NEUROPHYSIOLOGICAL CORRELATES OF MODERATE ALCOHOL USE IN OLDER ADULTS

By

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A DISSERTATION PRESENTED TO THE GRADUATE SCHOOL
OF THE UNIVERSITY OF FLORIDA IN PARTIAL FULFILLMENT
OF THE REQUIREMENTS FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY

UNIVERSITY OF FLORIDA

2012

To my family, my friends, and my love

ACKNOWLEDGMENTS

I would like to first acknowledge Sara Jo Nixon, Ph.D, for being as good a mentor as a student could possibly ask for. When starting in her laboratory I had no experience in human research whatsoever, and she knew it. Dr. Nixon took a chance in allowing me to join her team, and I will always appreciate her faith in me.

Over the last several years I've had the pleasure of working with current and past members of Dr. Nixon's lab. I would especially like to acknowledge Layla Lincoln for her effort in screening and running study participants; Alfredo Sklar, with whom I learned a great deal about programming E-prime and driving simulators; Rebecca Gilbertson, Ph.D., for her continued collaboration even as she braves the cold North; Ben Lewis, Ph.D., for his encouragement and patient proof-reading; and Robert Prather, who I am proud to call a friend and has always gone out of his way to give me a hand when I needed it. Natalie Ceballos, Ph.D., and Rick Tivis, MS, deserve thanks for resolving conundrums both electrophysiological and statistical.

Many thanks to my mom, dad, brother, and sister-in-law, who have each served in various critical roles including but not limited to: confidant, caretaker, handyman, coach, friend, challenger, sounding board, and dog-sitter. I cannot thank my fiancée Catherine enough for her incredible patience and unwavering support throughout the process of graduate school. My good friends Ian, Terry, Jen, and Cam also each deserve thanks for keeping me socialized and happy, even when my cortisol levels were at their highest.

I appreciate the assistance and feedback of my supervisory committee, Drs. Mark Lewis, Jacqueline Hobbs, William Perlstein, and Marieta Heaton. Thanks to them, I

have consistently looked forward to committee meetings and their ideas and suggestions. I realize that this is a rare situation for a Ph.D. student, and I am grateful.

New College professors Elzie McCord, Ph.D. and Alfred Beulig, Ph.D. each played an important role in sparking my interest in science and encouraging me to earn a Ph.D. The time they spent with me in one-on-one classes and discussions has helped enormously as I pursued my degree.

Finally, I acknowledge the National Institute on Alcohol Abuse and Alcoholism (F31AA019862; Boissoneault, PI; Nixon, Sponsor) and the University Of Florida Department Of Psychiatry for their support.

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By

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August 2012

Chair: Sara Jo Nixon
Major: Medical Sciences—Neuroscience

A moderate drinking lifestyle may help reduce the risk of cardiovascular disease, type 2 diabetes, and some types of cancer. However, the degree of risk associated with moderate drinking episodes is poorly understood. Impaired attentional and behavioral function has been identified as a consequence of both aging and acute low-to-moderate alcohol administration, yet studies of the interaction between these factors are largely lacking. This project was conducted to address this gap. We hypothesized age and moderate alcohol administration would have independent negative effects on both attentional function and behavioral performance, but that older adults would be more susceptible to alcohol-related decrements than younger adults. In addition, we predicted older adults would show dissociation between subjective and objective measures of intoxication and neurophysiological and behavioral performance.

Fifty-two (52) younger (25-35 years old; 20 women) and 42 older (55-70 years old; 25 women) healthy community-dwelling subjects (Ss) completed laboratory testing. Ss were administered either placebo or a dose of alcohol targeted to a blood alcohol concentration of 0.04 g/dL or 0.065 g/dL. Following absorption, Ss completed a remember/ignore task requiring attentional enhancement to relevant stimuli and

suppression of attention to irrelevant stimuli relative to a passive viewing condition. Amplitude and latency of several components of the event related potential (ERP) were assessed as well as accuracy and reaction time.

Results indicated that both enhancement and suppression were intact in younger Ss across alcohol groups. Enhancement correlated positively with task accuracy for younger Ss. Older Ss did not show suppression and demonstrated enhancement under active alcohol that did not correlate with improved accuracy or reaction time. Furthermore, breath alcohol concentration but not subjective intoxication correlated with behavioral decrements in older but not younger Ss.

These data provide new information about the acute effects of alcohol concentrations typical of a moderate drinking event on attentional function and working memory performance in older adults. Further study is necessary to determine whether older adults are at higher risk for moderate alcohol-induced injury or health-related consequences as a result of these effects.

CHAPTER 1
MODERATE DRINKING

Moderate Drinking

An ambivalent view of alcohol is common in Western society. While “social” and “moderate” drinking is increasingly recognized as being potentially beneficial for one’s health and well-being, the dangers of excessive consumption are clearly recognized. This conflict is eloquently represented by a story told by former Florida Representative D. R. “Billy” Matthews, in which he relates another Congressman’s response to the question “How do you stand on whisky?” from a constituent. On one hand, if by whisky the constituent is referring to “bloody monster which defiles innocence”, then he is against it. On the other, if the constituent regards whisky as “the ale consumed when good fellows get together”, then he is for it (Matthews, 1960).

Despite this equivocation, the majority of Americans at least occasionally use alcohol. Beginning in 1939, polling by Gallup, Inc. has annually tracked the number of Americans who report “having occasion to use alcoholic beverages such as beer, wine, or liquor,” and those who are “total abstainers”. Despite some fluctuations over time, roughly 60-70% of Americans report being at least occasional alcohol consumers (Gallup Inc., 2011). Data from the National Survey on Drug Use and Health (Substance Abuse and Mental Health Services Administration, 2006), suggest that 80% of American adults report lifetime use of alcohol with 50.1% indicating having had a drink in the past 30 days. Americans who drink account for a per capita consumption 8.5 liters (2.25 gallons) of absolute ethanol per year (Spanagel, 2009), although 73% of the alcohol consumed in the United States is drunk by just 10% of the population (Li, 2008).

According to the CDC, self-reported alcohol use accounts for only 22-32% of presumed alcohol consumption based on sales figures, suggesting that self-reports are conservative estimates of use (Kanny et al., 2012).

Health Benefits Associated with Moderate Drinking

Conventional wisdom and a substantial literature suggest that a lifestyle of moderate drinking poses little threat to one's health and may, especially in older adults, promote good health. Of the domains examined, cardiovascular function appears to show the most consistent benefit from a moderate drinking lifestyle. Using data from the Women's Health Study (N=26399; Ridker et al., 2005), one study found that women who reported consuming about 1 drink per day had a 32% reduction in risk of developing cardiovascular disease during a 12 year follow-up period relative to abstainers. They found that this reduction in risk was mediated by alcohol's effects on blood lipid levels, glucose metabolism, insulin sensitivity, and blood pressure (Djousse et al., 2009). Those consuming 2-3 drinks per day showed a lesser, non-significant reduction in risk. This pattern was maintained when death due to cardiovascular causes was considered as the outcome variable. Those women who consumed more than 3 drinks per day were significantly more likely to develop cardiovascular disease or experience cardiovascular mortality than abstainers or more moderate drinkers, reinforcing that any health benefits due to drinking are restricted to moderate levels.

Many other major cross-cultural efforts have revealed similar findings in both women (Freiberg et al., 2009) and mixed sex samples over the last three decades, including the Physicians' Health Study (Gaziano et al., 2000); National Health Interview Survey (Mukamal et al., 2010); Framingham Heart Study (Friedman and Kimball, 1986); the first wave of the National Epidemiologic Survey on Alcohol and Related Conditions

(Balsa et al., 2008); and surveys of British health professionals (Doll et al., 1994) and German (Keil et al., 1997), French (Renaud et al., 1998), Chinese (Yuan et al., 1997) and Japanese (Inoue et al., 2012) citizens. Broadly speaking, across studies, those individuals consuming between one and two drinks per day reported better health, had fewer heart problems, and reported fewer hospitalizations (cf. Fillmore et al., 2007). Consistent with these findings, a study of Medicare costs in adults over 65 years of age found that those who drank between one and six drinks a week had significantly less cost to the system due to decreased incidence of cardiovascular disease and its associated hospitalization (Mukamal et al., 2006). Moderate drinking is also associated with a reduction in the risk of developing type 2 diabetes and some types of cancer (Spanagel, 2009), as well as better ability to perform activities of daily living (Lee et al., 2009). Abstainers and moderate drinkers may differ with regard to important risk factors like socioeconomic status, cigarette smoking, body composition, exercise habits, chronic illness, daily function, and psychosocial factors (i.e., depression and social function). However, the benefits of moderate drinking are still apparent when these differences are statistically controlled (Lee et al., 2009).

Some alcohol-containing beverages are presumed more healthful than others. Red wine has achieved popular designation as a particularly healthy beverage, in part due to its association with the so-called “French Paradox”; a term coined in 1992 to describe the linkage of low cardiovascular disease incidence and mortality rates in France (known for its cultural predilection for rich foods) and consumption of red wines (Renaud and de Lorgeril, 1992). Extensive research in the last twenty years has revealed several antioxidant polyphenol compounds in red wine present only in small

amounts in white wines and distilled liquors (especially resveratrol; Nakata et al., 2012; Chachay et al., 2011; Wu et al., 2011), though this research is not without controversy (DeFrancesco, 2012). Notably, the quantity of these compounds in red wine varies considerably both between and within grape varieties (Yoo et al., 2010). Beer is also known to contain biologically available antioxidant polyphenols, though its properties are less well studied (Piazzon et al., 2010; Leitao et al., 2011). Despite the prevalence of popular diet books and magazine articles promoting frequent moderate red wine consumption, few clinical studies comparing the impact of red wine, white wine, beer, and spirits on biomarkers of cardiovascular health and mortality risk have been conducted. In one such study of 38,077 male health professionals over 12 years in the United States, no differences in risk of cardiovascular disease were noted between types of alcoholic beverage consumed (Mukamal et al., 2003). These results lend credence to the suggestion that it is the pattern of alcohol consumption that drives cardiovascular benefits rather than the beverage type (van de Wiel and de Lange, 2008).

Defining Moderate Drinking

Various US governmental organizations have published guidelines for reducing risk associated with drinking alcohol. The United States Departments of Agriculture and Health and Human Services 2010 *Dietary Guidelines for Americans* sets the recommended level for “low-risk” or “moderate” drinking at no more than two drinks a day for men and one drink per day for women (United States Department of Agriculture and United States Department of Health and Human Services, 2010). The National Institute on Alcohol Abuse and Alcoholism provides an additional guideline for weekly drinking: no more than 14 drinks a week for men and 7 for women while not exceeding

binge drinking limits (>5 drinks in a single sitting for men and >4 for women) (National Institute on Alcohol Abuse and Alcoholism, 2005). Data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC; Chen et al., 2006) from 2001-2002 validate these guidelines. In this sample, 72% of drinkers surveyed never exceeded daily or weekly moderate drinking guidelines. Compared to this group, those who exceeded either or both guidelines were between 7.8 and 219.4 times more likely to develop an alcohol use disorder depending on whether one or both guidelines were exceeded and how often (Li, 2008). Dawson and Grant (2011) examined risk of medical and mental health consequences associated with exceeding weekly limits and/or binge drinking guidelines and found that exceeding either guideline was associated with dramatically increased risk of having alcohol-related interpersonal problems, job loss, or organ damage.

Worldwide, consequences of alcohol consumption account for 4% of total disability-adjusted life years (DALYs; Spanagel, 2009; World Health Organization, 2004). DALYs are a measure of global disease burden which takes into account the impact of disease in terms of both years of life lost and years lived with disability (Pruss-Ustun et al., 2003). Thus, alcohol consumption accounts for twice the DALYs of HIV and AIDS (~2%). Within individual countries, the proportion of DALYs accounted for by alcohol in individual countries can be far higher. In the United States, alcohol accounts for 12.1% of DALYs in men and 4.5% in women. In Russia, the proportion reaches 28.1% in men and 10.7% in women (Rehm et al., 2009). Problematic alcohol use resulted in ~80,000 deaths and 2.3 million years of potential life lost (life expectancy - age at death) in the United States each year from 2001-2005, and $223.5 billion in costs

in 2006 (Spanagel, 2009). Alcohol is linked as a causative and/or exacerbating factor on a variety of diseases, including esophageal cancer, liver cancer, cirrhosis of the liver, epilepsy, diabetes, and cardiovascular conditions, and both intentional and unintentional injury (Li, 2008; Rehm et al., 2009).

