress nor anxiety showed a significant effect of alcohol consumption (Perceived Stress Score: F (32) = 2.02, p = 0.32 and Geriatric Anxiety Scale: F (31) = 0.02, 0.89). No significant effects of alcohol consumption were found in either personality measures of impulsivity (Barrett Impulsivity Scale: F (30) = 2.18, p = 0.11; Lifetime History of Impulsive Behavior Inventory: F (31) = 0.07, p = 0.79) or the behavioral measure of impulse control (Go No-Go Task: F (31) = 0.53, p = 0.60). See Table 3.9 for the estimated performance means and 95% confidence intervals for both light older and moderate older drinkers.
Table 3.7: Cognitive test performance in light and moderate older adult drinkers

<table>
<thead>
<tr>
<th></th>
<th>LIGHT OLDER DRINKERS</th>
<th></th>
<th>MODERATE OLDER DRINKERS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated Mean</td>
<td>95% CI</td>
<td>Estimated Mean</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>ATTENTION</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eriksen Flanker Test</td>
<td>Incongruent – Congruent Percent Accuracy</td>
<td>-19.98 %</td>
<td>-30.10 – (-9.86) %</td>
<td>-13.22 %</td>
</tr>
<tr>
<td></td>
<td>Incongruent – Congruent Reaction Time</td>
<td>165.31 ms</td>
<td>135.40 – 195.22 ms</td>
<td>129.93 ms</td>
</tr>
<tr>
<td><strong>WORKING MEMORY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1Back Test</td>
<td>Percent Accuracy</td>
<td>92.85 %</td>
<td>83.84 - 101.86 %</td>
<td>86.38 %</td>
</tr>
<tr>
<td></td>
<td>Reaction Time</td>
<td>877.98 ms</td>
<td>797.84 - 958.12 ms</td>
<td>836.58 ms</td>
</tr>
<tr>
<td>Delayed Match to Sample Test</td>
<td>Percent Accuracy</td>
<td>72.70 %</td>
<td>66.89 - 78.51 %</td>
<td>80.31 %</td>
</tr>
<tr>
<td></td>
<td>Reaction Time</td>
<td>4,198.06 ms</td>
<td>3,684.59 - 4,711.53 ms</td>
<td>4,244.20 ms</td>
</tr>
<tr>
<td><strong>SHORT – TERM MEMORY</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spatial Recognition Test</td>
<td>Percent Accuracy</td>
<td>58.95 %</td>
<td>52.75 - 65.89 %</td>
<td>62.10 %</td>
</tr>
<tr>
<td></td>
<td>Reaction Time</td>
<td>2,734.62 ms</td>
<td>2,325.73 – 3,215.40 ms</td>
<td>2,473.59 ms</td>
</tr>
<tr>
<td>Pattern Recognition Test</td>
<td>Percent Accuracy</td>
<td>90.80 %</td>
<td>86.73 - 95.07 %</td>
<td>91.94 %</td>
</tr>
<tr>
<td></td>
<td>Reaction Time</td>
<td>2,310.04 ms</td>
<td>2,075.45 – 2,571.14 ms</td>
<td>2,244.11 ms</td>
</tr>
<tr>
<td>Spatial Span Test</td>
<td>Maximum Span Recalled</td>
<td>5.16</td>
<td>4.58 - 5.81</td>
<td>5.31</td>
</tr>
<tr>
<td>Hopkins Verbal Learning Test</td>
<td>Retention</td>
<td>95.17 %</td>
<td>81.12 - 111.67 %</td>
<td>95.16 %</td>
</tr>
<tr>
<td><strong>PROCESSING SPEED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction Time Test</td>
<td>Reaction Time</td>
<td>319.72 ms</td>
<td>293.89 - 345.54 ms</td>
<td>326.66 ms</td>
</tr>
<tr>
<td>Symbol Digit Modality Test</td>
<td>Number Correct</td>
<td>40.50</td>
<td>35.26 - 45.74</td>
<td>43.42</td>
</tr>
<tr>
<td><strong>PLANNING</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stockings of Cambridge Test</td>
<td>Number Answered in Minimum Moves</td>
<td>7.54</td>
<td>6.50 - 8.59</td>
<td>7.72</td>
</tr>
<tr>
<td>Trails Making Test</td>
<td>Trials B – Trials A Completion Time</td>
<td>39.49 ms</td>
<td>16.21 - 62.77 ms</td>
<td>33.10 ms</td>
</tr>
<tr>
<td><strong>RULE LEARNING</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-Extra Dimensional Set Shift Test</td>
<td>Total Number of Errors</td>
<td>26.50</td>
<td>19.59 - 35.86</td>
<td>18.56</td>
</tr>
<tr>
<td><strong>MOTOR CONTROL</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple Reaction Time Test</td>
<td>Movement Time</td>
<td>486.81 ms</td>
<td>425.66 - 556.76 ms</td>
<td>513.36 ms</td>
</tr>
</tbody>
</table>
Table 3.8: Cognitive test performance in light and moderate young adult drinkers

<table>
<thead>
<tr>
<th></th>
<th>LIGHT YOUNGER DRINKERS</th>
<th>MODERATE YOUNGER DRINKERS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated Mean</td>
<td>95% CI</td>
</tr>
<tr>
<td><strong>ATTENTION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eriksen Flanker Test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incongruent – Congruent Percent Accuracy</td>
<td>10.51 %</td>
<td>-5.45 – 26.46 %</td>
</tr>
<tr>
<td>Incongruent – Congruent Reaction Time</td>
<td>43.75 ms</td>
<td>-3.41 – 90.91 ms</td>
</tr>
<tr>
<td><strong>WORKING MEMORY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 Back Test</td>
<td>Percent Accuracy</td>
<td>97.67 %</td>
</tr>
<tr>
<td>Reaction Time ²</td>
<td>844.19 ms</td>
<td>717.83 - 970.55 ms</td>
</tr>
<tr>
<td>Delayed Match to Sample Test</td>
<td>Percent Accuracy</td>
<td>85.61 %</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>1,490.44 ms</td>
<td>680.86 – 2,300.02 ms</td>
</tr>
<tr>
<td><strong>SHORT – TERM MEMORY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spatial Recognition Test</td>
<td>Percent Accuracy</td>
<td>86.92 %</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>1,555.55 ms</td>
<td>1,204.99 – 2,008.10 ms</td>
</tr>
<tr>
<td>Pattern Recognition Test</td>
<td>Percent Accuracy</td>
<td>92.94 %</td>
</tr>
<tr>
<td>Reaction Time</td>
<td>1,449.34 ms</td>
<td>1,224.18 – 1,715.92 ms</td>
</tr>
<tr>
<td>Spatial Span Test</td>
<td>Maximum Span Recalled</td>
<td>6.47</td>
</tr>
<tr>
<td>Hopkins Verbal Learning Test</td>
<td>Retention</td>
<td>95.02 %</td>
</tr>
<tr>
<td><strong>PROCESSING SPEED</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reaction Time Test</td>
<td>Reaction Time</td>
<td>266.46 ms</td>
</tr>
<tr>
<td>Symbol Digit Modality Test</td>
<td>Number Correct</td>
<td>59.47</td>
</tr>
<tr>
<td><strong>PLANNING</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stockings of Cambridge Test</td>
<td>Number Answered in Minimum Moves</td>
<td>9.64</td>
</tr>
<tr>
<td>Trails Making Test</td>
<td>Trials B – Trials A Completion Time</td>
<td>44.21 ms</td>
</tr>
<tr>
<td><strong>RULE LEARNING</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intra-Extra Dimensional Set Shift Test Total Number of Errors</td>
<td>9.07</td>
<td>5.63 - 14.61</td>
</tr>
<tr>
<td><strong>MOTOR CONTROL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simple Reaction Time Test</td>
<td>Movement Time</td>
<td>371.67 ms</td>
</tr>
</tbody>
</table>

= denotes a nearly significant finding of p = 0.08.
### Table 3.9: Assessment of stress, anxiety and impulsivity in older drinkers

<table>
<thead>
<tr>
<th></th>
<th>LIGHT OLDER DRINKERS</th>
<th>MODERATE OLDER DRINKERS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimated Mean</strong></td>
<td>95% CI</td>
<td>Estimated Mean</td>
</tr>
<tr>
<td><strong>STRESS</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perceived Stress Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Total Score</strong></td>
<td>2.24</td>
</tr>
<tr>
<td><strong>ANXIETY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geriatric Anxiety Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Total Score</strong></td>
<td>2.20</td>
</tr>
<tr>
<td><strong>IMPULSIVITY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barrett Impulsivity Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Total Score</strong></td>
<td>52.17</td>
</tr>
<tr>
<td>Lifetime History of Impulsive Behavior</td>
<td><strong>Total Score</strong></td>
<td>41.04</td>
</tr>
<tr>
<td><strong>IMPULSE CONTROL</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Go No-Go Task</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Cue Dependent Response Inhibition</strong></td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td><strong>Cue Dependent Response Time</strong></td>
<td>12.97 ms</td>
</tr>
</tbody>
</table>

3.4 Discussion

This study was specifically designed to measure the effect of long-term moderate alcohol consumption on cognitive health in older adult drinkers. Expected age-related deficits in cognitive performance were observed but no evidence was found to suggest that long-term moderate alcohol consumption in older adults exacerbated age-related cognitive decline.

Interestingly, moderate older drinkers outperformed light older drinkers on the Delayed Match to Sample Task. This finding suggests that long-term moderate alcohol consumption in older age may be associated with select benefits to cognition, and in particular the short-term memory of learned relationships. However, when interpreting this finding it is important to make note of studies that show parameter-dependent performance in alcoholics on this task (Oscarberman and Bonner 1985, Holden, Hoebel et al. 2012), and remember that potential benefits are likely to be highly specific and thus of have lower ecological relevance. This study also found that moderate younger drinkers responded to 1Back Task trials faster than light younger drinkers despite showing similar performance. This finding helps to support the idea that alcohol exposure can affect speed and accuracy on working memory tasks in different manners (Schweizer and Vogel-Sprott 2008, Wilcox, Dekonenko et al. 2014). It may also be indicative of a potential difference between younger drinkers in the interaction between impulsivity and different components of a working memory task. To help support this are previous alcohol research studies showing direct relationships between measures of impulsivity and working memory capacity (Gunn and Finn 2013, Noel, van der Linden et al. 2013, Ellingson, Fleming et al. 2014). Although studies were based on heavy alcohol drinkers,
our findings may point to the sensitivity of these relationships to alcohol exposure at lower quantities in younger individuals.