Exceptions to Moderate Drinking Guidelines

Consumers may presume that adherence to moderate drinking guidelines ensures little likelihood of experiencing alcohol-related health consequences. This assumption is generally supported by the literature (Li, 2008), yet guidelines include provisions suggesting that there is no safe level of drinking for certain special populations. These populations include individuals unable to control their alcohol intake; women who are or may become pregnant, or who are lactating; children and adolescents; those taking medications interacting with alcohol; or those for whom alcohol consumption would constitute an unacceptable risk (i.e., heavy equipment operators; Dawson and Grant, 2011). Some individuals may also be at increased risk for health-related consequences for even moderate drinking due to mutations in the gene encoding acetaldehyde dehydrogenase (ALDH2; Brooks et al., 2009; Bae et al., 2012). For these individuals, including 30-50% of people of East Asian origin, acetaldehyde, a normal product of alcohol metabolism, accumulates abnormally during drinking sessions and causes a characteristic flushing response. In Caucasians, mutations in this gene are very rare (Pavanello et al., 2012). Along with consequences including increased susceptibility to hangover (Yokoyama et al., 2005; Yokoyama et al., 2012), inactive ALDH2 is linked to a vastly increased risk of squamous cell carcinomas of the esophagus (~70x increased risk over non-ALDH2 deficient moderate drinkers; Brooks et al., 2009).

Even for individuals without special circumstances, confusion may arise as to whether any level of drinking is safe due to interactive effects of commonly prescribed prescription medications. Use of prescription drugs is very common in the United States; 45.3% of individuals consume at least one prescription drug per month and 17.7% consume 3 or more drugs per month (National Center for Health Statistics, 2006). As one might expect, the proportion of the population using prescription drugs increases with age. Those persons over the age of 65 consume 25-30% of all prescription medications despite constituting only 13% of the population (National Institute on Drug Abuse, 2005). A recent review determined that 76.9% of the 78 most commonly prescribed drugs in the US either interact with alcohol to modulate its effects (typically enhancing drowsiness, CNS depression or sedative effects, or causing dizziness). Alcohol consumption can also exacerbate adverse effects of the drug itself. Further, acute alcohol drinking inhibits metabolism for many drugs in the short term yet reduces availability chronically by inducing metabolizing enzymes (Smith, 2009). Important and potentially risky interactions may also result from the co-administration of alcohol with over-the-counter drugs such as diphenhydramine hydrochloride. These interactions may increase the risk associated with acute consumption of even light or moderate alcohol doses.

Recreational use of illicit drugs may also modulate the effects of both the drug(s) themselves and alcohol, increasing risk associated with drinking even small quantities. For example, alcohol and cocaine are commonly consumed together (Substance Abuse and Mental Health Services Administration, 2007). When cocaine is administered along with alcohol, its bioavailability is increased ~15% (Herbst et al., 2011; Parker and

Laizure, 2010) and biotransformation into its major metabolites (benzoylecognine and ecognine methyl ester) is disrupted. In addition to the two main inactive metabolites, 18-34% of ingested cocaine is transformed into cocaethylene (depending on route of administration), the ethyl ester of benzoylecognine (Herbst et al., 2011). Unlike benzoylecognine and ecognine methyl ester, cocaethylene is a potent psychostimulant with equivalent inhibitory potency on the dopamine transporter as cocaine itself, along with inhibitory action on serotonin and norepeniphrine transporters (Jatlow et al., 1996). The psychoactive properties of cocaethylene may at least partially underlie the greater subjective perception of the cocaine high observed with alcohol co-administration (Pennings et al., 2002), and may constitute a means by which abuse liability of both alcohol and cocaine is increased. Although the effects of cocaine and alcohol coadministration are one of the best studied examples, potentially harmful interactions have been noted between alcohol and many other recreational drugs including MDMA, opiates, nicotine, and others (Ralevski et al., 2012; Mohamed et al., 2011; Clark et al., 2006).

Sex Differences in Moderate Drinking

As noted above, USDA and NIAAA guidelines for moderate and low risk drinking are different for men and women. The sex specific guidelines are supported by a substantial literature indicating important differences in alcohol absorption and metabolism between men and women. For example, one study (Frezza, 1990) demonstrated that women had approximately 23% of the first-pass metabolism of alcohol and 59% of the gastric alcohol dehydrogenase activity of men. This resulted in significantly higher BACs in women than men from the same alcohol dose (0.3 g/kg). Studies in healthy college-aged young adults found that women binge drinking at the

cutoff level for men (5 drinks in a sitting) were significantly more likely to experience negative consequences than men, including missing class, experiencing hangover, falling behind in studies, or forgeting the events of a drinking session ("black out"; (White, 2003)). Body composition differences may partially underlie these effects; women tend to have a greater percent body fat than men and less lean muscle mass, resulting in lower total body water content. In turn, a given dose of alcohol has less area in which to distribute leading to a relatively higher alcohol concentration in women than men. Women also have enhanced bioavailability of orally ingested alcohol than men, perhaps due to previously noted reductions in gastric alcohol dehydrogenase activity and notably slower gastric emptying (Nolen-Hoeksema and Hilt, 2006). Similarly, a recent study comparing pharmacokinetics of acute alcohol doses in male and female regular drinkers found that alcohol elimination rates were significantly lower in women (Cohen's d = 1.41), and that this difference was due entirely to smaller average liver mass in women (1.56 kg vs. 1.99 kg; Dettling et al., 2007).

Women also experience increased risk of coronary heart disease from lower levels of regular alcohol consumption than men, perhaps due to these differences in alcohol distribution and metabolism. Meta-analysis and review by Corrao and colleagues (2000) found that the J-shaped curve describing cardiovascular risk from regular consumption was significantly left-shifted for women relative to men, with the maximal protective effect at ~1 drink/day (vs. 2 drinks/day for men), and significant risk beginning at ~4 drinks/day (vs. ~9 drinks/day for men). Indeed, the risk of mortality associated with heavy drinking is 4 times higher in women than it is in men. Taken in total, these

findings suggest women may have a narrower window of low-risk drinking than men (Nolen-Hoeksema and Hilt, 2006; Nolen-Hoeksema, 2004).

Awareness of Moderate Drinking Guidelines

Empirical studies show many individuals are unaware of guidelines for moderate drinking. In 2007, Green et al. (2007) conducted in depth interviews with 150 community dwelling individuals and examined common themes in their definitions of moderate drinking (see also Midanik, 2003). The themes fell into several basic categories, with moderate drinking being a) individually determined based on any number of social and physical factors (e.g., family history of alcoholism, sex, belief system, or drinking context); b) the result of any alcohol use failing to achieve overt intoxication; c) drinking not resulting in negative consequences; d) controlled drinking; or e) defined based on an individual's normative expectations (i.e., "Less than I drink."). Few responses conveyed knowledge of guidelines for low risk drinking; many had concerning implications for individual and public health. For example, at least one participant assumed the development of tolerance to alcohol corresponded to an increasing threshold for non-moderate or risky drinking. These findings underscore the heterogeneity of attitudes about moderate drinking in Americans and the potentially high risk that these attitudes may convey.

Effects of Acute Alcohol

Most discussions of the risks and benefits of a moderate alcohol consumption lifestyle do not account for the potential of risk associated with each individual session of drinking (Nixon, 2009). For individuals who are not at increased risk for alcohol related harm, these risks are primarily due to alcohol-related changes in performance for both simple and complex tasks. Alcohol concentrations in human studies are

generally derived from breath measurements, reported as breath alcohol concentration (BrAC). BrAC has been shown to reflect blood alcohol concentration (BAC), which is rarely measured directly. The effects of acute alcohol intake have been studied extensively at BrACs around and above the *per se* legal limit for operation of a motor vehicle in the US (0.08 g/dL). A review of older literature by Holloway (1994) showed that almost all acute administration studies achieving the *per se* limit or higher reported significant alcohol-related decrements in visual and psychophysical function (e.g., eye movement, vigilance, memory, posture and gait); performance on simple target tracking, reaction time, and mental arithmetic tasks; performance in tasks requiring cognitive control (difficult target tracking, divided attention, eye-hand coordination); and simulated vehicle operation. However, studies of alcohol effects at lower BACs (i.e., those ~0.065 g/dL or below) were less consistent. More recent work, reviewed by Fillmore (2007), has replicated and extended previous findings, showing that many task paradigms have threshold BAC levels of reliable impairment well above 0.065 g/dL; despite this, tasks requiring controlled, effortful attention or which involve multitasking are reliably impaired by BACs less than 0.05 g/dL. A selected overview of the effects of higher and lower doses of alcohol on performance follows.

Higher-dose Effects (≥ ~0.08 g/dL)

Recent studies on relatively higher alcohol doses have expanded knowledge of compromised processes, mechanisms of action, and consequences of those deficits in non-problem social drinkers. For instance, Nawrot et al. (2004) showed that a BrAC of around 0.1 g/dL, a level typically associated with eye movement deficits, resulted in poorer depth perception due to an inability to perceive motion parallax (i.e., objects which are closer appear to move more quickly than those that are far away; Rogers and

Rogers, 1992). Along similar lines, BrACs of ~0.08 g/dL resulted in additive psychomotor performance deficits while performing a target tracking task when combined with visual degradation of the target (Harrison and Fillmore, 2005). The same study revealed that participants were unable to accurately judge their level of impairment under the combined alcohol/visual degradation combination. This finding has important implications for public safety because activities for which alcohol-related impairment is risky are often undertaken in the evening (i.e., when vision is already environmentally obscured; Marczinski et al., 2008).

The ability to attend to multiple tasks at once has also been investigated at higher dose levels. Marczinski and Fillmore (2006) reported that BrACs of ~0.08 g/dL significantly reduced performance in a psychological refractory period paradigm (Moulton et al., 2005). In this study, subjects performed a go/no-go task, pressing a button if the ‘go’ stimulus was presented, and withholding a button press if the ‘no-go’ stimulus was presented. Immediately after each go/no-go trial, subjects pressed a button indicating whether an auditory tone was high- or low-pitched. Alcohol significantly increased interference between the two tasks and, on average, approximately doubled the number of errors on the auditory discrimination task.

Administration of relatively high doses of alcohol also impairs the ability to inhibit prepotent responses; that is, alcohol results in behavioral and cognitive disinhibition and may increase impulsivity (Oscar-Berman and Marinkovic, 2007). Studies by Fillmore and colleagues have shown an increase in commission errors and slower reaction times under alcohol in go/no-go tasks (Fillmore and Weafer, 2004; Marczinski and Fillmore, 2003; Marczinski et al., 2005), perhaps due to premature motor preparation (Marinkovic

et al., 2000). Continuing work by Fillmore et al. indicates a) alcohol exacerbates performance deficits on a go/no-go task that correlated to performance on complex behavioral tasks (Fillmore et al., 2008); and b) alcohol-induced inhibitory deficits are present on both the ascending and descending limbs of the BAC curve despite significantly lower subjective intoxication ratings on the descending vs. ascending limb (Weafer and Fillmore, 2012). Additional work has shown that social drinkers given a significant dose of alcohol (mean BrAC = 0.124 g/dL) were significantly slower in a Stop Signal task (in which participants withhold a frequent action, e.g., a button press, when a 'stop signal' is presented; Loeber and Duka, 2009a, 2009b) and a go/no-go task (Loeber and Duka, 2009b). These authors also showed that moderate drinkers at these BACs are also less sensitive to aversive consequences like monetary loss (Loeber and Duka, 2009a) or noxious white noise (Loeber and Duka, 2009b). Alcohol levels around ~0.07 g/dL also impaired drinkers' ability to optimize their responding when poorer outcomes were predicted in a gambling task, making them more likely to make risky decisions (George et al., 2005).

It has been suggested that alcohol's effects on impulsivity may be at least partially mediated by its effect on working memory. In a placebo-controlled study with target BACs ~0.08 g/dL, it was found that subjects with poor WM performance were particularly vulnerable to alcohol-related decrements in performance on a modification of the go/no-go task that required learning which stimuli required button presses and which did not. Other memory processes have also been found to be affected by alcohol intake. At levels of approximately 0.08 g/dL, Tulving and colleagues (Soderlund et al., 2005) found that alcohol impaired both cued and free recall regardless of whether

encoding occurred on the ascending or descending limb of the BAC curve. Recognition was affected only when encoding took place on the ascending limb. Neither process was compromised when encoding took place while participants were sober but retrieval took place while intoxicated. Weissenborn and Duka (2000) also reported alcohol-induced impairments in free recall. In their study, alcohol was administered prior to encoding, retrieval, or both encoding and retrieval in a placebo-controlled design. In contrast to Tulving and colleagues, they found that free recall was impaired by alcohol regardless of whether it was consumed before encoding or retrieval (Weissenborn and Duka, 2000).

Immediate recall in a task similar to the logical memory subsection of the WAIS-R (Wechsler, 1987) was also found to be impaired in a study of men at ~0.08 g/dL (Moulton et al., 2005; Poltavski et al., 2011). Finally, Ray and Bates (2006) found significantly fewer 'hits' and significantly more 'misses' under alcohol compared to placebo in a word recognition task at ~0.08 g/dL, perhaps due to disrupted encoding or storage of the context of the word lists.

This literature illustrates that higher doses of alcohol can have experimentally significant effects on many aspects of brain function, including memory function, multi-tasking ability, and inhibitory processes. However, these effects depend on a number of experimental and individual subject factors yet to be fully explored.

Lower-dose Effects (≤ ~0.065 g/dL)

Social drinking may result in blood alcohol levels substantially lower than those typically examined in laboratory settings. Holloway's (1994) review of the limited number of studies utilizing lower doses identified subjective intoxication and demanding controlled behavior tasks as sensitive to these dose levels, especially compared to

behaviors requiring little concentration (e.g., simple attentional tasks). Additional literature on low dose effects since that time is also scant, yet provocative, providing evidence that relatively low concentrations of alcohol can selectively disrupt critical neuropsychological processes.

As noted above, low to moderate doses of alcohol have been shown to negatively affect performance in divided attention tasks. One study requiring simultaneous performance of a visual sustained vigilance task and an auditory task requiring participants to indicate irregularities in a two-tone sequence found that BACs ~0.06 g/dL significantly impaired performance relative to a pre-dosing baseline in terms of increased reaction times and number of errors (Schulte et al., 2001). These authors also included an attentional task involving the covert shift of attention to cued targets (Posner, 1980) and found that alcohol appeared to differentially affect responding to invalidly cued stimuli appearing in the right visual field. This finding is consistent with a lateralized effect of alcohol on covert attentional performance in line with previous fMRI work (Levin et al., 1998).

Breitmeier et al. (2007) examined the effects of a BrAC of ~0.03 g/dL on performance in several neuropsychological areas in a small group of young men aged 22-29 years. Although most showed no effects, reaction time in a visual processing task was significantly delayed at this level (Cohen's d = 0.83; Cohen, 1988). Likewise, a study of performance on a difficult visuospatial discrimination task requiring the determination of which of two parallel vertical lines was shorter at BrACs ~0.055 g/dL in young adults revealed consistent impairments for at least 2 hours following beverage consumption (Friedman et al., 2011). This result was complementary to another, earlier

study showing deficits in a rapid visual information vigilance task after a 24g dose of alcohol (~2-2.5 standard drinks; Lloyd and Rogers, 1997). At BrACs ~ 0.06 g/dL, de Wit and colleagues (2000) demonstrated significant increased impulsivity on a stop-signal task relative to a placebo dose. This effect was not noted at BrACs ~ 0.03 g/dL.

Alcohol-induced deficits in recognition memory have also been reported at relatively low doses. In a multiple dose study of verbal recall and recognition with low, moderate, and high dose groups (achieving mean BrACs of 0.033, 0.059, and 0.074 g/dL, respectively), Bisby et al. (2009) found significant recognition memory impairment relative to a placebo for both the moderate and high doses. Subjects receiving either of these doses produced fewer 'remember' responses (i.e., responses indicating recollection of encoding context; no deficits in simple familiarity, or 'knowing', were detected). The lowest dose group showed impairment that did not reach statistical significance. An earlier study using a similar recognition memory paradigm but a significantly lower alcohol dose (producing BrACs ~ 0.02 g/dL) showed no deficits in remembering, knowing, or rates of false memories, but did find that subjects who received alcohol made more 'remember' responses for falsely recognized items than those who did not (Milani and Curran, 2000). This result suggests that even where behavioral deficits are not detected, low doses of alcohol can be responsible for subtle changes in memory function. Prospective memory (remembering to perform an action at a future time or in response to a future event) has also been shown to be impaired at BrACs between 0.04 and 0.06 g/dL (Paraskevaides et al., 2010; Leitz et al., 2009). This impairment suggests another potential avenue of risk from moderate alcohol consumption (i.e., forgetting to take a critical medication or to perform an important

task). Deficits in prospective memory have been noted by other groups at significantly lower BrACs in ecologically valid tasks (~ 0.02 g/dL; Montgomery et al., 2011).

Neuroimaging Studies of Acute Alcohol Administration

Undetectable behavioral and neuropsychological impairment under low alcohol doses does not imply the absence of changes in neurophysiological function that are either a) insufficient to produce an overt behavioral impairment; or b) successfully compensated for. Acute administration of higher doses of alcohol are recognized to have measurable impacts on neurophysiological indices of information processing (for review, see Polich and Criado, 2006). For instance, it has been demonstrated using positron emission tomography (PET) that two low-to-moderate doses of alcohol dose-dependently decreased glucose metabolism in the human brain, despite non-significant changes in performance on a neuropsychological test battery (Volkow et al., 2006). At the lower dose of alcohol (0.25 g/kg, resulting in mean BACs of 0.033 g/dL), significant reductions of glucose metabolism were noted predominantly in cortical regions. At the higher dose (0.5 g/kg, resulting in mean BACs of 0.071 g/dL), glucose reductions were noted in subcortical regions including the basal ganglia, thalamus, and cerebellum, as well as cortical regions. These dose-dependent changes in glucose usage in affected brain areas provide a potential explanation for why tasks requiring top-down (selective) attentional control have a lower threshold for alcohol effects than simple tasks.

Functional Magnetic Resonance Imaging (fMRI) Studies of Acute Alcohol Intake

fMRI determines areas of functional activation with high spatial accuracy by measuring blood oxygenation level dependent (BOLD) signal changes presumed to correspond to increased neuronal activity. Thus, fMRI is able to provide critical

information about the neuronal substrates underlying alcohol-induced changes in neurobehavioral function.

Using an interval estimation task adapted for fMRI, Klahr et al. (2011) identified changes in functional activation under a moderate dose of alcohol (mean BrAC = 0.05 g/dL) in the absence of observable behavior impairment. BOLD signal increases were detected in several brain areas noted to be activated in timing tasks vs. simple counting tasks. These included left cerebellum, right inferior parietal lobe, right insula, and medial frontal gyrus, perhaps reflecting compensatory brain activation in response to even moderate alcohol challenge.

In a placebo-controlled within-subjects study utilizing target BrACs of 0.05 and 0.1 g/dL, Anderson and colleagues (2011) found dose-dependent performance decrements (i.e., increased reaction time and increased false alarm rates) in a go/no-go task. These decrements corresponded with reduced BOLD activity in areas associated with error detection, including the anterior cingulate gyrus, medial frontal gyrus, orbitofrontal cortex, insula, thalamus, and cerebellum. Another study examining alcohol effects on error detection and response inhibition found that BrACs ~0.043 g/dL disrupted anterior cingulate gyrus activation, and marginally significant behavioral deficits (Marinkovic et al., 2012). Likewise, reduced bilateral prefrontal cortical activity has been found to be associated with poorer episodic memory performance at BrACs ~0.069 g/dL compared to placebo (Soderlund et al., 2005). At the same dose, impaired performance in a visual psychomotor task corresponded to increased BOLD activity in the bilateral fusiform gyri and left cerebellum and decreased activity in the left inferior and middle frontal gyrus,

cerebellum, left precuneus and cuneus, and the right superior and middle frontal gyrus (Van Horn et al., 2006).

Acute Alcohol Studies Utilizing Electroencephalography (EEG)

Recent studies using EEG have attempted to further characterize the impact of non-intoxicating alcohol doses on the time course and magnitude of brain activity during cognitive processing. Using an event-related potential (ERP) paradigm involving frequent presentation of a visual stimulus interspersed with a rare variant, Kenemans et al. (2010) found that participants produced a rareness-related negativity in visual cortical areas upon deviant stimulus presentation after consuming a placebo but not after a beverage producing a mean BrAC of 0.051 g/dL. Behavioral analysis revealed only modest effects of alcohol on reaction time, and none on accuracy measures. This suggests that processing of rare visual stimuli is disrupted even at relatively low BACs. In another study with mean BrACs of 0.029 g/dL, a significant increase in theta power associated with performance on a mental arithmetic task was noted relative to placebo, but no differences in task performance were noted. This disruption suggests participants may have manifested compensatory brain activation to maintain performance despite the very low BAC levels achieved (Boha et al., 2009).

Using a vigilance task where stimuli were ‘flanked’ by visually compatible or incompatible stimuli and two dose levels plus a placebo control, Barthalow et al. (2003) showed that BrACs of 0.035 and 0.07 g/dL resulted in significant reductions in P3 amplitude (presumed to index the magnitude of attentional mechanisms involved in updating memory representations of the stimulus and its context; Polich and Criado, 2006) regardless of compatibility of ‘flankers’ with target stimuli. The 0.035 and 0.07 g/dL dose levels did not differ from one another on these measures, and no reliable

main effects of alcohol dose were detected for either reaction time or accuracy. Moderate alcohol mediated P3 amplitude reductions and latency increases may be more pronounced in individuals with inactive ALDH2 (Shin et al., 2006), suggesting genotype may also influence the degree of neurophysiological disruption induced by low alcohol doses (~0.04 g/dL).

In studies where BAC levels are elevated to ≥ 0.08 g/dL, concurrence of ERP and behavioral disturbances become more frequent, providing the opportunity to better study the relationship between ERPs and performance. For instance, Euser and colleagues (Euser et al., 2011) found that at a mean BrAC of 0.08 g/dL, subjects took longer to optimize their behavior on a test of risky decision making. At the same time, P3 amplitudes were diminished in the alcohol vs. placebo conditions. P3 amplitude was correlated with risk taking behavior, but only in the alcohol group. Thus, the authors concluded that diminished P3 amplitudes in the alcohol group may reflect poorer integration of negative feedback across trials.

Sources of Heterogeneity

Alcohol's effects are recognized to be extremely heterogeneous at both lower and higher blood concentrations (e.g., Steele and Josephs, 1990). Although a comprehensive review of the large and still growing literature on this topic is beyond the scope of this work, it is critical to recognize that alcohol's effects can vary widely based on many factors. This brief review of potential sources of heterogeneity in response to alcohol is meant to illustrate the difficulty in discussing risk associated with consuming quantities of alcohol widely assumed to be "safe".

Level of Response to Alcohol

One of the longest-running lines of investigation in this area is the characterization of individuals who are low- and high-responders to alcohol related effects on affect and behavior. Work for several decades by Schuckit and colleagues has described the importance of family history of alcoholism as well as level of response (LR) to alcohol as an indicator of acute behavioral risk associated with drinking as well as eventually acquiring an alcohol use disorder (Schuckit et al., 2012). Though a full reivew is beyond the scope of this work, several especially salient points can be drawn from it.

First, people with a low subjective response to alcohol (which includes 40% of individuals with a direct relative with alcoholism and 10% of those who do not; Schuckit et al., 2005; Schuckit, 1994) show diminished physiologic responses to acute alcohol intake. These include a lesser hypothalamic-pituitary-adrenal axis mediated stress response (Schuckit et al., 1988; Schuckit, 1987) mirroring that of heavy social drinkers (King et al., 2006). Second, children of alcoholics (non-alcoholics themselves; both male and female) report lower levels of subjective intoxication in acute administration studies relative to demographically and alcohol-use matched children of nonalcoholics (Eng et al., 2005; Newlin and Thomson, 1990). Third, children of alcoholics (and presumably those with a low response to alcohol generally) show less severe deficits in logical memory (Erblich and Earleywine, 1999) and less alcohol-induced attenuation of functional activation during a stop-signal task (Schuckit et al., 2012) than children of non-alcoholics at blood alcohol levels around 0.08 g/dL.

It is still unclear whether consuming quantities of alcohol typical in social settings will cause less impairment in low responders on complex tasks, especially under demanding conditions. Given that low responders (including many children of

alcoholics) are less likely to perceive themselves as intoxicated due to reduced internal and external impairment cues, they may be more likely to perform activities after drinking which places themselves and others at risk for injury.