Accounts detailing the effects of long-term moderate alcohol consumption on cognitive health were first published approximately 30 years ago (Goodwin, Sanchez et al. 1987, Herbert, Scherr et al. 1993, Hendrie, Gao et al. 1996, Anstey, Mack et al. 2009). These and subsequent studies have been predominately epidemiologic in nature and dominated by analyses that use secondary outcome measures from large-scale clinical trials, like the Framingham Heart Study (Elias, Elias et al. 1999), the Seattle Longitudinal Study (Zanjani, Downer et al. 2013) and the Women’s Health Initiative (Espeland, Gu et al. 2005, Espeland, Coker et al. 2006). Although these analyses benefit from large sample sizes and longitudinal queries have been able to explore causal relationships between alcohol consumption and cognition (Edelstein, Kritz-Silverstein et al. 1998, Virtaa, Järvenpää et al. 2010), the parent clinical trials were not specifically designed to measure the effect of moderate alcohol consumption on age-related cognitive decline as the primary outcome. Consequently, there is little consensus in the literature, and the effect of moderate alcohol consumption on cognitive health in older age is unclear. To illustrate this point, studies have shown a negative effect (Dufouil, Tzourio et al. 2000, Zhou, Deng et al. 2003), a positive effect (Arntzen, Schirmer et al. 2010, Zanjani, Downer et al. 2013), as well as no consistent effect (Almeida, Hankey et al. 2014, Sabia, Elbaz et al. 2014).

Strengths associated with this report include the definition of moderate alcohol consumption. In previous research, the definition of moderate has been broad and has ranged from 5 to 60 grams of alcohol per day (approximately 1 to 6 drinks per day).
depending on the tool used for assessment. In this study, the definition for moderate alcohol consumption was based on alcohol use trends observed in older American drinkers (NIAAA 1998, Fryar, Hirsch et al. 2006, NIAAA 2006) and helped make study criteria more generalizable. Another important addition to literature provided by this study was the attention paid to the quantity and frequency of alcohol consumption. Although the aggregate weekly intake volume for moderate consumption (approx. 91–273 grams of alcohol) may seem lenient, the pattern with which it was consumed was considered in detail. For example, moderate consumption was not allowed to exceed 3 drinks (approx. 39 grams of alcohol) per day and individuals that reported binge-drinking habits were not included in the study. Participants were also explicitly asked about their lifetime alcohol consumption habits, and were balanced in terms of the number of years they had maintained their consumption level as well as the total number of years they were exposed to alcohol. Individuals were thoroughly questioned about their drinking habits using a series of validated questionnaires to ensure those with present or past problematic drinking patterns were excluded. Furthermore, light drinkers were used as the control group. This bolstered ecological validity given recent census data and avoided any differences between non-drinkers and drinkers that are difficult to account for during analysis (e.g. religion or distaste for alcohol) (Green and Polen 2001, Rehm, Irving et al. 2008). In addition, the study population was specifically restricted to healthy, active and community dwelling adults. Older adults who fulfilled these criteria but who were also on a stable medication regimen were also enrolled. This helped to make findings generalizable to a growing number of older American adults, who are living longer and healthier lives thanks to medications designed to stabilize conditions like high blood
pressure, depression, and hypothyroidism. The extensive cognitive battery used in this study adds to current research that has predominately used global assessments of mild cognitive impairment and dementia (Dent, Sulway et al. 1997, Dufouil, Tzourio et al. 2000, Bond, Burr et al. 2001, Bond, Burr et al. 2005, Chan, Chiu et al. 2010). The assessments used in this study are validated measures of specific cognitive domains (i.e. short term memory vs. working memory) and have been widely used in aging and substance use literature. To our knowledge, this is the first study specifically designed to measure an extensive list of cognitive abilities in older social drinkers. Analyses included cognitive aspects but also explored stress, anxiety and impulsivity, which are directly relevant to the effects of alcohol on both physical and cognitive health.

Research limitations include the TLFB method used to quantify alcohol consumption in this study. Although underrepresentation is a common concern with self-report alcohol consumption questionnaires, it should be noted that this phenomenon is more common to populations that consume alcohol in larger quantities than those discussed in this study (Stockwell, Donath et al. 2004). Limitations to the study also include a relatively small sample size when compared to previous research based on large-scale clinical trials. Despite this, confidence in our findings was strengthened by the fact that the presented estimated performance means are similar to those previously reported in healthy older adults (Sahakian, Morris et al. 1988, Downes, Roberts et al. 1989, Owen, Downes et al. 1990, Sahakian, Downes et al. 1990, Robbins, James et al. 1998, Shapiro, Benedict et al. 1999, de Jager, Milwain et al. 2002, Hogervorst, Combrinck et al. 2002, De Luca, Wood et al. 2003, Hoyer, Stawski et al. 2004, Tombaugh 2004, Van Gerven, Meijer et al. 2008).
In summary, this study showed that long-term moderate alcohol consumption in older age is neither harmful nor beneficial to overall cognitive health. Given the fact that previous findings in this field have been inconsistent (i.e. both positive and negative) the finding of this tailored experiment likely represents the most probable effect of long-term light to moderate alcohol consumption on cognitive performance in older adults: little to none. It is important to note, of course, that this finding is specific to healthy, community-dwelling and social drinkers. Findings should not be generalized to individuals with other consumption patterns, like heavy drinkers, binge drinkers and ex-drinkers.
REFERENCES


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10.1016/j.addbeh.2014.01.004


CHAPTER IV

SOCIAL ALCOHOL CONSUMPTION IN OLDER AGE IS ASSOCIATED WITH DECREASED FUNCTIONAL COMMUNITY CONSISTENCY IN THE FRONTOPARIETAL ATTENTION SUB-NETWORK

Malaak N. Moussa, Sean L. Simpson, Rhiannon E. Mayhugh, Robert G. Lyday, Linda J. Porrino, Paul J. Laurienti

The following chapter is in preparation for submission to the journal Alcoholism: Clinical and Experimental Research
Abstract

Older adults drink more alcohol than previous generations, and the majority of these adults are considered light to moderate consumers of alcohol. Light to moderate alcohol consumption has been associated with positive cardiovascular effects and a reduced risk of acquiring dementia syndromes. Nevertheless, adult brains become more vulnerable to the effects of alcohol with age. The goal of this study was to determine whether or not long-term moderate alcohol use in older age (≥ 65 years old) exacerbated age-related brain changes. The primary objective of this study was to compare light and moderate older drinkers (LODs and MODs, respectively), with comparisons between younger (24-35 years old) and older adults (65-80 years old) serving to inform the primary outcome.

Magnetic resonance imaging data was collected at rest and during 1-back task performance from 63 individuals, who consumed either light (≤ 2 drinks per week) or moderate amounts of alcohol (7-21 drinks per week). Whole-brain measures of functional network topology were calculated and included average connectivity and efficiency. Regional analyses included an evaluation of community structure surrounding default mode (DMN) and attention – related brain regions (ATN). Measures of brain structure (brain volume and white matter integrity) were also collected. Results showed that regardless of condition the functional brain networks of older adults were more connected but less specialized than younger adults, and that long-term moderate alcohol consumption in older age was not associated with changes to this overall topology. DMN and ATN community structure was significantly less consistent in older adults than in younger adults in the task condition. Comparisons between LODs and MODs in the task condition showed that long-term moderate alcohol consumption was associated with an
exacerbated age-related decrease in ATN community consistency despite both groups performing similarly on the task. Age-related declines in brain volume and white matter integrity were documented but long-term moderate alcohol consumption in older age was not associated with any further decline in these measures. This study directly addressed a lack of functional neuroimaging research on a socially accepted and common level of alcohol consumption in the rapidly growing older adult population. Findings suggest that social alcohol consumption in older age has little to no effect on age-related brain changes.
4.1 Introduction

An increasing number of adults aged 65 years and older are consuming alcohol (USDA & USDHHS, 2010). These older drinkers are not considered heavy or binge drinkers; instead, they are considered light (≤ 3 drinks per week) to moderate (7 – 14 drinks per week) consumers of alcohol (Fryar et al., 2006; NIAAA, 1998; SAMHSA, 2013). Such ‘non-problematic’ patterns of alcohol consumption have been linked to a lower risk of Alzheimer’s disease and vascular dementia (Panza et al., 2009; Panza et al., 2012; Peters, Peters, Warner, Beckett, & Bulpitt, 2008). Nevertheless, older adults experience negative age-related brain changes, including gray matter atrophy, decreased white matter integrity, and functional deficits at rest and in task (Bozzali, Cercignani, & Caltagirone, 2008; Eyler, Sherzai, Kaup, & Jeste, 2011; Park & Reuter-Lorenz, 2009). Natural changes in body composition expose social drinkers in older age to higher blood alcohol content (BAC) levels than younger adults (Vestal et al., 1977), which potentially leaves them more vulnerable to age-related brain changes.

Brain research on the effect of social alcohol consumption in older adults has predominately focused on analyses of structural morphology. Findings vary considerably and range from studies that have demonstrated a positive relationship (Downer, Jiang, Zanjani, & Fardo, 2014; Gu et al., 2014) to those that have shown a negative relationship (Ding et al., 2004; Kapogiannis et al., 2012; Mukamal, Longstreth, Mittleman, Crum, & Siscovick, 2001; Taki et al., 2006). Moreover, there are just as many studies that have reported no relationship between social drinking in older age and measures of brain volume (Cherbuin et al., 2008; E. A. de Bruin et al., 2005; Preti et al., 2014). Similar inconclusive findings have been found in studies measuring white matter integrity.
Completely unexplored are the effects of social drinking in older age on functional brain connectivity. Current literature has focused on the effect of alcoholism and methods used to measure functional connectivity have relied predominately on seed-based correlation analyses. Together, this research has shown that brain regions associated with the default mode (DMN) and the task-elicited attention (ATN) sub-networks are vulnerable to heavy alcohol exposure. For instance, a negative relationship between ATN connectivity and alcohol use severity has been reported (Weiland et al., 2014). Research has also shown that decreased DMN connectivity and increased ATN connectivity is associated with successful abstinence in alcoholics (Camchong, Stenger, & Fein, 2013). Furthermore, disruption of DMN and ATN connectivity due to heavy alcohol use has been documented in utero (Jeffrey R. Wozniak et al., 2013), younger (Beltz et al., 2013; Han et al., 2014; Thayer, Montanaro, Weiland, Callahan, & Bryan, 2014), and middle age (Maurage et al., 2013; Müller-Oehring, Jung, Pfefferbaum, Sullivan, & Schulte, 2014).

This study directly addressed social alcohol consumption in older age (≥ 65 years old) and primarily focused on whether or not it was associated with exacerbated age-related changes to functional interactions in the brain. Functional interactions in the brain were modeled as an integrated network using principles of graph theory. This approach has been adopted with increasing frequency and a burgeoning field of network science in neuroimaging research has emerged as a result. A network-based perspective is focused on understanding brain function in terms of relationships across the entire brain and not
relative a particular region of interest. It therefore lends itself well to pharmacological neuroimaging research in older adults as it helps capture both distributed and localized brain changes that are associated with alcohol consumption and aging. Various measures of network structure can be used to help understand important features of information processing in the brain. For example, degree is the number of connections to an element in a network and serves as a general measure of connectivity, or reach. Efficiency is a measure of how easily information can be transferred locally or across the entire the network. Building on these concepts is a measure of community structure called modularity, which is used to detect communities, or modules, that are more interconnected with each other than with the rest of the network. It serves as a particularly powerful measure because it simultaneously captures both integration (within-community connections) and segregation (between-community connections).

The overall goal of this study was to determine whether or not social alcohol use (7-21 drinks per week) in older age exacerbated age-related brain changes at rest and during task engagement. In order to establish age-related effects to the brain, comparisons between younger (24-35 years old) and older adults (65-80 years old) were made before comparisons between light and moderate older drinkers (LODs and MODs, respectively). Like previous research in this field, measures of brain structure (volume and white matter integrity) were collected. In addition to this, measures of functional brain network structure were calculated and included average connectivity and efficiency. An analysis of community structure was also conducted and a focus was put on communities that overlapped with the DMN and ATN. This was motivated by previous research showing that these sub-networks are particularly vulnerable in alcoholics. Given the vulnerability
of the aging brain to alcohol exposure, it was hypothesized that long-term moderate alcohol consumption in older age would be associated with exacerbated age-related brain changes.
4.2 Methods

4.2.1 Sample Demographics

A total of 63 individuals were enrolled in the study, and of these individuals 22 were younger adults (24-35 years old) and 41 were older adults (65-80 years old). The study focused on low and moderate consumers of alcohol, and participants were specifically recruited based on their alcohol consumption patterns. Daily alcohol intake over 3 months was measured using the Time Line Follow Back (TLFB) questionnaire (Sobell & Sobell, 1992); a 12 oz. (beer), 5 oz. (wine) and a 1.5 oz. (hard liquor) glass were used to help represent standard drink sizes. Low alcohol consumption was defined as 1-8 drinks per month and did not exceed 2 drinks per week. Moderate alcohol consumption was defined as 7-21 drinks per week and did not exceed 3 drinks per day. Of the younger adults 11 were low drinkers and 11 were moderate. Of the older adults 20 were low drinkers and 21 were moderate. These individuals were previously included in a manuscript (Moussa et al., 2014, In Press) evaluating results from a full cognitive assessment to measure the effect of moderate alcohol consumption on age-related cognitive decline. All participants were recruited via local advertisements (physical flyers and internet) or by word-of-mouth and were compensated for their participation. The Institutional Review Board of Wake Forest University School of Medicine approved the study and all participants gave written informed consent.

4.2.2 Screening

Participants were excluded if they did not report maintaining either a low or moderate alcohol consumption pattern for at least 3 years. They were also excluded if they reported more than 1 binge in the last 3 months (≥5 drinks for men and ≥4 drinks for women in
less than 2 hours) (NIAAA, 2004). Disqualification from the study included a > 0.00 alcohol reading as measured by an Intoxilyzer $S – D5$ breath alcohol screen (www.alcoholtest.com), or a positive test for substances of use and abuse as measured by an Alere iCassette $6 – panel$ drug screen at the start of any study visit (cocaine, THC, opiates, amphetamines, methamphetamines or benzodiazepines, www.alere.com). Verbal report of illicit drug use within the last 3 months was also grounds for disqualification. Subjects were excluded if they had a history of alcohol or drug abuse/dependence and/or current (within the last 6 months) Axis I disorders as determined by the Structured Interview for DSM Disorders (SCID) (Fist, Spitzer, Gibbon, & Williams, 2002), if they smoked more than 30 cigarettes a day, or if they consumed greater than 500 mg of caffeine per day.

In addition to alcohol and drug use exclusions, all subjects were evaluated for neurological and psychiatric conditions. Exclusion criteria included: being at high risk for dementia as measured by the Modified Mini Mental State Exam (3MSE score ≤ 80) (Jones et al., 2002), having active neurological dysfunction that may affect cognitive processing (i.e., schizophrenia, Alzheimer’s disease, Parkinson’s disease, prior history of stroke, epilepsy, mental retardation and attention deficit-hyperactivity disorder) as well as the use of antipsychotic and/or antiepileptic medications with known neurological/cognitive side effects were grounds for exclusion. Individuals with previous brain surgery, serious CNS trauma as defined by a history of acquired sub - or epidural hematomas, or loss of consciousness for greater than 5 minutes were not included. Participants taking antidepressants were enrolled if they had been on stable treatment for more than 2 months and were not depressed according to the Center for Epidemiological
Studies Depression Scale (CES-D) (Haringsma, Engels, Beekman, & Spinhoven, 2004) or Profile of Moods Survey (POMS) (Shacham, 1983). Participants with a body mass index (BMI, kg/m2) of less than 18 (normal) or greater than 35 (moderately obese) were excluded from the study in order to help control for the interaction of weight and alcohol metabolism (Sayon-Orea, Martinez-Gonzalez, & Bes-Rastrollo, 2011). Adults with diabetes (insulin-dependent) were also excluded, and individuals with high blood pressure were only included if they had been on stable treatment for at least 1 year (Hillbom, Saloheimo, & Juvela, 2011). Other physical exclusions included visual acuity less than 20/40 (corrected), hearing loss, left-handed individuals, and positive pregnancy test results.

4.2.3 Image Collection

Participants arrived approximately 1 hour prior to MR scanning and were briefed on safety and imaging protocols. The imaging protocol was performed in the following order: a T1-weighted structural scan, a blood-oxygen-level-dependent (BOLD) – weighted resting scan, a BOLD-weighted working memory performance scan and a diffusion-weighted scan. Participants were told to fixate on a cross that was projected onto a screen during resting scans. The N-Back Task was used as a measure of working memory (Kirchner, 1958). It is a continuous performance task that was also used to help capture brain differences relative to a resting state. The task can vary in cognitive load and this report focused on percent accuracy achieved on the 1-back condition. Participants were presented with white letters one at a time on a black background. After the first letter was presented, individuals responded with either a right (yes) or left (no) finger press to indicate whether or not the letter they were viewing was identical to the
one that preceded it. The task lasted for a total of 6 minutes and consisted of 120 trials. Each trial lasted for a total of 3,000 milliseconds. A letter was presented for the first 300 milliseconds and afterwards a blank black screen was presented for 2,700 milliseconds. Participants could respond at any point during a trial. Participants were also given time to practice the task for 1 minute outside of the scanner and for 1 minute inside of the scanner.

MRI data were obtained on a 3T Siemens Skyra with a 32-channel head coil, a rear projection screen, and both left and right hand response boxes. High-resolution (0.98 x 0.98 x 1.0 mm) T1-weighted structural scans were acquired in the sagittal plane using a single-shot 3D MPRAGE GRAPPA2 sequence (acquisition time = 5 minutes and 30 seconds, TR = 2.3 seconds, TE = 2.99 ms, 192 slices). BOLD-weighted images (3.5 x 3.5 x 5.0 mm) were acquired in the transverse plane using an echo-planar imaging sequence (acquisition time = 6 minutes and 20 seconds, TR = 2.0 seconds, TE = 25 ms, flip angle = 75°, 35 slices per volume, 187 volumes). Diffusion-weighted images (2.2 x 2.2 x 3.0 mm) were acquired in the transverse plane using an echo-planar imaging sequence (acquisition time = 4 minutes and 49 seconds, TR = 8.5 seconds, TE = 82 ms, b value = 1400 s/mm2, 30 directions).

4.2.4 Image Preprocessing

Image pre-processing was performed using SPM8 software (www.fil.ion.ucl.ac.uk/spm/). Structural image data were first skull-stripped. They were then segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) and normalized to MNI template space (Montréal Neurological Institute, www.mni.mcgill.ca) using the unified segmentation algorithm (Ashburner & Friston, 2005). BOLD-weighted (functional)
image data were realigned to the first volume and slice-time corrected. Functional image data were then co-registered to the accompanying skull-stripped structural image data. The normalization parameters derived from the unified segmentation of the structural image data were then applied to the functional image data. A band-pass filter (0.009–0.08 Hz) was applied to the functional image data to filter out physiological noise and low-frequency drift. Confounding signals were regressed out of the functional image data and included 6 rigid-body transformation parameters generated during the realignment process, and 3 mean signals (whole-brain, WM, and CSF). The mean signal from a small region of interest (ROI) in the superior sagittal sinus was also included in the regression analysis. This was done to avoid the introduction of false correlations caused by pulsating blood drainage in this area. Functional image data were also motion corrected using a protocol designed to eliminate scan volumes with both excessive frame-wise displacement and BOLD signal change (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012).