Attention Deficit/Hyperactivity Disorder (ADHD)

Risk for consequences associated with moderate alcohol use may be elevated for individuals with ADHD. It has been speculated that the attentional dysfunction characterizing ADHD may have consequences similar to those of acute moderate alcohol intake (Fillmore, 2007). Recent research indicates this may indeed be the case. In a recent simulated driving study designed to determine whether the decrements in driving performance associated with ADHD (tested off-medication) and moderate alcohol consumption were additive, two important conclusions arose. First, sober drivers with ADHD were found to perform indistinguishably from non-ADHD drivers at a BrAC of ~ 0.08 g/dL. Second, persons with ADHD given alcohol performed significantly more poorly than those given a placebo and perceived themselves as more able to drive (Weafer et al., 2008). A follow-up study at the same dose level showed that individuals with ADHD may be more sensitive to alcohol-induced impairment of inhibitory control using a go/no-go task (Weafer et al., 2009). Individuals with ADHD may also be more prone to developing alcohol use disorders due to alcohol-induced attentional modulation not seen in controls (Roberts et al., 2012).

Environmental and Contextual Factors

The above examples illustrate the extent to which individual factors can change the degree of neurobehavioral compromise assumed by consuming a moderate dose of alcohol. However, other environmental and contextual variables can also exert significant influence. Provision of strong incentives for good performance can partially

counteract alcohol-induced behavioral deficits (Grattan-Miscio and Vogel-Sprott, 2005). In addition, an individual's expectation of alcohol-related impairment or lack thereof can have a substantial impact on observable behavioral decrements due to acute moderate alcohol intake (e.g., Vogel-Sprott, 1992; Fillmore and Vogel-Sprott, 1995; Fillmore and Vogel-Sprott, 1998; Fillmore and Vogel-Sprott, 1996; Leigh and Stacy, 2004).

Age

Although age-related attentional (Gazzaley, 2011) and behavioral deficits (e.g., Collins and Mertens, 1988) are well documented, very little research has systematically examined the interaction between acute alcohol and aging effects. A limited older literature reports mixed findings on differential effects of alcohol on middle-aged and older adults, showing increased body sway and postural disturbance under moderate alcohol doses in older adults (Jones and Neri, 1994; Vogel-Sprott and Barrett, 1984) but no differences on a simulated driving task (Quillian et al., 1999).

Research on the interaction between alcohol and aging effects conducted in our laboratory suggests intriguing differences in behavioral and neurophysiological effects associated with moderate alcohol between younger and older adults. These effects appear to be sensitive to task modality and whether performance measures are taken on the ascending or descending limb. In general, older adults show deficits in both neurobehavioral performance and in neurophysiological indices of attentional processing at alcohol dose levels where younger adults do not (~0.04 g/dL; Lewis et al., in revision; Gilbertson et al., 2010; Gilbertson et al., 2009). Importantly, this work has utilized modified Widmark equations (Watson et al., 1981) in order to account for sex and age differences in total body water, lean muscle mass, and other factors influencing the distribution and pharmacokinetics of alcohol (e.g., Vogel-Sprott and Barrett, 1984).

Discussion and Conclusions

Acute moderate alcohol consumption may result in significant behavioral and neurophysiological compromise, accounting for reports of elevated car accident rates at levels well below the legal limit (e.g., 3-4x increased risk at BACs ~ 0.05 g/dL; National Highway Traffic Safety Administration, 2000). Despite the effort of governmental entities like the USDA and NIAAA to release guidelines for safer drinking, it is clear from the extant literature that even the very low BACs resulting from the practice of a moderate drinking lifestyle are not without risk. Even if an individual is aware of and adheres to these guidelines (see above discussion of Green et al., 2007), the risk assumed by the consumption of even low levels of alcohol can be modulated by a number of factors including sex, behavioral disorders, genetic factors, or context. Critically, recent studies indicate aged individuals may assume disproportionate risk from a moderate drinking session (Gilbertson et al., 2010; Gilbertson et al., 2009). It is suggested that the purported benefits of a moderate drinking lifestyle, particularly for cardiovascular health, be weighed against risk assumed due to acute neurobehavioral effects.

CHAPTER 2
COGNITIVE AGING

Introduction

Cognitive decline is frequently reported in aging studies (Verhaeghen and Cerella, 2002). Results from the Seattle Longitudinal Study (SLS), conducted since 1956, indicate most aspects of cognition either plateau or show slight improvement until the mid-fifties in the absence of age-related neuropathology (e.g., Alzheimer's disease). At this point, performance begins to decline steeply such that subclinical deficits relative to young adulthood are typically apparent by the mid-seventies. However, verbal ability continues to improve until the late sixties and only then begins a slow decline (Schaie and Zanjani, 2006). The rate and degree of decline of mental abilities is highly individual; although almost every participant in the SLS showed declines in at least one ability by age 60, none had declines in all abilities by age 88 (Schaie et al., 1989, see also Gerstorf et al., 2011).

Several theories have been developed to explain these sub-clinical declines. Although conceptually distinct, they are not mutually exclusive. The ‘frontal aging’ and ‘inhibitory control’ hypotheses propose that age-related cognitive deficits can be accounted for by inefficiency in processes mediated by the frontal lobe, especially inhibition (West, 1996; Raz et al., 1997; Greenwood, 2000; Drag and Bieliauskas, 2010). Reuter-Lorenz and colleagues (1999) hypothesized that cognitive processes require attentional resources, conceptualized as neural units with processing capacity. In this view, diminishing efficiency of neural units in older adults may require the recruitment of more units than younger adults to accomplish a given cognitive task.

Progressive declines in information processing speed are also proposed to account for age-related cognitive impairment because of their negative effect on cognitive performance when demanding tasks must be accomplished quickly (Lockenhoff, 2011; Salthouse, 2010; Hasher and Zacks, 1988). Although not the focus of this work, multiple neurotransmitter systems are affected by age (e.g., norepinephrine and dopamine). Attempts to consider the effects of aging-related neurochemical changes on cognition have been made, however further research in this area is needed (Ding et al., 2010; Backman et al., 2010).

Given the breadth of the literature, a comprehensive review of cognitive aging is beyond the scope of the current work. Instead, this review focuses on three aspects of neurocognitive function, and their structural and neurophysiological correlates: a) episodic memory (declarative memory pertaining to past personal experiences); b) working memory; and c) top-down or voluntary control of attention. There is a tendency to locate processes within distinct areas of the cerebrum; however, cognitive processes necessarily involve the intersecting functions of specific brain areas. That said, control of attention is thought to rely upon structures within the frontal lobe, especially the prefrontal cortex (PFC). Likewise, episodic memory functions are often attributed to the medial temporal lobe (MTL).

This review will focus on ‘healthy’ aging processes. It will not address perturbation of cognitive trajectories in aging by neuropathologies like Alzheimer’s disease, stroke, or Parkinson’s disease. For a comprehensive review regarding distinguishing normal from pathological cognitive aging, see Salmon and Bondi (2009). Learning difficulties are

also characteristic of advancing age (Salthouse, 2011), but are not the focus of this review.

Neuroimaging Studies in Cognitive Aging

Gray Matter Imaging

Many studies utilizing structural magnetic resonance imaging (MRI) have revealed age-related general brain atrophy as well as regionally specific degradative effects. The most common marker of such atrophy is expansion of the entire ventricular system, which appears to occur at the expense of cortical gray matter with little volume change in white matter (for review, see Sullivan et al., 2010b). This expansion has been reported to occur at yearly rates of 0.43-1.2% in young adults and increase to 4.25-8.2% after age 70 (Drag and Bieliauskas, 2010; Sullivan et al., 2010a; Sullivan et al., 2010b; Raz et al., 1997).

A recent cross-sectional study of 69 individuals between 22 and 84 years of age found that age accounted for 76% of the variance in total brain volume and 75% of the variance in gray matter volume (Michielse et al., 2010). Gray matter shrinkage is more likely to reflect a decline in volume of the soma as opposed to neuronal loss (Burke and Barnes, 2006). However, neuronal loss does occur in some brain areas, especially the prefrontal cortex (PFC; Burke and Barnes, 2006; Raz et al., 1997).

Gray matter volume has been correlated with cognitive performance in healthy older individuals, reflecting the practical importance of these measures. For example, hippocampal atrophy has been associated with episodic memory deficits (Head et al., 2008). Prefrontal cortical volume, on the other hand, has been positively correlated with performance on tasks involving response inhibition and interference, spatial working

memory performance (Weinstein et al., 2011), and a task requiring the identification of objects drawn with varying degrees of visual degradation (Kennedy and Raz, 2009).

White Matter Imaging

In contrast to gray matter, white matter volume increases with age until the 60s, when age-related declines begin (Michielse et al., 2010). Furthermore, age-related changes vary across the brain. For example, the frontal lobes generally show greater loss than the temporal or occipital lobes (Allen et al., 2005). The increased susceptibility of the frontal lobes to age-related decline is consistent with theories of cognitive aging that emphasize declines in efficiency of frontal lobe function and inhibitory function (Drag and Bieliauskas, 2010).

The structural integrity of white matter structures is also affected by age. By measuring the degree to which the random motion of water molecules is constrained in white matter using diffusion tensor imaging (DTI), fractional anisotropy (FA) can be determined. An FA value of 0 implies unconstrained random motion, whereas values near 1 indicate near-perfect constraint along a single axis. FA can be measured in both myelinated and non-myelinated axons. Thus, low FA in a given area of white matter suggests a loss of integrity (Rosenbloom et al., 2003).

DTI also measures mean diffusivity (MD), an indicator of the magnitude of water diffusion. FA declines may correspond with increased MD if lost myelin is replaced by interstitial fluid. However, FA declines will correspond with decreased MD if tissue loss results in glial scarring (Pfefferbaum and Sullivan, 2003). Many studies using these techniques have demonstrated general age-related declines in white matter integrity with an inverse relationship between FA and MD (reviewed in Sullivan et al., 2010a).

Although FA declines are linear after age 20, rates of mean diffusivity accelerate with increasing age (Sullivan and Pfefferbaum, 2007).

Progressive age-related FA decreases/MD increases in the cerebral cortex appear to be most concentrated in frontal regions [especially the prefrontal cortex (PFC)], followed by the medial temporal lobe (MTL; Sullivan et al., 2010b; Michielse et al., 2010; Raz et al., 1997). Consistent with these findings, studies of specific fiber tracts throughout the cortex indicate that fiber bundles in anterior cortical areas are differentially vulnerable to declines in integrity (Michielse et al., 2010; Sullivan and Pfefferbaum, 2006; Salat et al., 2005; but see Westlye et al., 2010). Preferential loss of white matter integrity in these areas is correlated with well-documented age-related deficits in attentional processing and various aspects of memory function including working memory, episodic memory, and source memory (Sullivan et al., 2010a; Zahr et al., 2009; Persson et al., 2006).

Patterns of Functional Activation in Older Adults

In addition to age-related structural changes in gray and white matter, the pattern and magnitude of brain activity during various cognitive tasks in aging persons have been extensively explored in the past ten years. In that time, two major changes in *patterns of functional activation* have been observed in cross-sectional studies of younger and older adults.

Hemispheric Asymmetry Reduction in Older Adults (HAROLD)

HAROLD describes the persistent observation that PFC activation is more symmetrical in older than younger adults (Cabeza, 2002). This phenomenon was originally observed in the context of episodic memory retrieval, during which older adults showed bilateral PFC activation vs. right-lateralized activation in younger adults

(Nyberg et al., 1998). Several teams have reported that older adults show bilateral PFC activation during both verbal (Madden et al., 1999; Cabeza et al., 1997; Nyberg et al., 1997) and non-verbal (Grady et al., 2002) episodic memory recall and recognition tasks. Asymmetry reduction in PFC activity in older adults has also been found using tasks tapping working memory (Reuter-Lorenz et al., 2000), visual perception (Grady et al., 2005), and inhibitory control (Nielson et al., 2002).

HAROLD may reflect the recruitment of additional neural units to accomplish a given task. This recruitment appears to at least partially compensate for age-related deficits in processing speed, with older adults showing bilateral PFC activation having faster reaction times in working memory tasks than those who do not (Rypma and D'Esposito, 2000; Reuter-Lorenz et al., 2000). In addition, PFC activity is strongly linked to performance in tasks requiring inhibition of response to irrelevant stimuli and has an important role in the prevention of irrelevant stimuli from occupying limited space in working memory (e.g., Cabeza, 2002; D'Esposito and Postle, 1999). Thus, bilateral recruitment of PFC may help older adults maintain inhibitory capabilities.