4.2.5 Generating Whole-Brain Functional Networks

Voxel-based brain networks were generated from pre-processed functional image data. First, the analysis was restricted to gray matter as specified by the Automated Anatomical Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002). A Pearson correlation coefficient matrix of times series data from each of the voxel pairs after regressing out confounding signals was then generated. To threshold correlation matrices, edge density across subjects was matched to ensure that comparisons were being made between networks of comparable density relative to the number of network nodes. This was done using the formula $N = K^s$, with $N$ equal to the number of nodes and $K$ equal to average degree
(Watts & Strogatz, 1998). Networks were thresholded with $S = 2.5$ as prior work has shown that brain networks fragment when $S > 3$ (Hayasaka & Laurienti, 2010) and that the reproducibility is highest with an $S$ between 2 and 3 (Telesford, Burdette, & Laurienti, 2013). Correlation values equal to or greater than the correlation coefficient solving the threshold formula were set to 1 and all others set to 0 to produce undirected, unweighted networks.

4.2.6 Whole-Brain Summaries of Functional Network Topology

A detailed review of network metrics has been reported previously (Rubinov & Sporns, 2010); what follows is a brief synopsis of the metrics used in this study. Degree ($K$) was used as a measure of connectivity and is equal to the number of links connected to a node. Efficiency is a measure of how easily information can transfer within a network (Latora & Marchiori, 2001). Values for local efficiency ($E_{loc}$) range from 0 to 1, where a value of 1 represents a node whose neighbors are entirely interconnected. Values for global efficiency ($E_{glob}$) also range from 0 to 1, where a value of 1 represents a node directly linked to all other nodes in the network (i.e. maximum capacity for distributive processing). The metrics $K$, $E_{loc}$, and $E_{glob}$ were first calculated at the individual-node level. Values across all the nodes within the network were then averaged in order to summarize topological features of functional brain networks at the whole-brain level.

4.2.7 Functional Brain Network Community Structure

A community can be thought of as a group of nodes within a network that exhibit high intra-connectivity with each other but low inter-connectivity with nodes in other communities. Modularity ($Q$) is a quantitative measure of community structure; it measures the quality of a network partition into modules (i.e. communities) (Newman,
In this study, the Louvain method was used to optimize the modularity of a network partition (Blondel, Guillaume, Lambiotte, & Lefebvre, 2008). It was run 10 times for each individual’s network and the partition representing the best solution (i.e. highest Q value) was chosen for further analysis. The scaled inclusivity (SI) algorithm was then used to quantitatively assess the overlap of communities across individuals (Steen, Hayasaka, Joyce, & Laurienti, 2011). This analysis considers overlap and disjunction between all modules in a whole-brain analysis and does not require subjective determination of module pairs across individuals. Brain images resulting from this analysis depict the consistency of a community across subjects including how similar it is in both location and size (Moussa, Steen, Laurienti, & Hayasaka, 2012; Moussa et al., 2014). For the current study, the SI methodology was used to determine the consistency of communities that intersected with brain regions associated with the default mode network (DMN), and the attention network (ATN). ROIs for the DMN and ATN were based on community partitions detected during repeated resting-state and working memory task conditions from an independent study (Rzucidlo, Roseman, Laurienti, & Dagenbach, 2013). The DMN ROI was identified using the resting-state functional imaging data and included bilateral portions of the medial prefrontal cortex, posterior cingulate cortex, precuneus, and inferior parietal cortex (Figure 4.1). The ATN ROI was identified using the n-back task performance functional imaging data and included bilateral portions of the dorsal lateral prefrontal
DMN and ATN ROIs were based on community partitions detected during repeated resting-state and working memory task conditions from an independent study (Rzucidlo, Roseman, Laurienti, & Dagenbach, 2013), and have been recently used to identify similar sub-networks in (Stanley et al., 2014). The DMN ROI (green) included bilateral portions of the medial prefrontal cortex, posterior cingulate cortex, precuneus, and inferior parietal cortex. The ATN ROI (red) included bilateral portions of the dorsal lateral prefrontal cortex, superior medial frontal cortex and the superior parietal cortex. DMN and ATN ROIs were used to measure the consistency of communities containing default mode, and attention – related brain regions. Individual ROI-specific SI images were generated by calculating SI values for each node in a network relative to the DMN and ATN ROIs, respectively. The higher the SI value for a node the more consistently it fell within the same community within the area of an ROI across individuals in a group, and the lower the SI value for a node the more consistently it fell in a community outside the area of an ROI across individuals in a group.
cortex, superior medial frontal cortex and the superior parietal cortex (Figure 4.1). Statistical analyses compared the average SI values within the DMN and ATN.

4.2.8 Brain volume and White Matter Integrity

Subject-specific GM, WM and CSF segments generated during T1-weighted structural scan preprocessing were used to calculate measures of brain volume, including total brain volume (TBV) and total gray matter volume (TGMV). TBV was calculated by summing voxel values across the GM and WM segments. TGMV was calculated by only summing voxel values within the GM segment. Both measures were corrected for total intracranial volume (TIV), which was calculated by summing voxel values across all three segments. Fractional anisotropy (FA) images were derived from diffusion-weighted images, and FA values within WM voxels were used to calculate an average measure of white matter integrity. The WM segment map of the SPM8 template brain was used to identify the WM voxels used for analysis. This was done to avoid tissue misclassification that can occur during segmentation of subject-specific T1-weighted structural scans in populations that are more likely to have WM lesions (e.g. older adults). The WM template was first made into a binary mask by applying a 60% threshold. It was then reverse warped into subject-specific space based on the transformation calculated during the warping of the anatomical image and intersected with FA images. The average of FA values across all WM voxels that fell within the mask was then calculated. Second, intersecting the mask with relCBF images identified the voxels used for analysis, and the average of relCBF values in GM voxels inside the mask was calculated.
4.2.9 Statistics

Double multivariate analyses of covariance (DMANCOVA) were used to assess the relationships between age (young, old) and condition (rest, task) with whole-brain measures of network topology, and community structure. Separate double DMANCOVAs were used to assess the relationships between alcohol consumption in old drinkers (light, moderate) and condition (rest, task) with whole-brain measures of network topology, and community structure. The following were treated as confounding variables: presence or absence of high blood pressure, BMI, total number of years consuming alcohol and the total number of years the individual maintained either a light or moderate alcohol consumption pattern. Age, alcohol consumption and condition groups were collapsed across sex if sex-differences were found to be non-significant. Tests of normality were performed for each set of dependent variables (given the covariates) and any non-normally distributed variables were transformed appropriately. Co-linearity and outlier assessments were also performed to ensure model validity. Step-down tests of the least square means were performed employing Tukey’s adjustment for multiple comparisons if a significant main effect of age, alcohol consumption or condition was found. Estimated means and 95% confidence intervals are presented, and all statistical analyses were performed using SAS software version 9.3.
4.3 Results

4.3.1 Demographics

Younger and older adult group means and standard deviations for demographic variables are presented in Table 4.1. Younger adults (n = 22) were on average 27.3 ± 3.4 years old and older adults (n = 41) were 70.61 ± 3.8 years old. Younger and older adults were balanced in terms of the number of males and females within each group, and scored similarly on measures of depression and mood, and the 3MSE screen for dementia. Adult groups consumed a similar number of alcoholic drinks per week (younger: 6.2 ± 5.1; older: 6.6 ± 6.2 drinks). Older adults had consumed alcohol for a greater number of years than younger adults. This was expected given their difference in age and analyses were corrected for this fact.

Older adults were split into Light Older Drinkers (LODs, n = 20), who were on average 71.1 ± 3.4 years old, and Moderate Older Drinkers (MODs, n = 21), who were 70.1 ± 4.2 years old. LOD and MOD group means and standard deviations for demographic variables are presented in Table 4.2. Older drinkers were balanced in terms of the number of males and females within each group. MODs consumed significantly more alcoholic drinks per week than their lower drinking counterparts (LODs: 1.1 ± 0.7; MODs: 11.8 ± 4.1 drinks). Careful enrollment ensured that important factors related to alcohol drinking history were not significantly different between LODs and MODs, including the number of years each group had maintained their light or moderate alcohol consumption level and the total number of years they had been drinking alcohol. The groups scored similarly on measures of depression and mood, and the 3MSE. Physiological factors that are known to influence the effect of alcohol consumption, like
Table 4.1: Younger and older adult group demographics

<table>
<thead>
<tr>
<th></th>
<th>YOUNGER ADULTS</th>
<th>OLDER ADULTS</th>
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<tbody>
<tr>
<td></td>
<td>$N = 22$</td>
<td>$N = 41$</td>
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<tr>
<td></td>
<td>$Mean \pm SD$</td>
<td>$Mean \pm SD$</td>
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<tr>
<td>Age (years)</td>
<td>27.3 ± 3.4</td>
<td>70.6 ± 3.8</td>
</tr>
<tr>
<td>Sex (M</td>
<td>F)</td>
<td>10</td>
</tr>
<tr>
<td>Drinks / Week</td>
<td>6.2 ± 5.1</td>
<td>6.6 ± 6.2</td>
</tr>
<tr>
<td>Total Alcohol Exposure (years)</td>
<td>8.3 ± 3.5</td>
<td>44.8 ± 10.7†</td>
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Table 4.2: Light and moderate older drinker group demographics

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<th>LIGHT OLDER DRINKERS</th>
<th>MODERATE OLDER DRINKERS</th>
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<tbody>
<tr>
<td></td>
<td>N = 20</td>
<td>N = 21</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>71.1 ± 3.4</td>
<td>70.1 ± 4.2</td>
</tr>
<tr>
<td>Sex (M</td>
<td>F)</td>
<td>12</td>
</tr>
<tr>
<td>Drinks / Week</td>
<td>1.1 ± 0.7</td>
<td>11.8 ± 4.1†</td>
</tr>
<tr>
<td>Maintenance of Alcohol Level (years)</td>
<td>21.0 ± 16.1</td>
<td>16.1 ± 14.4</td>
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<tr>
<td>Total Alcohol Exposure (years)</td>
<td>46.3 ± 10.0</td>
<td>43.4 ± 11.5</td>
</tr>
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high blood pressure and body mass index, were also balanced between older drinker groups. Sixteen out of twenty LODs were on a stable regimen of prescription medication. This included seven individuals on medication to treat high blood pressure, four individuals on medication to treat high cholesterol, two individuals on medication to treat Type II diabetes, and one individual on anti-depressants. Only one individual smoked (less than thirty cigarettes per day) and there were no ex-smokers. Seventeen out of twenty-one MODS were also on a stable regimen of prescription medication. This included ten individuals on medication to treat high blood pressure, three individuals on medication to treat high cholesterol, one individual on medication to treat Type II diabetes, and five individuals on anti-depressants. There were no MODs that actively smoked cigarettes; one individual was an ex-smoker. Other commonly cited conditions that required prescription medication in both light and moderate older drinkers included hypothyroidism, arthritis, osteoporosis, and heartburn.