Posterior-to-Anterior Shift in Aging (PASA)

Whereas HAROLD describes a loss of asymmetry in PFC activation, PASA describes an age-related reduction in occipitotemporal activity and corresponding increase in frontal activity (Grady et al., 1994). This pattern has been confirmed in many domains including visual perception, working memory, episodic memory encoding and retrieval, attention, and visuospatial processing (e.g., Cabeza et al., 2004; for review, see Davis et al., 2008). The degree to which a PASA-like activation pattern relates to performance in older adults has only recently been investigated.

In a study by Davis et al. (2008), PFC activation was negatively correlated with occipital activity (r=-0.61) in older adults, and accounted for 40% of the variance in performance on tasks of episodic memory retrieval and visual perception. These authors also found that PASA is not due to a relative increase in the difficulty of a given task for older adults; the PASA pattern was apparent even after matching accuracy and response confidence between younger and older participants.

The fMRI literature is supported by studies measuring brain electrophysiology. Electroencephalography (EEG), in concert with event-related potential (ERP) paradigms, has been used to characterize the topography of brain activation with high temporal resolution. For instance, although practice on a rare target detection task reduces activity in frontal areas in young adults (suggesting a diminishing need for frontal activity during stimulus processing), older adults continue to show activation (Friedman, 2003; Fabiani and Friedman, 1995). In addition, older but not younger participants show significant inter-individual variability in whether the P3 component of the ERP is maximal in frontal or parietal areas. Older individuals who had higher frontal than parietal P3s during rare target detection had significantly more perseverations on a set-shifting task (Fabiani et al., 1998). While it may appear discrepant with the PASA model that a maximal frontal P3 was associated with poorer performance than a maximal parietal P3, it suggests that those older adults who recruit PFC on simple tasks like rare target detection may have insufficient resources to enable optimal performance on more difficult tasks. Thus, this result is consistent with an interpretation of PASA as compensatory in older adults, but also indicates this compensatory activation is not always completely successful (Friedman, 2003).

HAROLD and PASA: Summary and Caveats

Taken together, investigations of HAROLD and PASA constitute convincing evidence of compensatory recruitment of PFC during a variety of tasks in older adults. Because the majority of these studies are cross-sectional, the trajectory of these patterns in aging is still unknown (Raz and Lindenberger, 2011).

Patterns of compensatory activation imply fewer resources will be available during divided attention or multitasking situations. Thus, older adults may be particularly vulnerable to performance decrements (Anderson et al., 1998) in conditions where cognitive resources are additionally limited (e.g., acute alcohol consumption; Gilbertson et al., 2010; Gilbertson et al., 2009). Finally, although the study of the HAROLD model has thus far been limited to loss of asymmetry in PFC activation there is a body of evidence showing that other brain areas including the parietal and temporal regions may also show a loss of lateralized activity in aging (see Cabeza, 2002 for review).

Attentional Processing and Working Memory in Aging

Age-related deficits are evident on many tasks depending on intact frontal lobe function, especially those requiring the processing of multiple information streams or top-down attentional modulation (i.e., selective attention). In contrast, attentional processes driven by stimulus characteristics such as color, shape, or luminance (bottom-up attention) are generally unaffected by age (Glisky, 2007).

Critically, top-down attentional deficits in older adults tend to be characterized by a diminished capacity to ignore irrelevant information (e.g., Andres et al., 2006). This inability may be the result of less discriminant neural networks in older adults. That is, older adults' attentional networks may be more likely to activate in response to stimuli bearing little resemblance to a given target (Drag and Bieliauskas, 2010). This network

characteristic may underlie older adults' deficits in tasks requiring selective attention, like auditory word repetition with distractors (Barr and Giambra, 1990), interference and inhibition tasks (Brink and McDowd, 1999), or directed remembering tasks (Gazzaley et al., 2008).

Effects of Aging on Top-down Control of Attention

Over the last decade, Gazzaley, d'Esposito, and colleagues (Gazzaley, 2011; Gazzaley et al., 2008; Gazzaley et al., 2007) have directly examined the effects of age on top-down attentional control. Their work has focused especially on the impact of top-down attentional control on working memory, which is impaired in normal aging (Craik and Salthouse, 2000). Their studies build on previous work demonstrating impaired suppression of attention to irrelevant stimuli (e.g., Chao and Knight, 1997).

In each trial of the remember/ignore task, subjects are presented with two cue stimuli of one class (e.g., faces) and two stimuli of another class (e.g., landscapes) in random order. After the last cue stimulus, a fixation cross appears. Finally, a probe stimulus is presented; subjects must determine whether this probe was among the cue stimuli presented. Three counterbalanced trials blocks are performed. In one block, subjects are instructed to remember one class of stimuli and ignore the other; in another, these instructions are reversed. A third block requires subjects to passively view both types of stimuli and press a button indicating the direction of an arrow presented in place of the cue stimulus (see Figure 3.1). This task structure allows for examination of two aspects of top-down attention using multiple modalities: *enhancement* of response to a given stimulus type during the 'remember' condition; and *suppression* of response to a given stimulus type during the 'ignore' condition (Gazzaley, 2011). Assessments of enhancement and suppression may take the form of

BOLD activation patterns in fMRI, ERP component characteristics (latency and amplitude), and behavioral outcomes (reaction time and accuracy).

One study examining early and middle components of the ERP with this task found that whereas younger adults showed significant enhancement to relevant stimuli and significant suppression to irrelevant stimuli, older adults showed significant enhancement only (Gazzaley et al., 2008). These findings complemented an earlier report of intact enhancement but impaired suppression reflected by BOLD signal changes during fMRI (Gazzaley et al., 2005a).

Older adults have shown lower accuracy and slower reaction times than younger adults in the remember/ignore task. Importantly, significant positive correlations between suppression of attention to irrelevant stimuli and working memory performance have been reported (Gazzaley et al., 2005b). Likewise, a median split of older adults by their remember/ignore task accuracy revealed that poorly performing but not higher performing older adults showed impaired suppression (Gazzaley, 2011).
Bollinger et al. (2011) modified the remember/ignore task by informing subjects of the order in which face and scene stimuli would be presented. Thus, subjects were not required to categorize stimuli as they were presented. Despite this manipulation, older adults still showed suppression deficits, suggesting that these deficits are not accounted for by delayed stimulus categorization in older adults. Thus, suppression deficits cannot be attributed to slower processing speed. Rather, the PFC's well described role in inhibitory processing and top-down attentional control suggests that PFC dysfunction may underlie age-related deficit. Indeed, direct studies of the contribution of PFC to top-

down function suggest this area is necessary for efficient attentional modulation (Zanto et al., 2011).

As a whole, this body of work provides evidence of important attentional deficits in older adults. Top-down control of attention, and particularly suppression of attention to irrelevant stimuli, is critical because “optimal [working memory] performance is dependent on effectively filtering irrelevant information at early processing stages to prevent overloading a limited working memory capacity” (Gazzaley, 2011).

Episodic Memory Retrieval and Aging

Many studies examining age-related deficits in episodic memory performance have used verbal remember/know tasks. During remember/know tasks participants are presented with a word list during a study period. This period is followed by a testing session during which both studied and new words are presented. For each word, participants indicated either a) the word was new; b) they recollected studying the word (“remembering”); or c) they thought they had seen the word before but did not recollect studying it ("knowing"; Tulving, 1985). A recent meta-analysis found that 85% of 27 cross-sectional studies using this procedure demonstrated retrieval deficits in older adults (≥60 years of age) compared to younger adults (≤45 years of age; McCabe et al., 2009). Across all studies, older adults recalled 39% of words on previously presented word lists compared to younger participants’ 54%. Conceptually more interesting was that older adults committed significantly more false alarms (i.e., false remembrances) than young adults. In fact, rates of false alarms were more than doubled in the older groups (6.2% vs. 2.5%).

In contrast, familiarity-based memory (i.e., “knowing”) appears to be relatively spared in older adults. Using the remember/know task paradigm, McCabe and

colleagues (2009) found essentially no effects of age on recognition and only small effects of age on recognition false alarms. This discrepancy may be due to the significant effort needed to ignore irrelevant information retrieved from memory during recall (Drag and Bieliauskas, 2010). In contrast, recognition is significantly less demanding because only the *availability* of information stored in memory is required.

Relationship Between Age-related Episodic Memory and Inhibitory Deficits

Hasher, Zacks, and colleagues (Radvansky et al., 1996; Zacks et al., 1996; Gerard et al., 1991; Hasher et al., 1991; Hasher and Zacks, 1988) proposed that memory retrieval deficits in older adults may be due to increased interference from semantically related but contextually irrelevant facts and information. This model is supported by a recent study demonstrating a critical contribution of the frontal lobe in preventing false memories (McCabe et al., 2009). McCabe and colleagues constructed indices of frontal and MTL function using separate neuropsychological testing batteries for each region. Subsequent path analysis revealed that although the MTL index was positively correlated with true remembering, the frontal lobe index was inversely correlated with false alarms.

The frontal lobe's role in preventing false alarms, and error checking in general, may be subserved by its massive network of connections with virtually all cortical and subcortical structures (Gazzaley, 2011; Barbas, 2000; Friedman and Goldman-Rakic, 1994). Studies of both humans and animals models suggest that age-related increases in the rate of false memories may be the result of regionally specific age-associated neuronal loss, changes in dendritic arborization, declines in white matter integrity, and aberrations in neuronal microstructures in the prefrontal cortex (reviewed by Burke and Barnes, 2006).

Additional Influences on Cognitive Aging

Although there is general consensus about changes in cognition over the lifespan, inter-individual variability is prevalent (Salthouse, 2011; Wilson et al., 2002). Some factors that can influence the trajectory of cognitive aging are briefly described below.

Education and Cognitive Reserve

Educational level correlates positively with performance on tasks in many domains (Drag and Bieliauskas, 2010). Educational attainment may reflect 'cognitive reserve': an ability, whether passive or active, to cope with age-related changes in brain structure and function. In brief, the greater an individual's cognitive reserve, the deeper their pool of functional neural units (i.e., cognitive "scaffolds"; Park and Reuter-Lorenz, 2009) available to handle a given task. Especially demanding tasks appear to benefit from a large cognitive reserve to a greater extent than easier tasks (Drag and Bieliauskas, 2010). Because indices of cognitive reserve do not appear to alter the slope of age-related cognitive changes, individuals with a deep cognitive reserve may simply take longer to show significant deficits (Tucker-Drob et al., 2009).

Exercise and Diet

There is growing interest in the beneficial effects of physical fitness and exercise on cognitive performance and risk reduction for dementia and cognitive impairment in older adults (e.g., Hamer and Chida, 2009). A recent meta-analysis of 29 trials examining the effects of sustained aerobic exercise on cognition in healthy older adults ranging in age from ~55 to 90+ years of age found that individuals assigned to exercise groups showed moderate improvements in attentional function, processing speed, executive function, and episodic memory not seen in sedentary controls (see also Smith et al., 2010; Colcombe and Kramer, 2003). Likewise, aerobic exercise regimens

sustained over a 12-month period have been shown to improve functional brain connectivity and increase cortical and hippocampal volumes in healthy seniors (Ahlskog et al., 2011).

Longitudinal studies of health and cognitive outcomes in older adults grouped by activity level support these findings, showing an active lifestyle is associated with significant reductions in risk of developing mild cognitive impairment (odds ratio [OR= 0.58), Alzheimer's disease (OR=0.50), or dementia of any type (OR=0.63, Laurin et al., 2001). Potential beneficial effects of resistance exercise (i.e., weight training) on cognitive function have been less frequently studied. However, the current literature suggests significant benefits at least equal to those for aerobic exercise both in healthy older adults (Voss et al., 2011; Smith et al., 2010) and in a cohort of 70-80 year old women with mild cognitive impairment (Nagamatsu et al., 2012). Thus, regular physical exercise may represent a viable intervention for preserving cognitive function in older adults.

Though the mechanism through which exercise exerts this effect is unclear, it may involve modulation of dopaminergic and cholinergic neurotransmitter systems, induction of brain derived neurotrophic factor (BDNF) expression, or stimulation of hippocampal neurogenesis (Colcombe and Kramer, 2003). A controlled diet may also promote healthy cognitive aging. A limited literature on caloric restriction building on work with animal models has shown some beneficial effects on memory function in both normal and overweight older individuals (Witte et al., 2009). The effects may be mediated by changes in BDNF expression similar to those seen in aerobic exercise (Depp et al., 2010).

Intentional Practice

In the multisite Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) trial, 2,832 participants were randomly assigned to one of three cognitive training interventions or a control group receiving no training. Participants ranged between 65 and 94 years of age (mean age = 74 years), had ~13.5 years of education, and had average Mini-Mental State Examination scores of 27.3. Regardless of assignment to memory, reasoning, or processing speed training, older adults showed significant improvement in the cognitive area in which they were trained at two-year follow-up. Furthermore, all participants receiving training demonstrated improved ability to perform activities of daily living at five-year followup (Depp et al., 2010; Willis et al., 2006; Jobe et al., 2001). Long-term follow-up of participants in the Seattle Longitudinal Study discussed previously revealed similar positive outcomes. Older adults receiving training experienced significantly slower decline than untrained counterparts in several domains, including inductive reasoning and spatial orientation, at seven year follow-up (Schaie and Zanjani, 2006).

Other cognitively challenging activities may also be beneficial. Studies examining the cognitive effects of community education theater classes have found benefits on cognition in both middle-class older adults and lower-income, retirement-home dwelling individuals (Noice and Noice, 2009; Noice et al., 2004). However, the persistence of these effects has yet to be ascertained. There are also a number of commercial “brain training” products available for home video game systems (e.g., Brain Age©, Nintendo Co., Ltd., Kyoto, Japan) for which limited evidence of efficacy is available (Nouchi et al., 2012).

Other Factors

Lifestyle circumstances and certain individual characteristics also influence cognitive function in older age. Diverse factors including cohabitation with a well-educated and intelligent partner, continued employment in a complicated and engaging workplace, an active and stimulating retirement, and maintained social engagement all predicted healthy cognitive aging (Schaie and Zanjani, 2006). In contrast, high trait anxiety levels, a rigid cognitive style, or a history of a stressful home environment during childhood were shown to be associated with poorer cognitive outcomes in later life (Schaie and Zanjani, 2006).

Summary

By the year 2015, it is estimated that over 46 million Americans will be 65 years of age or older. This group will grow to include 72 million Americans by 2030 (US Census Bureau, 2008). Thus, it is critical to characterize the functional and structural correlates of aging as fully as possible. Though there are areas where our understanding of cognitive aging is limited (e.g., potential cross-cultural differences and potential sex effects; Schaie and Zanjani, 2006), age-related decline is consistently reported.

Affected neurocognitive domains include episodic and working memory, top-down attentional control, and executive functions. These deficits are accompanied by diminishing efficiency and quantity of neural and attentional resources in older adults. Recruitment of the PFC and potentially other brain areas may compensate for declining efficiency and resources.

Although aging is associated with statistically significant cognitive deficits, these deficits have only a limited impact on real world function under normal circumstances (Salthouse, 2012, cf. Burton et al., 2006). Furthermore, it is not known if common

challenges such as acute alcohol intake may exacerbate these deficits to the point where they become dangerous or problematic, even for relatively young older adults ~60 years of age.

CHAPTER 3
STUDY AIMS AND METHODS

Study Aims

On the basis of the work covered in Chapters 1 and 2, we conducted a study of the neurophysiological and behavioral correlates of moderate acute alcohol in younger (25-35 years of age) and older (55-70 years of age) adults. The age range for younger adults was chosen to exclude those individuals in an environment where heavy drinking is common (i.e., college), and to provide a sufficient age gap for meaningful comparisons with the older group. The age range for older adults began at 55, corresponding with a typical trajectory of age-related cognitive decline, and was capped at 70 years of age to ensure feasibility of recruitment. It is poorly understood how neurophysiological responses (as assessed by event-related potential [ERP] paradigms) to moderate drinking events might change as humans age, and how these responses might relate to behavior.

A recent study from our laboratory suggested older adults were more sensitive to negative effects of moderate alcohol consumption on set-shifting ability. In addition, older adults but not younger adults manifested dissociation between performance and perceived vs. measurable impairment (Gilbertson et al., 2010; Gilbertson et al., 2009). The objective of this dissertation was to extend this work, expanding our understanding of the effects of moderate alcohol on attentional function and behavior in older adults using neurophysiological assessments and two moderate alcohol doses (0.04 g/dL and 0.065 g/dL).

To this end, we examined several components of the ERP previously shown to be sensitive to age effects on top-down attentional function (Gazzaley et al., 2008). The P1 is a positive visually evoked potential occurring approximately 100 ms after stimulus presentation. Generated in dorsal occipital areas, it is modulated by selective attention such that greater attentional allocation to a stimulus results in higher amplitude (Luck et al., 1994; Mangun and Hillyard, 1991). The N1 is a negative visually evoked potential occurring approximately 150 ms after stimulus presentation. Greater attentional focus to a stimulus results in faster N1 latency (Luck et al., 2000). Finally, the P3 is a positive visually evoked potential occurring 300-500 ms after stimulus presentation thought to reflect processes related to working memory updating. Its sources include the temporal-parietal junction and the anterior cingulate cortex (Polich and Criado, 2006). Greater attention to a stimulus results in higher P3 amplitude (Polich and Kok, 1995).

Thus, the specific aims of the project were:

Aim 1

Compare brain electrophysiology and behavior in younger and older adults under placebo and two moderate alcohol doses using a task manipulating stimulus relevance. We predicted Hypothesis 1. Older as compared to younger adults would demonstrate less suppression. Hypothesis 2. Alcohol would decrease suppression regardless of age. Hypothesis 3. Alcohol would affect suppression to a greater extent in older adults. Hypothesis 4. Enhancement would be less affected by alcohol, age, and/or their interaction than suppression. Hypothesis 5. Younger adults would have shorter latency and higher amplitude ERP components of interest compared to older adults. Hypothesis 6. Consistent with existing literature, alcohol administration would decrease amplitude and increase latency of ERP components relative to placebo

(Polich and Criado, 2006). Hypothesis 7. Alcohol would decrease ERP amplitude and increase latency to a greater extent in older adults. Hypothesis 8. Older age and alcohol would have independent negative effects on accuracy and reaction time. Hypothesis 9. Older adults would be more sensitive to alcohol-induced behavioral decrements. Empirical question E1. We asked whether the 0.04 and 0.065 g/dL doses would differ in their effects on neurophysiological indices of top-down control of attention and behavior. Empirical question E2. We asked whether neurophysiological indices of enhancement and suppression would correlate with behavioral outcomes (i.e., accuracy and reaction time), and whether this relationship would differ between age and alcohol dose groups.

Aim 2

Examine the correlation of subjective ratings of intoxication with neurophysiological indices of top-down attentional control and behavioral outcomes. Hypothesis 10. We predicted that older adults would demonstrate dissociation between subjective intoxication, alcohol dose, and neurophysiological and behavioral impairment.

Methods

Study Design

The study used a 2 (Age: Older, 55-70; Younger, 25-35) X 3 (Alcohol Dose: placebo; low [0.04 g/dL]; moderate [0.065 g/dL]) X 2 (Sex: Male; Female) double blind, placebo-controlled factorial design. Younger individuals between 25-35 years of age and older individuals between 55-70 years of age were recruited using practices consistent with previous work from our laboratory (Lewis et al., in revision; Sklar et al., 2012; Gilbertson et al., 2009). All procedures were approved by the University of Florida Health Science Center Institutional Review Board (protocol #403-2010).

Screening

Interested individuals contacted the laboratory by telephone after learning about the study via flyers, word of mouth, and advertisements on local radio stations. They were informed of basic inclusionary and exclusionary criteria by trained research assistants. These criteria included a) age between 25 and 35 or 55 and 70; b) being a non-smoker; c) being in good physical health; d) having at least a high school diploma but not more than a Master's degree; e) having no significant history of head injury or unconsciousness; f) history of consuming alcohol in the past but not of treatment for alcohol or other substance abuse. If, after hearing the criteria, an individual remained interested, they were scheduled for a screening session in the laboratory. Written informed consent was obtained prior to any screening measure.

During screening, a variety of questionnaires were administered including age-appropriate measures of depressive symptomatology (Younger: Beck Depression Inventory, 2nd Ed. [BDI-II]; Beck et al., 1996, Older: Geriatric Depression Scale [GDS]; Yesavage et al., 1982). To avoid inclusion of older adults with mild cognitive impairment, this group was also screened using the Mini-Mental State Examination (Folstein et al., 1975) and Hopkins Verbal Learning Test (Benedict et al., 1998) with exclusionary cutoffs derived from previous literature (Wierenga et al., 2008). An inventory of screening measures, along with their exclusionary cutoffs, are noted in Table 3-1. Individuals completing initial screening were paid $15 for their time.

Persons continuing to qualify following screening provided a self-report of their medical history and height and weight was obtained. Probabilistic psychiatric diagnoses were assessed with the computerized Diagnostic Interview Schedule IV (cDIS-IV; American Psychiatric Association Task Force on DSM-IV., 2000, Robins et al., 1995).

Exclusionary psychiatric criteria included 1) current or lifetime diagnosis of alcohol dependence; 2) lifetime diagnosis of any psychotic disorder; and 3) current diagnosis of major depressive disorder (or lifetime diagnosis if electroconvulsive therapy was used for treatment). Current nicotine dependence or self-report of current smoking was also exclusionary. In addition, a history of serious medical illness including uncontrolled Type II diabetes, epilepsy, HIV/AIDS, past incidence of powerful electric shock, prolonged periods of unconsciousness or skull fracture was exclusionary. Women who were pregnant or breastfeeding were also disqualified.

In a previous study from our laboratory, 40% of participants reported over-the-counter (OTC) and prescription medicine use. To enhance ecological validity while controlling potential confounds, use of prescription medications was allowed provided the volunteer had been using these medications at current doses for at least three months and the drug(s) did not contraindicate alcohol use (Gilbertson et al., 2009). All individuals who completed the interview process received $37.50. Participants who continued to qualify were invited to participate in the laboratory session. Those individuals agreeing were provided with a set of instructions for the laboratory session. These instructions requested that participants a) abstain from consuming any alcohol in the 24 hours prior to their laboratory session; b) fast for four hours prior to their scheduled session; c) take normal morning medications; and d) avoid over-the-counter allergy or sinus medications on the morning of testing.

Laboratory Phase

Subjects arrived at the laboratory between 8:00 and 11:00 AM. Subjects (Ss) provided separate written informed consent for the laboratory session prior to any study procedures. Pre-session instructions were reviewed and recent abstinence from alcohol

consumption was confirmed using standard instruments (Intoxylizer® 400PA; CMI, Inc., Owensboro, KY). Initial breath alcohol concentrations (BrACs) were required to be 0.000 g/dL. Ss then provided a urine sample for drug and pregnancy testing (pre-menopausal women only). Ss consumed a light snack (~220 kcal) approximately one hour prior to alcohol administration. While consuming the snack, they were re-administered the age-appropriate affective measures given during screening (see Table 3.1).

Neurophysiological Recording

Neurophysiological recordings were conducted in an electrically shielded, sound attenuated Eckel Model 98S M (Eckel Industries of Canada Limited, Morrisburg, Ontario) recording booth. Ss were seated at a table in the booth and fitted with an elastic cap (Electro-Cap International, Eaton, OH) containing an array of 64 electrodes in an expanded International 10/20 System configuration. Linked electrodes attached to the earlobes were used as a reference with a mid-forehead ground. Electrodes were placed above and below the outer canthus of the left eye to detect blinks. Conductive gel was placed in each electrode using blunted syringes to maintain impedances at or below 5 kOhms. Stimuli were presented on a 17” LCD monitor placed inside the recording booth 70 cm from Ss. This monitor was connected to a personal computer (PC) running Windows XP (Microsoft, Redmond, WA) and E-Prime stimulus presentation software (Psychology Software Tools, Inc., Sharpsburg, PA). Another PC recorded continuous electroencephalography (EEG) at a sampling rate of 500 Hz using NeuroScan 4.4 Acquire software (Compumedics USA, Charlotte, NC). Cap application and impedance optimization occurred prior to beverage administration.