4.3.2 Working Memory Task Performance

Percent accuracy for younger adults on the 1-back task was 98.43 ± 1.73% and for older adults was 89.47 ± 17.70%. Younger adults significantly outperformed older adults when the statistical model was not corrected for confounding variables (t (1, 61) = 2.36, p = 0.02). Confounding variables included BMI, presence or absence of high blood pressure, years an individual maintained their alcohol consumption pattern, and the total number of years an individual had been consuming alcohol. The significant age-related deficit in working memory performance was no longer present when these variables were included in the statistical model (F (5, 57) = 1.22, p = 0.24). When older adult drinker groups were considered separately percent accuracy for LODs on the 1-back task was 91.76 ± 15.75%
and for MODs was 87.27 ± 19.51%. Despite a significant difference in the average number of alcoholic beverages consumed each week by LODs and MODs, no difference in their working memory performance was found in the final statistical model correcting for cofounding variables (F (5, 35) = 1.35, p = 0.25).

4.3.3 Whole-brain Summaries of Functional Brain Networks

The number of nodes in a functional brain network did not differ between younger and older adults; values ranged from 19,204 – 21,785 nodes in younger adults and 19,575 – 22,576 nodes in older adults. The number of nodes in a functional brain network also did not significantly differ between older adult drinker groups; values ranged from 19,772 – 22,555 nodes in LODs and 19,575 – 22,576 nodes in MODs. The Pearson correlation coefficient (R) represented the strength of association used in the network thresholding procedure and it was not significantly affected by age. R values were, however, significantly affected by condition (F (1, 61) = 31.86, p < 0.0001). Specifically, the average strength of association was higher for both younger and older adults when they were at rest than when they were in a task. R values were unaffected by alcohol consumption level when LODs and MODs were considered separately. Like younger and older adult comparisons, the average strength of association was significantly higher for both LODs and MODs when they were at rest than when they were in a task (F (1, 39) = 11.45, p = 0.002). Together these findings showed that for all adults the average strength of association between nodes in a network was lower during task engagement and that to maintain edge densities to similarly sized networks at rest the R values were lowered during the thresholding procedure. Younger and older adult estimated group means and 95% confidence intervals for whole-brain summaries of network topology are presented
in Table 4.3. An overall effect of age (F (4, 54) = 3.99, p = 0.01) and condition (F (4, 54) = 5.08, p = 0.002) was found on whole-brain summaries of network topology. At rest, older adult functional brain networks trended towards higher average connectivity than younger adults (K; t (57) = -1.80, p = 0.08) and had greater capacity for distributive information processing (Eglob; t (57) = -2.35, p = 0.02). On the other hand, younger and older adults showed similar capacity for local information processing at rest (Eloc; t (57) = 0.81, p = 0.42). Older adult functional brain networks also trended towards higher average connectivity than younger adults in task (t (57) = -1.77, p = 0.08). In contrast to what was found at rest, adult groups had similar capacity for distributive information processing in task (t (57) = 0.04, p = 0.97) while younger adults trended towards greater capacity for local information processing (t (57) = 1.75, p = 0.08).

LOD and MOD estimated group means and 95 % confidence intervals for whole-brain summaries of network topology are presented in Table 4.4. Comparisons between LODs and MODs showed that neither alcohol consumption level nor condition significantly influenced whole-brain summaries of network topology. In other words, network features like connectivity, local and distributive information processing, and degree mixing were similar between light and moderate alcohol consuming older adults regardless of whether or not they were resting or engaged in a working memory task.

4.3.4 DMN and ATN Community Structure at Rest and in Task

Figure 4.2 shows the community structure consistency maps for the DMN and ATN from younger and older adults at rest and during task. Statistical analyses revealed a trend suggesting that the conditions influenced overall community consistency (F (56) = 2.95, p = 0.07). This effect was driven in part a by an overall decrease in DMN community
### Table 4.3: Younger and older adult group whole-brain summaries of network structure

<table>
<thead>
<tr>
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<th><strong>YOUNGER ADULTS</strong></th>
<th></th>
<th><strong>OLDER ADULTS</strong></th>
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<tbody>
<tr>
<td></td>
<td><em>N</em> = 22</td>
<td><em>Mean ± SD</em></td>
<td><em>N</em> = 41</td>
<td><em>Mean ± SD</em></td>
</tr>
<tr>
<td>Number of Network Nodes</td>
<td>20,576.4 ± 636.67</td>
<td>20,733.5 ± 845.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Threshold (Pearson’s R)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>0.67 ± 0.03</td>
<td>0.66 ± 0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Task</td>
<td>0.63 ± 0.03</td>
<td>0.63 ± 0.04</td>
<td></td>
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</tr>
<tr>
<td>Estimated Mean</td>
<td>95% CI</td>
<td>Estimated Mean 95% CI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Degree (K)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rest</td>
<td>52.51</td>
<td>51.84 - 53.19</td>
<td>53.41</td>
<td>53.01 - 53.81</td>
</tr>
<tr>
<td>Task</td>
<td>52.52</td>
<td>51.84 - 53.20</td>
<td>53.40</td>
<td>53.00 - 53.80</td>
</tr>
<tr>
<td>Local Efficiency (E&lt;sub&gt;loc&lt;/sub&gt;)</td>
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<td></td>
<td></td>
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<tr>
<td>Rest</td>
<td>0.51,</td>
<td>0.49 - 0.54</td>
<td>0.51</td>
<td>0.49 - 0.51</td>
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<tr>
<td>Task</td>
<td>0.52</td>
<td>0.50 - 0.54</td>
<td>0.49</td>
<td>0.48 - 0.50</td>
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<tr>
<td>Global Efficiency (E&lt;sub&gt;glob&lt;/sub&gt;)</td>
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<tr>
<td>Rest</td>
<td>0.16</td>
<td>0.14 - 0.19</td>
<td>0.21</td>
<td>0.19 - 0.22</td>
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<tr>
<td>Task</td>
<td>0.22</td>
<td>0.19 - 0.24</td>
<td>0.22</td>
<td>0.20 - 0.23</td>
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Table 4.4: Light and moderate older drinker group whole-brain summaries of network structure

<table>
<thead>
<tr>
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<th>LIGHT OLDER DRINKERS</th>
<th>MODERATE OLDER DRINKERS</th>
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<tr>
<td></td>
<td>N = 20</td>
<td>N = 21</td>
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<tr>
<td>Mean ± SD</td>
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<tr>
<td>Number of Network Nodes</td>
<td>20,731.1 ± 848.6</td>
<td>20,735.9 ± 863.1</td>
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<td>Threshold (Pearson’s R)</td>
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<tr>
<td>Rest</td>
<td>0.66 ± 0.03</td>
<td>0.65 ± 0.04</td>
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<tr>
<td>Task</td>
<td>0.63 ± 0.05</td>
<td>0.62 ± 0.03</td>
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<tr>
<td>Estimated Mean</td>
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<tr>
<td>95% CI</td>
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<tr>
<td>Degree (K)</td>
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<td></td>
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<tr>
<td>Rest</td>
<td>53.18</td>
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<tr>
<td>Task</td>
<td>53.18</td>
<td>52.78 - 53.58</td>
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<td>Light Efficiency (E_{loc})</td>
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<tr>
<td>Rest</td>
<td>0.50</td>
<td>0.49 - 0.51</td>
</tr>
<tr>
<td>Task</td>
<td>0.49</td>
<td>0.48 - 0.50</td>
</tr>
<tr>
<td>Global Efficiency (E_{glob})</td>
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<td></td>
</tr>
<tr>
<td>Rest</td>
<td>0.20</td>
<td>0.18 - 0.21</td>
</tr>
<tr>
<td>Task</td>
<td>0.22</td>
<td>0.21 - 0.24</td>
</tr>
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</table>
Figure 4.2: DMN and ATN community consistency in younger and older adult groups at rest and in task

Individual ROI-specific SI images were generated using the scaled inclusivity (SI) algorithm, which calculated a measure of overlap between each community in a network partition and the DMN and ATN ROI, respectively. Individual ROI-specific SI images were then used to generate adult group average SI images for the rest (top panel) and task conditions (bottom panel). DMN community consistency decreased in the task condition relative to the rest condition in both adult groups, and it appeared as though consistency preferentially decreased in the frontal portions of the DMN before posterior regions, like the precuneus. DMN community consistency was generally higher in younger adults at rest; however, greater variability in the older adult group kept this difference from reaching significance. A trend did suggest that DMN community consistency was lower in older adults in the task condition. ATN community consistency in older adults decreased in task relative to rest, while it increased in younger adults. ATN community consistency was similarly low in both younger and older adult groups in the rest condition but was significantly lower in older adults in the task condition. These data showed that an age-related loss in network specialization captured by whole-brain summaries of network topology (e.g. K, Eloc and Eglob) was driven in part by a loss in organization at the community level. These data also showed that community structure surrounding attention-related brain regions was decreased, not increased, in older adults during an attention-demanding task.
consistency in both groups during task relative to rest. No main effect of age was found (p=0.19). However, when older adults were engaged in task performance they exhibited statistically lower ATN community consistency than younger adults (t (57) = 2.11, p = 0.04) and trended towards lower DMN community consistency (t (57) = 0.17, p = 0.09). No age*condition interaction effect was observed (p = 0.21). The ATN community consistency did decrease during task relative to rest in older adults, but increased in younger adults. This phenomenon also contributed to the statistical difference between younger and older adults in ATN community consistency observed when adults were engaged in task performance (t (57) = 2.11, p = 0.04). Younger and older adult estimated group means and 95 % confidence intervals for DMN and ATN SI values at rest and in task are presented in Table 4.5.

Figure 4.4 shows the DMN and ATN community structure consistency maps for both LODs and MODs at rest and during task. Comparisons between LODs and MODs revealed that long-term moderate alcohol consumption was associated with differences in overall community consistency (F (34) = 5.08, p = 0.01). During the task, the consistency of the ATN community was significantly lower in the MODs compared to the LODs (t (35) = 3.47, p = 0.001), while the DMN community was comparable across groups. At rest, the groups exhibited similar DMN community consistency but MODs trended towards lower ATN community consistency relative to LODs (t (35) = 1.83, p = 0.08). Neither a main of effect of condition nor an alcohol consumption level*condition interaction effect was observed. LOD and MOD estimated group means and 95 % confidence intervals for DMN and ATN SI values at rest and in task are presented in Table 4.6.
Table 4.5: Younger and older adult group consistency of DMN and ATN communities at rest and in task

<table>
<thead>
<tr>
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<th>YOUNGER ADULTS</th>
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<th>OLDER ADULTS</th>
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<tbody>
<tr>
<td></td>
<td>Estimated Mean</td>
<td>95% CI</td>
<td>Estimated Mean</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>N = 22</td>
<td></td>
<td>N = 41</td>
<td></td>
</tr>
<tr>
<td>REST</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMN SI</td>
<td>0.10</td>
<td>0.06 - 0.14</td>
<td>0.07</td>
<td>0.05 - 0.10</td>
</tr>
<tr>
<td>ATN SI</td>
<td>0.05</td>
<td>0.03 - 0.06</td>
<td>0.04</td>
<td>0.03 - 0.05</td>
</tr>
<tr>
<td>TASK</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMN SI</td>
<td>0.09</td>
<td>0.06 - 0.12</td>
<td>0.05</td>
<td>0.03 - 0.06</td>
</tr>
<tr>
<td>ATN SI</td>
<td>0.07</td>
<td>0.05 - 0.10</td>
<td>0.03</td>
<td>0.02 - 0.05</td>
</tr>
</tbody>
</table>
Figure 4.3: DMN and ATN community consistency in light and moderate older drinker groups at rest and in task

Individual ROI-specific SI images were generated using the scaled inclusivity (SI) algorithm, which calculated a measure of overlap between each community in a network partition and the DMN and ATN ROI, respectively. Individual ROI-specific SI images were then used to generate adult group average SI images for the rest (top panel) and task conditions (bottom panel). **DMN community** consistency was similar between light older drinkers (LODs) and moderate older drinkers (MODs) in rest and task conditions. Like the comparisons made between younger and older adults, DMN community consistency generally decreased when in the task condition relative to the rest condition. DMN consistency also appeared to decrease in the frontal portions of the DMN before posterior regions, like the precuneus. **ATN community** consistency was lower in MODs than LODs at rest, and statistically lower in MODs than LODs when engaged in a task. These data showed that LOD and MOD functional brain networks exhibited ATN-specific differences in community organization despite sharing similar whole-brain topology profiles. They also showed that community structure surrounding attention-related brain regions was especially lower in MODs than LODs when engaged in a task. This finding suggested that moderate alcohol consumption in older age was associated with an exacerbated age-related decrease in community structure surrounding attention-related brain regions during an attention-demanding task.
Table 4.6: Light and moderate older drinker group consistency of DMN and ATN communities at rest and in task

<table>
<thead>
<tr>
<th></th>
<th>LOW OLDER DRINKERS</th>
<th>MODERATE OLDER DRINKERS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 20</td>
<td>N = 21</td>
</tr>
<tr>
<td></td>
<td>Estimated Mean</td>
<td>Estimated Mean</td>
</tr>
<tr>
<td></td>
<td>95% CI</td>
<td>95% CI</td>
</tr>
<tr>
<td>REST</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMN SI</td>
<td>0.08</td>
<td>0.07</td>
</tr>
<tr>
<td>ATN SI</td>
<td>0.05</td>
<td>0.03</td>
</tr>
<tr>
<td>TASK</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMN SI</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>ATN SI</td>
<td>0.04</td>
<td>0.02</td>
</tr>
</tbody>
</table>
4.3.5 Brain volume and White Matter Integrity

A significant main effect of age was found on measures of brain volume (F (2, 55) = 12.02, p < 0.0001). Specifically, younger adults were found to have significantly greater TBV (t (57) = 4.82, p < 0.0001) and TGMV (t (57) = 4.73, p < 0.0001). Younger adults also had a higher measure of white matter integrity than older adults (t (57) = 3.20, p = 0.002). Younger and older adult estimated group means and 95% confidence intervals for measures of brain volume and white matter integrity are presented in Table 4.7. Comparisons between LODs and MODs found that alcohol consumption did not directly affect TBV (t (34) = -0.94, p = 0.35) or TGMV (t (34) = -0.18, p = 0.86). LODs and MODs were also similar in measures of white matter integrity (F (2, 33) = 0.0025, p = 0.96). LOD and MOD estimated group means and 95% confidence intervals for measures of brain volume and white matter integrity are presented in Table 4.8.
Table 4.7: Younger and older adult group measures of brain volume and white matter integrity

<table>
<thead>
<tr>
<th></th>
<th>YOUNGER ADULTS</th>
<th></th>
<th>OLDER ADULTS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Estimated Mean</td>
<td>95% CI</td>
<td>Estimated Mean</td>
<td>95% CI</td>
</tr>
<tr>
<td>Brain Volume</td>
<td>N = 22</td>
<td></td>
<td>N = 41</td>
<td></td>
</tr>
<tr>
<td>TBV</td>
<td>302,334</td>
<td>290,269 - 314399</td>
<td>259,694</td>
<td>252,573 – 266,815 †</td>
</tr>
<tr>
<td>TGMV</td>
<td>178,487</td>
<td>169,687 – 187,287</td>
<td>147,955</td>
<td>142,761 – 153,149 †</td>
</tr>
<tr>
<td>White Matter Integrity</td>
<td>FA</td>
<td>0.43</td>
<td>0.40</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.41 – 0.44</td>
<td></td>
<td>0.39 – 0.40 †</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LOW OLDER DRINKERS</td>
<td>MODERATE OLDER DRINKERS</td>
<td></td>
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<tr>
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<td>--------------------</td>
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<td></td>
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<tr>
<td></td>
<td>( N = 20 )</td>
<td>( N = 21 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brain Volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TBV</td>
<td>262,154</td>
<td>266,968</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TGMV</td>
<td>149,488</td>
<td>150,156</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated Mean</td>
<td>254,839 – 269,470</td>
<td>259,836 – 274,100</td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>144,276 – 154,699</td>
<td>145,075 – 155,236</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White Matter Integrity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FA</td>
<td>0.40</td>
<td>0.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estimated Mean</td>
<td>0.39 – 0.40</td>
<td>0.39 – 0.40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4.8: Light and moderate older drinker group measures of brain volume and white matter integrity
4.4 Discussion

The overall goal of this study was to determine whether or not social alcohol use (7-21 drinks per week) in older age (≥ 65 years old) exacerbated age-related brain changes at rest and during task engagement. Results showed that regardless of condition the functional brain networks of older adults were more connected but less specialized than younger adults, and that long-term moderate alcohol consumption in older age was not associated with changes to this overall topology. DMN and ATN community structure was significantly less consistent in older adults than in younger adults in the task condition. Comparisons between LODs and MODs in the task condition showed that long-term moderate alcohol consumption was associated with an exacerbated age-related decrease in ATN community structure despite both groups performing similarly on the working-memory task. Expected age-related declines in brain volume and white matter integrity were documented but long-term moderate alcohol consumption in older age was not associated with any further decline in these measures.

Our functional neuroimaging findings could be interpreted as being a more sensitive indication of accelerated brain aging due to social alcohol consumption in older age. Literature showing that long-term heavy alcohol use is associated with negative changes to attention-related brain function help support this interpretation. For example, functional activation studies have shown that alcoholics with poor working memory performance have decreased activation in attention-related brain regions, including the DLPFC, and greater activation in the parietal lobes. Also, the effect of long-term heavy alcohol consumption on functional connectivity has been explored in a variety of populations, including subjects in utero (Wozniak, Mueller et al. 2013), younger (Beltz,
Gates et al. 2013, Karoly, Stevens et al. 2013, Han, Han et al. 2014, Thayer, Montanaro et al. 2014), and middle age (Maurage, Joassin et al. 2013, Sullivan, Muller-Oehring et al. 2013, Muller-Oehring, Jung et al. 2014). These studies have shown that some of the most robust differences in connectivity are found among attention-related brain regions. For example, one study has shown that heavy drinkers have weaker connectivity among attention-related brain regions (Muller-Oehring, Jung et al. 2014) while another has shown that stronger connectivity is associated with successful abstinence in alcoholics (Camchong, Stenger et al. 2013). A recent pharmacological study also supports the notion that ATN functional connectivity is particularly vulnerable to the negative effects of alcohol. The study demonstrated a Modafinil-related increase in the cognitive performance in alcohol dependent drinkers and showed that the increase in performance was related to an increase in connectivity among attention-related brain regions (Schmaal, Goudriaan et al. 2013). Aging literature could also be used to support this alternative interpretation. For example, studies have shown that functional dedifferentiation is indicative of brain decline and negative cognitive effects. Findings have demonstrated that aging alters the number, size, and connectivity structure of communities (Meunier, Achard et al. 2009) and that it is also associated with an overall breakdown in the balance between integration within and separation between communities (Brier, Thomas et al. 2014). Age-related increases in the recruitment of more general instead of specific functional networks have also been associated with lower performance on several cognitive tasks (Wang, Li et al. 2010, Spreng and Schacter 2012, Geerligs, Maurits et al. 2014).
If social alcohol consumption in older age is associated with accelerated brain aging, then functional differences could be interpreted as a compensatory mechanism that supports normal cognitive performance. Hypotheses related to neural reserve, might help to explain this phenomenon (Bartres-Faz and Arenaza-Urquijo 2011). The cognitive reserve (CR) hypothesis emphasizes the effective recruitment of neural networks and cognitive processes in order to compensate for negative changes to the brain (Stern 2009). In this study, we found that despite similar working memory task performance moderate older drinkers exhibited greater variability than light older drinkers in the way attention-related brain regions functionally interacted with the rest of the brain. This finding could be related to functional compensation in the brain that occurs due to long-term exposure to moderate amounts of alcohol in older age. In this case, a decrease in ATN functional community consistency would be an example of dedifferentiation that served to maintain rather than enhance cognitive performance.