Alcohol Administration

Ss were randomly assigned to one of three alcohol dose conditions: placebo (no alcohol), low alcohol (0.04 g/dL target), or moderate alcohol (0.065 g/dL target). The quantity of medical grade alcohol (100% ethanol) necessary to achieve the desired peak BrAC was calculated using a modification of the Widmark formula. For men, this formula takes into account age and weight; for women, height and weight are considered (Watson et al., 1981; Widmark, 1932). Two research assistants not involved in cognitive or neurophysiological assessment were responsible for calculating alcohol doses and mixing drinks. A double sign-off procedure was used to verify that drinks were measured and dosed correctly. Alcohol was mixed with ice-cold sugar-free lemon lime soda in a 1:3 ratio. Placebo beverages consisted of soda only. Both alcohol-containing and placebo drinks were misted with alcohol to enhance placebo effectiveness. Beverages were split into two servings consumed by the S in no more than two minutes per serving with a one minute break in between servings. BrAC measurements were taken at 10, 25, 60, and 75 minutes post-beverage administration. Twenty-five minutes after alcohol administration, Ss assigned an active alcohol dose were provided with a “booster” beverage containing half their initial dose if their BrAC was ≤ half of target. All other Ss received a “booster” containing only soda. Participants were provided transportation home when their BrAC reached a level less than or equal to 0.01 g/dL.

Remember/Ignore Task

Approximately thirty minutes after beverage administration, Ss completed a three-part remember/ignore task (Gazzaley et al., 2008). The task consisted of three blocks of stimuli with counterbalanced instructions (Figure 3-1). Each of the 20 trials per block

consisted of two neutral face and two scene stimuli, presented one after another in pseudo-random order so Ss were unaware of the sequence in which relevant and irrelevant stimuli would be presented. Cue stimuli were grayscale to avoid luminance issues and were presented for 800 ms each with a 200 ms interstimulus interval (ISI) filled by a fixation '+'. After a nine second delay, a probe image was presented. Ss responded whether the probe image was present in the preceding set of cue stimuli (50% probability/trial). In one trial block, subjects were instructed to remember faces and ignore scenes. In another, subjects remembered scenes and ignore faces. The third task condition served as a control and required only passive viewing of both faces and scenes. In this condition, Ss pressed a button indicating the direction of an arrow shown at the end of each trial. The task required approximately 25 minutes to complete.

Subjective Intoxication

Using a procedure adapted from Harrison et al. (2007), subjective intoxication was assessed using a 10-point Likert scale immediately prior to the remember/ignore task. After the last block of the task, Ss completed an additional scale assessing their current subjective intoxication and the degree to which they felt their drink impaired performance on the task. Placebo effectiveness was assessed with a simple questionnaire at the end of the study session asking whether they felt they had received alcohol. Ss indicating that they did not receive alcohol were also asked when they made that determination.

Study Timeline

The timeline for laboratory sessions is illustrated in Table 3-2.

Data Analysis Strategy

Participant Characteristics

SAS 9.3 (SAS Institute, Inc., Cary, NC) was used for all analyses. In an effort to be comprehensive and better characterize study groups, we used a conservative approach for the analysis of participants' demographic, affective, and substance use data. Variables shared by older and younger participants were subjected to 2 (age group) X 3 (alcohol dose) ANOVA (SAS PROC GLM; Table 3-1). Follow-up t-tests were conducted to characterize detected interactions. One-way ANOVA was conducted to determine whether participants differed by dose within each age group on unshared demographic variables. Follow-up t-tests were conducted to characterize detected dose effects. Consistent with our conservative approach, family-wise error corrections were not applied in follow-up t-tests to better describe potential between-group differences. Pearson's r correlation matrices including demographic variables (e.g., age and years of education) and dependent variables (P1/N1/P3 characteristics) were generated.

ERPs

Consistent with previous research, P1, N1, and P3 measures were derived from face stimuli for correct trials in each remember/ignore condition (i.e., faces 'relevant', faces 'irrelevant', and passive viewing) and analyzed at the electrode sites where they had maximal amplitude in a grand average waveform (Gazzaley et al., 2008). Mean P1 and P3 amplitudes were determined by finding the average amplitude at the O2 electrode in windows determined by visual examination of the grand average waveform (120-170 ms and 360-420 ms, respectively; Luck, 2005). N1 peak latency was determined by visual identification of the maximal negative deflection between 120 and 220 ms at the P6 electrode (Figure 3-2). This set of dependent variables was chosen to

replicate analyses from Gazzaley et al. (2008). For each measure, enhancement was defined as the difference in response between the relevant and passive viewing conditions; suppression as the difference between the passive and irrelevant conditions. Outliers (observations greater or less than two standard deviations from the age-appropriate mean) were excluded from analyses for each measure of enhancement and suppression. In addition, Ss producing fewer than 20 acceptable epochs for a given task condition were excluded from analyses involving data from that condition. Thus, degrees of freedom may vary across analyses.

To determine whether effects of the 0.04 g/dL and 0.065 g/dL dose levels differed, 2 (active dose: 0.04/0.065 g/dL) X 2 (age group) analysis of variance (ANOVA) was conducted for each enhancement/suppression variable using SAS PROC GLM. Because these analyses were preliminary, a Bonferroni correction for multiple comparisons was applied resulting in a threshold significance level of 0.008. Results suggested no significant age, dose level, or interactive effects (ps>0.04). Because differences between the 0.04 g/dL and 0.065 g/dL dose levels were not detected, they were collapsed for subsequent analyses resulting in a 2 (age group) X 2 (dose group: placebo vs. active dose) design.

To address Specific Aim 1, we determined whether enhancement and suppression of N1 latency and P1/P3 amplitude occurred in each combination of age and dose group using pre-planned paired t-tests. Next, derived enhancement and suppression variables were subjected to multiple regression to determine variance accounted for by alcohol, age, and their interaction. The relationship between these variables and

behavioral outcomes (accuracy and reaction time) was assessed using Pearson's r correlation matrices.

To assess potential effects of age, alcohol, and their interaction on ERP measures themselves, 2 (age group) x 2 (active dose group) repeated measures ANOVA (repeated: task condition; SAS PROC GLM) was conducted. Where significant interactions were detected, follow-up t-tests were conducted.

Behavioral Analyses

Accuracy and reaction time in response to the probe items in the remember/ignore task (Figure 3.1) were recorded. Descriptive univariate statistics indicated accuracy was not skewed or kurtosed in either the 'remember face' or 'remember scene' task conditions. In the passive viewing condition, accuracy was substantially negatively skewed and kurtosed due to the very high accuracy in this condition across age and dose groups. Because performance under the passive viewing condition was not of primary interest, accuracy data were not transformed. Reaction time was not skewed and kurtosed for any task condition (Tabachnick and Fidell, 1989). Thus, no transformations were applied to behavioral data.

To determine whether the 0.04 and 0.065 g/dL dose levels could be collapsed, 2 (active dose level) X 2 (age group) ANOVA was conducted for accuracy and reaction time with a focus on dose main effects and the dose by age group interaction. The Bonferroni correction resulted in a threshold significance level of 0.025. Results indicated a significant effect of dose for accuracy ($F_{1,168}$=7.64, p=0.006) with the .065 g/dL dose level being associated with lower accuracy than the 0.04 g/dL level. No main effect of dose on reaction time was detected (p>0.80). Likewise, no age group X dose

interactions were detected for either accuracy or reaction time ($F_{1,168}$=3.12, p>0.08). Thus, the 0.04 g/dL and 0.065 g/dL were not collapsed for analyses of behavioral data.

2 (age group) X 3 (dose group) X 3 (repeated: task condition; 'Remember Face', passive viewing, 'Remember Scene') ANOVA was conducted for behavioral outcomes (reaction time and response accuracy; repeated: task condition). Simple main effects analyses were conducted to characterize detected interactions.

Correlational Analyses

To address our second aim, the relationship between subjective intoxication, BrAC, enhancement/suppression, and behavioral measures was assessed for younger and older adults using Pearson's r correlation matrices. These analyses were conducted separately for accuracy and reaction time from the 'Remember Face' and 'Remember Scene' conditions because of a) the greater difficulty of the 'remember scene' condition; and b) so that the potential relationships between enhancement/suppression and behavior could be better described.

Power Analysis

The original power analysis used to determine the target sample size for this study utilized effect sizes from behavioral tasks in a recent study from our laboratory with similar age groups (N=32, 20 older) and dose levels (placebo and 0.04 g/dL; Gilbertson et al., 2009). In brief, this initial analysis suggested ~160 participants equally split by age group would be necessary for adequate power to detect an age group by alcohol dose interaction, the point of primary interest. Since that time, additional analysis on neurophysiological measures (P3 amplitude/latency) from the same study was conducted (Lewis et al., in revision). Effect sizes of age group, alcohol dose, and their interaction on P3 amplitude and latency were greater than for behavioral outcomes.

Because these measures are conceptually closer to neurophysiological measures of interest in the current report, power to detect differences was reassessed at our current sample size of 92 participants (40 older). All power analyses were conducted using the PASS 2008 software package (NCSS, Kaysville, UT, USA).

Multiple Regression

Power analysis was conducted to detect main effects of age group, alcohol dose, and their interaction on neurophysiological correlates of top-down attention using multiple regression. In determining power to detect each main effect and the interaction, estimated variability due to the other two factors was controlled for. Age accounted for substantial variance in this recent publication (R^2 = 0.17). Thus, we estimated 99% power to detect the main effect of age in the current sample. Alcohol accounted for significantly less variance than age (R^2 = 0.03), resulting in 45% power to detect the main effect of alcohol. Of primary interest, we had 99% power to detect an age X alcohol interaction, which had a medium-large effect size (R^2=0.14).

Between-group Differences

As noted above, age effects were large in previous work (Lewis et al., in revision; Cohen's d= 1.24). Thus, with the current sample we estimated 99% power to detect the main effect of age. Alcohol effects in the previous study were of lesser magnitude (d = 0.56). This study's current power to detect these effects was adequate at 83%. As for multiple regression, power to detect an age X alcohol interaction with between group differences was high (99%).

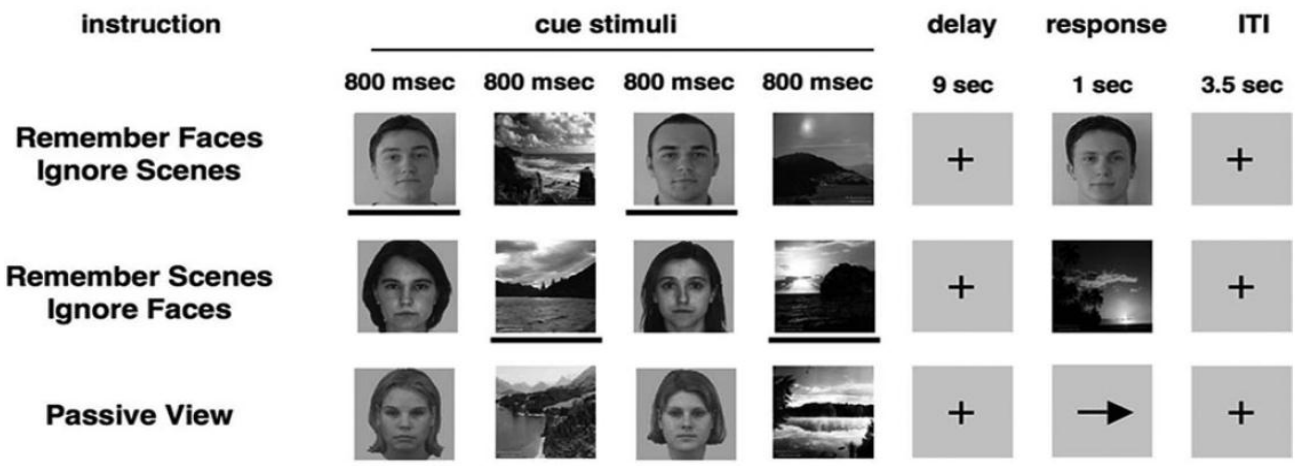

Figure 3-1. Remember/ignore Task Schematic (Gazzaley et al., 2005b).

Underlines indicate which images Ss were told to remember in a given block. Cue stimuli were presented within trials in pseudo-random order. A 200 ms ISI with a fixation '+' separated the presentation of cue stimuli. See text for additional description.