Research limitations include the method used to quantify alcohol consumption in this study. Although underrepresentation is a common concern with self-report alcohol consumption questionnaires, it should be noted that this phenomenon is more common to populations that consume alcohol in larger quantities than those discussed in this study (Stockwell et al., 2004). Limitations also include a relatively small sample size when compared to previous research based on large-scale clinical trials that explored volumetric brain differences in moderate older drinkers. To compensate for this, a great deal of attention was paid to screening and recruitment of participants, which were healthy community dwelling adults, who consumed alcohol within ranges most common to the older American adult demographic (NIAAA, 1998, 2006). Moreover, a great deal
of attention was paid to the quantity and frequency of alcohol consumption so as to represent a truly moderate consumption pattern, and all adults were screened for signs of alcohol or substance use/abuse. Together, these features helped to make study findings more ecologically relevant to today’s older adult population. Future research in this field is encouraged and would benefit from studies adopting a longitudinal design so as to better address questions of causality. Studies that address other features of network structure and the source of increased variability in functional connections out from the ATN will also help to create a clearer picture how alcohol affects the brain and ultimately cognitive health.

To conclude, long-term moderate alcohol consumption in older adults was not associated with behavioral deficits in working memory performance, or any differences in whole-brain summaries of functional network topology. Results did suggest that long-term moderate alcohol consumption in old age was associated with exacerbated age-related decreases in connectivity among attention-related brain regions, especially when actively engaged in a task. This finding may point to the accelerated brain aging due to social alcohol consumption in older age.
REFERENCES


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CHAPTER V
DISCUSSION
5.1 Summary of the results

The central goal of this dissertation was to investigate whether or not non-problem moderate, or social, alcohol consumption in older age was associated with exacerbated age-related cognitive decline and changes to brain health. To do this, certain methodological constraints were addressed, and a research study specifically designed to measure these effects was conducted. The work done as part of this dissertation has generated important and novel findings related to alcohol consumption and the aging brain.

Chapter II specifically addressed a major challenge in examining network community structure and making group-based comparisons. Using neuroimaging data from the 1,000 Functional Connectomes Project, we showed that using scaled inclusivity (SI) to quantify inter-subject community consistency was not only feasible but also more useful than methods based on creating average networks. We showed how an average network did not accurately represent community structure across subjects in a group and that in some cases it was distinctly altered from the individual networks used to generate the average. Examples included community structure of the default mode network (DMN) and the attention network (ATN). In the average network, the DMN consisted of two distinct anterior and posterior communities despite being part of the same community when examined at the individual level. The average network also distorted community structure of the ATN by separating the left from the right dorsal lateral prefrontal cortex (DLPFC) and excluding the superior portions of the parietal lobules. This finding was critical to the current project as both the DMN and the ATN were the focus of the network analysis used in Chapter IV. Once methodological constraints to comparing
functional brain networks at the group-level were addressed, this dissertation focused on analyses that directly measured the effect of social alcohol consumption in older age on brain health.

Chapter III showed that non-problem social alcohol consumption in older age was not associated with exacerbated age-related cognitive decline. This was concluded using a comprehensive battery of tests designed to capture a wide range of cognitive abilities, and this approach was a unique contribution to this field of research. This chapter also showed that non-problem social alcohol consumption in older age was marginally associated with some beneficial effects to cognitive performance, including better attention and rule learning. Positive findings were interpreted with caution but lent support to the overall notion that social alcohol consumption in older age was not associated with exacerbated age-related cognitive decline.

Chapter IV showed that non-problem social alcohol consumption in older age was associated with an exacerbated age-related decrease in ATN community consistency during working memory task performance. This was the case despite the fact that light and moderate older drinkers performed similarly on the task, and exhibited no differences in gray matter volume or white matter integrity. This dissertation showed that, if anything, non-problem moderate alcohol consumption in older age was associated with limited benefits to cognition, including attention, short-term memory and rule learning. Non-problem moderate alcohol consumption in older age was also associated with increased variability in the way the ATN functionally connected with the rest of the brain. This pattern of functional connectivity was most prominent during working
memory task performance, and suggested that moderate older drinkers completed the task on par with light older drinkers by engaging different neural circuitry.

5.2. **Social alcohol consumption and age-related cognitive decline**

Age-related cognitive decline has been repeatedly demonstrated in literature (Hedden and Gabrieli 2004, Dennis and Cabeza 2008, Salthouse 2010). This dissertation reproduced this finding and showed that younger adults outperformed older adults in several cognitive domains, including attention, working-memory, short-term memory, processing speed, and rule learning. However, when the behavioral findings are considered as a whole, they showed that moderate alcohol consumption in older age was not associated with any obvious differences in cognitive health. What follows is a discussion on possible interpretations to the findings of this research. First, it will address the small significant positive effects on cognition and possible mechanisms to support these effects. Afterwards, an alternative interpretation to the findings of this study will be addressed. The focus will shift to the possibility that these data are a sensitive indicator of accelerated brain aging, and possible mechanisms to support this interpretation despite an overall null effect on behavior will also be discussed.

5.3 **Social alcohol consumption may help to enhance cognition in older age**

All of the alcohol-induced effects on cognition that were found were marginally significant; however, they all suggested that social alcohol consumption in older age improved the speed to accuracy ratio of cognitive function (Schouten and Bekker 1967, Wickelgren 1977, Chittka, Skorupski et al. 2009). For both short-term memory and rule-learning cognitive domains, moderate older drinkers tended to do better than light drinking counterparts in similar amounts of time. Results also showed that moderate
older drinkers tended to perform better and faster than light older drinkers on the Eriksen Flanker Task, suggesting that attention was most sensitive to the beneficial effects of social alcohol consumption in older age. We did not find a direct relationship between ATN community structure and performance on these tasks but it is important to remember that these tasks were administered on Testing Visit II and that brain function was not recorded in the MRI scanner. Nevertheless, differences observed in ATN functional community structure could be related to better performance in attention, short-term memory and rule learning cognitive domains. Theories related to neural dedifferentiation can help explain how this may be the case (Bartres-Faz and Arenaza-Urquijo 2011).

Neural dedifferentiation suggests that brain areas can lose their functional specialization and eventually become involved in many different tasks (Goh 2011). This concept is familiar to aging research and support for this in literature includes studies that have demonstrated age-related reorganization and shifts in activation patterns when older adults perform on par with younger adults on certain cognitive tests (Park, Polk et al. 2004, Rajah and D'Esposito 2005, Heuninckx, Wenderoth et al. 2008, Goh, Suzuki et al. 2010). This study found that non-problem moderate alcohol consumption in older age was associated with differences in how the ATN functionally connected with the rest of the brain. In fact, the study showed that attention-related brain areas interacted with regions outside of the ATN community more often in moderate older drinkers than in light older drinkers. These findings could therefore be taken to suggest that social drinking in older age brings about increases in neural dedifferentiation that ultimately
work to counteract age-related declines in attention, short-term memory and rule learning.

It is also important consider the influence of the environment when interpreting the positive alcohol-related effects on cognition that were observed in this study (McClearn, Johansson et al. 1997). For example, the lifestyle-cognition hypothesis holds that maintaining an active lifestyle and engaging in certain activities during one’s life may help to prevent cognitive decline. Several longitudinal studies, including the Seattle Longitudinal Study, the Bronx Aging Study, and the Victoria Longitudinal Study, have attempted to answer the question of whether certain activities may prevent or delay cognitive decline (Harada, Love et al. 2013). Findings support the lifestyle-cognition hypothesis and have shown that older adults with high cognitive function participate in certain activities (e.g. socializing, volunteering, leisure activity) with greater frequency, and have higher levels of education and occupational training (Fratiglioni, Paillard-Borg et al. 2004, Marioni, van den Hout et al. 2012). The primary outcome of those studies was performance on cognitive tests but more recent analyses have used measures of structural brain health to show that physical activity and engagement in complex activities in late life have a positive impact on gray matter atrophy, white matter lesions and brain function (Fotuhi, Do et al. 2012, Gow, Bastin et al. 2012). The older participants in this study were relatively healthy and community-dwelling adults. They were highly educated and had at one time or another been active participants in the work force. Most of them were retired and reported to spend their time enjoying the company of family and friends, volunteering, exercising and travelling. It is therefore entirely
possible that these variables interacted positively with social alcohol consumption to confer some benefit to cognitive health in older age.

5.4 Social alcohol consumption may accelerate brain aging

An age-related decline in ATN functional community consistency was observed in this study, and an exacerbated decline was observed in moderate drinkers when comparisons between older drinkers were made. This was the case despite no differences between light and moderate older drinkers in working memory task performance, brain volume and white matter integrity. Our functional neuroimaging findings could therefore be interpreted as being a more sensitive indication of accelerated brain aging due to social alcohol consumption in older age.

Literature showing that long-term heavy alcohol use is associated with negative changes to attention-related brain function help support this interpretation. For example, functional activation studies have shown that alcoholics with poor working memory performance have decreased activation in attention-related brain regions, including the DLPFC, and greater activation in the parietal lobes. Also, the effect of long-term heavy alcohol consumption on functional connectivity has been explored in a variety of populations, including subjects in utero (Wozniak, Mueller et al. 2013), younger (Beltz, Gates et al. 2013, Karoly, Stevens et al. 2013, Han, Han et al. 2014, Thayer, Montanaro et al. 2014), and middle age (Maurage, Joassin et al. 2013, Sullivan, Muller-Oehring et al. 2013, Muller-Oehring, Jung et al. 2014). These studies have shown that some of the most robust differences in connectivity are found among attention-related brain regions. For example, one study has shown that heavy drinkers have weaker connectivity among attention-related brain regions (Muller-Oehring, Jung et al. 2014) while another has
shown that stronger connectivity is associated with successful abstinence in alcoholics (Camchong, Stenger et al. 2013). A recent pharmacological study also supports the notion that ATN functional connectivity is particularly vulnerable to the negative effects of alcohol. The study demonstrated a Modafinil-related increase in the cognitive performance in alcohol dependent drinkers and showed that the increase in performance was related to an increase in connectivity among attention-related brain regions (Schmaal, Goudriaan et al. 2013). Aging literature could also be used to support this alternative interpretation. For example, studies have shown that functional dedifferentiation is indicative of brain decline and negative cognitive effects. Findings have demonstrated that aging alters the number, size, and connectivity structure of communities (Meunier, Achard et al. 2009) and that it is also associated with an overall breakdown in the balance between integration within and separation between communities (Brier, Thomas et al. 2014). Age-related increases in the recruitment of more general instead of specific functional networks have also been associated with lower performance on several cognitive tasks (Wang, Li et al. 2010, Spreng and Schacter 2012, Geerligs, Maurits et al. 2014).

If social alcohol consumption in older age is associated with accelerated brain aging, then functional differences could be interpreted as a compensatory mechanism that supports normal cognitive performance. Hypotheses related to neural reserve, might help to explain this phenomenon (Bartres-Faz and Arenaza-Urquijo 2011). Brain reserve capacity (BRC) is an example of passive reserve, and refers to how an individual’s particular capacity to endure neuropathological processes is genetically determined by characteristics like brain volume and the number of neurons and synapses (Stern 2002).
This perspective is largely concerned with anatomical correlates that help to prolong a critical threshold at which vulnerability to brain damage is unavoidable and, eventually, clinically evident. This dissertation took this perspective into consideration by looking at correlates of both structural and physiological brain health. This study was able to reproduce age-related declines in brain volume and white matter integrity. However, the study did not show that these features differed between light and moderate older drinkers. Instead, neuroimaging findings suggested that compensatory efforts were achieved via alternate functional connectivity patterns in the brain.

The cognitive reserve (CR) hypothesis emphasizes the effective recruitment of neural networks and cognitive processes in order to compensate for negative changes to the brain (Stern 2009). Neural compensation is a mechanism used to describe how such processes may be possible, and is not a new concept to either alcohol or aging literature. Commonly recognized examples of neural compensation include the scaffolding theory of aging and cognition (STAC) (Park and Reuter-Lorenz 2009) and the hemispheric asymmetry reduction model (HAROLD) (Cabeza 2002), which suggest that in some circumstances older adults achieve a cognitive goal using alternative functional processes than those used by younger adults. In this study, we found that despite similar working memory task performance moderate older drinkers exhibited greater variability than light older drinkers in the way attention-related brain regions functionally interacted with the rest of the brain. This finding could be related to functional compensation in the brain that occurs due to long-term exposure to moderate amounts of alcohol in older age. In this case, a decrease in ATN functional community consistency would be an example of dedifferentiation that served to maintain rather than enhance cognitive performance.
5.5 Social alcohol consumption likely has differential effects on cognition in older age

Findings from Chapter III showed that moderate older drinkers tended to outperform light older drinkers in tasks designed to measure attention, short-term memory and rule learning. An interpretation to this finding included the concept of neural dedifferentiation, and the possibility that changes to functional connectivity helped to improve behavior in these domains. Chapter IV showed that the two groups performed similarly to each other on a working-memory task but that moderate older drinkers demonstrated greater variability in the way attention-related brain regions functionally interacted with the rest of the brain. Given an overall age-related increase in this variability, these findings pointed to a sign of accelerated brain aging due to social alcohol use in older age. Interpretations included the possibility that changes to functional connectivity represented a compensatory mechanism, which helped maintain similar performance in moderate older drinkers.

These interpretations are in conflict with each other, as one assumes that changes in functional connectivity are beneficial and the other assumes that changes are compensatory and a sign of future cognitive decline. One way to reconcile this discrepancy involves an interpretation that allows for differential effects of alcohol on cognition via its effect on functional connectivity. More specifically, increased variability in the way attention-related brain regions interacted with the rest of the brain as a result of social alcohol consumption in older age could have in and of itself accounted for the variability in behavioral performance across cognitive domains (i.e. no effect, positive effects, and a potentially negative effect). This study did not address alternative profiles of connectivity surrounding attention–related brain regions (i.e. the
source of increased variability). However, characterizing where ATN connections are located when older social drinkers perform different tasks is one of the first steps in understanding how different cognitive abilities may be differentially influenced by moderate amounts of alcohol in older age.

5.6 Limitations

Limitations to this dissertation include a relatively small sample size when compared to previous research based on large-scale clinical trials. Despite this, confidence in our behavioral findings is strengthened by the fact that the confidence intervals presented for each cognitive domain were within the range of performance data previously reported in healthy older adults (Sahakian, Morris et al. 1988, Downes, Roberts et al. 1989, Owen, Downes et al. 1990, Sahakian, Downes et al. 1990, Robbins, James et al. 1998, Shapiro, Benedict et al. 1999, de Jager, Milwain et al. 2002, Hogervorst, Combrinck et al. 2002, De Luca, Wood et al. 2003, Hoyer, Stawski et al. 2004, Tombaugh 2004, Van Gerven, Meijer et al. 2008).

It is important to note there are several other neuroimaging modalities and analyses that were not addressed but that could have offered greater insight to the results presented in this dissertation. For example, fMRI based studies offer greater spatial resolution at the expense of lower temporal resolution. Imaging modalities that offer greater temporal resolution and that could be better suited to recording brain activity at specific times during cognitive performance include electroencephalography and magnetoencephalography. Also, network based analyses were used in this dissertation in order to model data as an integrated whole and these analyses are useful in understanding the brain as a system. However, they do not address specific regional changes at the
molecular level. These changes may have been present but undetected at the whole brain network level. Potential imaging modalities that could have been used to address changes at the molecular level include positron emission tomography.

Finally, the studies described in this dissertation focused solely on long-term social alcohol consumption. They did not address other alcohol consumption patterns that that may have had a more obvious effect on brain health in older adults. For example, long-term exposure may not be associated with negative effects on brain health but acute exposure to moderate alcohol in older adults may present greater risks immediately following exposure (i.e. risk of falling, impaired driving).

5.7 Future directions

Individual susceptibility to alcohol-induced changes in brain health is highly variable and related to many factors, including sex and socio-demographics. These variables should be considered more thoroughly when designing future research on social drinking in older age. Gender-specific census data reveal a narrowing gap between the drinking patterns exhibited by men and women (Grant 1997). To illustrate this point are data that show that men born before World War II were 2.4 times more likely as females to drink alcohol and data that show that men born in the Vietnam era were only 1.2 times more likely as females to drink alcohol (Nelson, Heath et al. 1998). Understanding whether or not social drinking affects the brain health of women differently than men can only help to better characterize alcohol-induced brain changes and help to improve the identification of alcohol-related cognitive decline and dementia (Oslin, Atkinson et al. 1998).

Notwithstanding gender-specific influences, it is also important for future research to recognize that there is a great deal of sub-group heterogeneity within the older
adult demographic (Midanik and Clark 1994, Midanik and Clark 1995). Racial differences have already been identified as important considerations in alcohol research design. For example, Asians are known to exhibit differences in alcohol metabolism that make them more vulnerable to the negative effects of alcohol exposure (Zakhari 2006). Aside from racial differences in the metabolism of alcohol are differences in drinking patterns demonstrated among elderly ethnic groups. An emerging example includes the Hispanic demographic, which demonstrated an increase in alcohol consumption within the last decade and is expected to show the largest rate of increase of any racial/ethnic elderly subgroup over the next couple decades (Caetano and Kaskutas 1995, Caetano and Clark 1998). It is therefore important to consider how alcohol-induced brain changes may differ based on sub-group heterogeneity when designing translational research. One way to address this is to design an experiment focused on individual differences as opposed to group means. It is especially important in this type of experiment to recruit an adequate number of individuals to represent each of the various sub-groups (e.g. females, males, Hispanics, Asians, etc.). Analytical techniques based on factor or cluster analysis could then be used to explore whether or not there are inherent groupings within the data (e.g. low, medium and high connectivity) that are specific to certain levels of cognitive performance in specific sub-groups.

Our study found that social alcohol consumption in older age was associated with changes in the way brain regions functionally interacted with each other when engaged in a task. However, interpretations to these findings remain unclear and suggest that dedifferentiation in ATN community connectivity could either serve to enhance or maintain cognitive ability in older age. Further research is required in order to elucidate
the nature of dedifferentiation in this research study. Given positive behavioral findings related to attention, short-term memory and rule learning, an experiment measuring functional community organization during task performance may help to address whether or not non-problem moderate alcohol consumption also confers beneficial changes to functional connectivity. For example, this research showed an age-related decline in ATN community consistency during working memory performance, and an exacerbated decline in moderate older drinkers. Determining whether or not moderate older drinkers exhibit a reversal of this trend when performing tasks they did well on will help to interpret our findings. Also, additional network analyses could help reveal whether or not connectivity away from attention-related brain regions is similar in situations where moderate drinkers perform better and just as well as light older drinkers. This type of experiment could help identify functional relationships that are indicators of brain insult (compensatory relationships) and/or relationships that help counteract age-related cognitive decline (performance enhancing relationships).

Finally, determining how the trajectory of brain decline differs in people as a result of alcohol consumption and pinpointing divergence from healthy older adults is a critical step in understanding alcohol-induced cognitive decline and dementia in older adults. The results of this dissertation and the potential avenues for future research work towards improving public health recommendations for older adults. Public policy, as it relates to older adults and alcohol consumption, is largely based on research in younger adults. For example, current BAC standards for intoxicated driving may need to be altered for adults aged 65 years or older due their sensitivity to alcohol exposure. Also, dietary guidelines may need to be reevaluated to directly apply to the older adult
population. This and other research focused on older adults and how alcohol affects them directly is important to ensure the safety and health of what is currently the fastest growing demographic in America.
REFERENCES


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