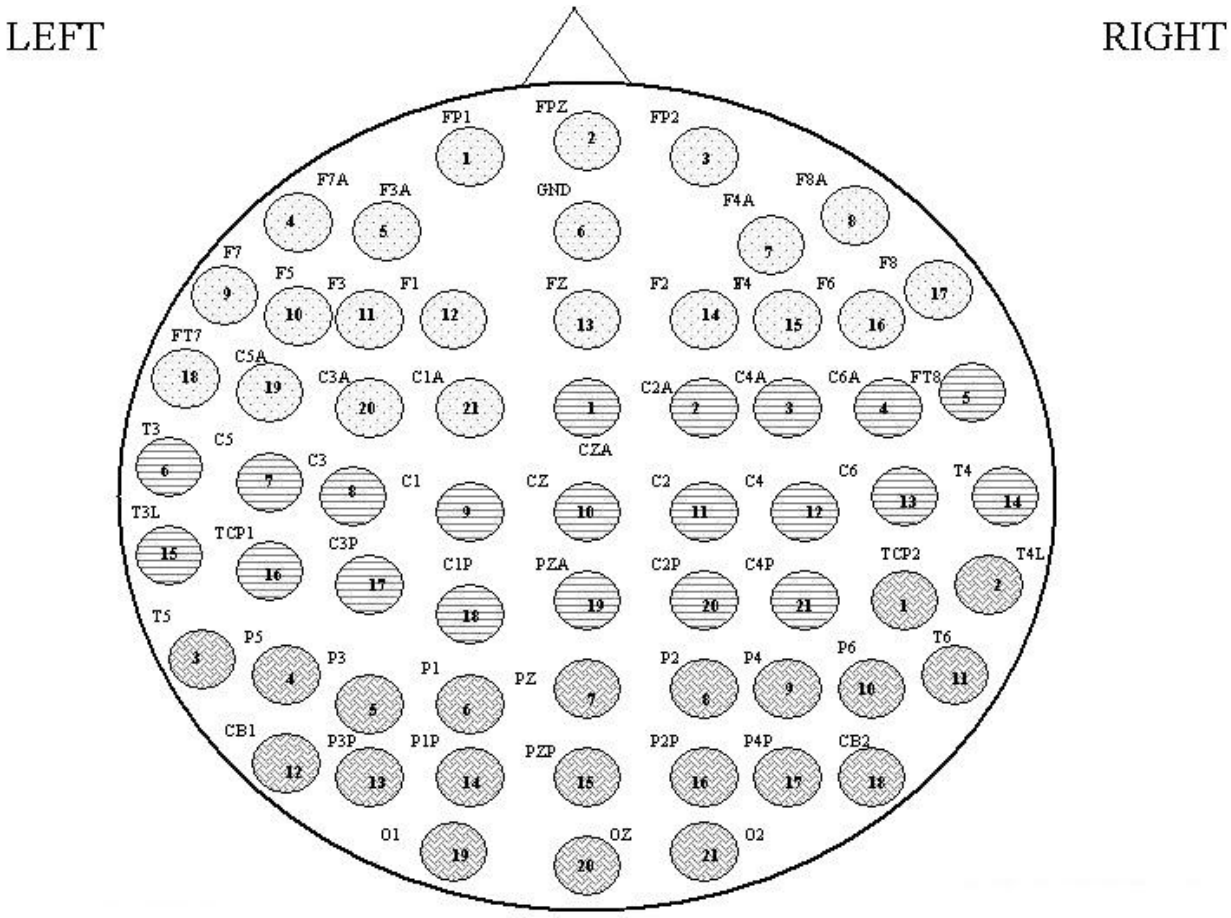

Figure 3-2. Map of Electrode Layout.

Table 3-1**.** Screening measures and exclusionary cutoffs.

Screening measure	Domain assessed	Younger adults	Older adults	Exclusionary cutoff	Citation
Beck Depression Inventory, 2nd ed. (BDI-II)	Depressive symptomatology	X	-	≥20	Beck et al., 1996
Geriatric Depression Scale (GDS)	Depressive symptomatology	-	X	≥11	Yesavage et al., 1982
State Anxiety Inventory (STAI)	State anxiety	X	X	Not exclusionary	Spielberger, 1983
Shipley Institute of Living Scale – Verbal (SILS-V)	Verbal ability	X	X	<12.9 Verbal age	Zachary, 1986
Alcohol Use Questionnaire (AUQ)	Past 6 mo. alcohol drinking	X	X	>2 drinks/day (men) >1 drink/day (women)	Cahalan et al., 1969
Alcohol Effects Questionnaire (AEQ)	Alcohol expectancies	X	X	Not exclusionary	Goldman et al., 1997
Hopkins Verbal Learning Test (HVLT)	Verbal memory	-	X	≤15 (total recall)	Benedict et al., 1998
Mini-mental State Examination (MMSE)	Mental status	-	X	≤26	Folstein et al., 1975

Table 3-2. Timeline for testing day.

0:00	+1:00	+1:30-1:45	+2:00	+2:30
• Consent • Review Meds, etc. • Drug/Pregnancy Testing	• Baseline BrAC • Breakfast • Affective Measures • ERP Hookup	• Beverage Administration • Absorption • BrAC	• Booster Dose • Subjective Intoxication • Remember/Ignore Task	• Subjective Intoxication/Perceived Impairment • BrAC • Lunch • Rest*

*Ss rested until BrAC ≤ 0.01, at which time they were transported home by laboratory staff.

CHAPTER 4
RESULTS

Participants

Subjects (Ss)

Ss were older (N=40; 15 men) and younger (N=52, 32 men) community dwelling moderate drinkers: 91% were Caucasian, 4% were African-American, and 4% reported another race or multiple races. 11% were Hispanic. 46% of older adults reported no over-the-counter or prescription medication use, 26% reported use of a single medication, 15% used two medications, and 13% used 3 or 4 medications. The majority of younger adults, in contrast, reported no regular over-the-counter or prescription medication use (79%). 11% of the younger sample reported a single medication and 10% reported two (including contraceptives). None reported routine use of more than two medications. See Table 4.1 for sample sizes in each of the dose groups for both younger and older adults. Placebo effectiveness was very high in older adults (85%), but significantly less so in younger adults (42%; χ^2=5.13, p=0.02).

Descriptive Variables

As noted in Chapter 3, a conservative approach towards detecting potential age and dose subgroup differences was taken in order to thoroughly characterize the study population. Thus, no corrections for family-wise error were employed. Means of demographic and affective variables by age group and dose assignment are presented in Table 4-1. Means of alcohol-related variables are presented in Table 4-2.

Education

A significant age group X dose interaction was detected for years of education ($F_{2,86}$=5.20, p=0.007). Follow-up analyses revealed that years of education were

equivalent between dose groups for younger adults (M_{plac}=16.84±1.26; $M_{.04}$=17.00±1.10; $M_{.065}$=16.41±1.18), but that older adults at the 0.04 g/dL dose level had significantly fewer years than those at the 0.065 g/dL level ($M_{.04}$=15.77±1.54; $M_{.065}$=17.21±1.19; t_{25}=2.88, p=0.05). Years of education did not correlate with any measure of top-down attention (rs<0.17, ps>0.15).

Verbal Ability

A significant main effect of age group was identified for Shipley verbal age ($M_{younger}$=18.18±1.10; M_{older}=19.06±1.25; $F_{1,86}$=12.08, p=0.0008). Mean verbal age was slightly higher among older participants than younger participants. All other effects were non-significant (Fs<1). Verbal age did not correlate with measures of top-down attention (rs<0.14, ps>0.23).

Mild Cognitive Impairment Screening

Older adults completed the Mini-mental State Examination and Hopkins Verbal Learning Test in order to exclude those with mild cognitive impairment. As expected, Mini-mental State Examination scores (M_{plac}=29.00±0.91; $M_{.04}$=29.54±0.66; $M_{.065}$=29.36±0.63) and Hopkins Verbal Learning Test scores (M_{plac}=27.31±4.35; $M_{.04}$=25.15±4.18; $M_{.065}$=24.29±3.97) did not differ between dose groups (ps>0.16).

Affective State

State anxiety was higher in older than younger participants (M_{older}=43.87±6.61; $M_{younger}$=40.85±4.92; $F_{1,85}$=5.85, p=0.02), but levels were not indicative of significant distress. No main effect of dose or age by dose group interaction was detected (Fs<1). Within older adults, a trend towards dose group differences on Geriatric Depression Scale scores was detected ($F_{2,37}$=2.99, p=0.06). Follow-up comparisons indicated depressive symptomatology was slightly lower among those assigned to the 0.04 g/dL

level than those assigned to placebo ($M_{.04}$=0.92±1.19; M_{plac}=2.77±2.09; t_{26}=2.41, p=0.05). No differences were detected between the 0.04 and 0.065 g/dL levels or the 0.065 g/dL level ($M_{.065}$=2.07±2.34) and placebo (ps>0.28). No differences were detected between dose groups for Beck Depression Index scores in younger adults (M_{plac}=2.32±2.75; $M_{.04}$=2.63±2.92; $M_{.065}$=3.29±2.31; p>0.54).

No affective measures correlated with measures of enhancement/suppression (rs<0.16, ps>0.15).

Alcohol Use Measures

A significant age group by dose group interaction was noted for QFI (average ounces of absolute ethanol consumed per day; $F_{2,86}$=4.03, p=0.02). Follow-up analyses indicated that among older participants, those in the placebo group (M_{plac}=0.55±0.39) had higher average daily alcohol consumption than the 0.04 g/dL dose group ($M_{.04}$=0.22±0.20; t_{26}=2.87, p=0.02). The placebo group also had a higher mean QFI than the .065 g/dL dose group, although this difference was non-significant ($M_{.065}$=0.28±0.23; t_{26}=2.39, p=0.06). No differences in QFI were detected between dose groups in younger adults (M_{plac}=0.35±0.25; $M_{.04}$=0.41±0.25; $M_{.065}$=0.42±0.35). An age main effect was detected for maximum absolute ethanol consumption in a single 24 hour period during the last six months (MaxQFI; $F_{1,86}$=40.90, p<0.0001) with younger adults reporting higher quantities than older adults ($M_{younger}$=4.00±1.81; M_{older}=1.92±1.03). Neither QFI nor MaxQFI correlated with dependent variables of interest (rs<0.14, ps>0.21).

BrAC Results

BrACs achieved in each age group and active dose condition are shown in Figure 4.1. As expected, mean BrACs differed significantly between the two active dose levels

at every time point ($F_{1,53}$>21, ps<0.0001). No significant differences in BrAC between older and younger participants were noted at any time point in any dose group (all ps > 0.40).

ERP Results

Grand average waveforms for younger and older participants who received a placebo beverage are shown in Figures 4-2 and 4-3, respectively.

Enhancement/Suppression

Paired t-tests indicated that under placebo, younger adults showed enhancement of N1 latency and P3 amplitude (M_{N1}=6.40±12.05 ms, t_{14}=2.06, p=0.06, Figure 4-4; M_{P3}=1.59±2.01 μV, t_{18}=3.35, p=0.0004, Figure 4-5). They also showed significant suppression of N1 latency (M=5.75±10.55 ms, t_{15}=2.18, p=0.004, Figure 4-4). This pattern was largely unperturbed under active alcohol doses, with younger adults demonstrating enhancement of P3 amplitude (M_{P3}=1.05±2.15 μV, t_{30}=2.71, p=0.01, Figure 4-5), non-significant enhancement of P1 amplitude (M_{P1}=0.52±1.47 μV, t_{29}=1.95, p=0.06, Figure 4-6), and suppression of N1 latency (M=7.38±15.40 ms, t_{28}=2.58, p=0.02, Figure 4-4). In contrast, older adults showed only weak enhancement of P3 amplitude under placebo (M=0.81±2.21 μV, t_{11}=1.67, p=0.12; Figure 4-8). Under active doses, they showed enhancement of N1 latency and P3 amplitude (M_{N1}=12.75±19.75 ms, t_{23}=3.16, p=0.004, Figure 4-7; M_{P3}=1.23±1.73 μV, t_{24}=3.58, p=0.002, Figure 4-8).

Regression Analyses

Stepwise multiple regression was used to model the effects of age, alcohol, and their interaction on derived measures of enhancement and suppression. These regressions revealed a significant interaction of age group and alcohol on N1 latency enhancement ($F_{1,73}$=6.30, p=0.01, R^2=0.08). Follow-up analyses indicated active alcohol

doses predicted disruption of N1 latency enhancement for younger but not older adults (Figure 4-9), but no significant independent contribution of age group or alcohol (ps>0.15). No significant effects of age, alcohol, or their interaction were detected for P3 amplitude enhancement, P1 amplitude enhancement, or N1 latency suppression (ps>0.15).

Subjective Intoxication, BrAC, and Enhancement/Suppression

To examine the relationship between enhancement/suppression, subjective intoxication, and BrAC measures, correlation matrices were constructed for each combination of age group and alcohol condition (placebo vs. active dose). No significant correlations between measures of enhancement or suppression and subjective intoxication were detected (ps>0.12). Likewise, no relationship between BrAC measures and enhancement or suppression were noted for younger adults (ps>0.33). However, P3 amplitude enhancement in older adults was significantly negatively correlated with BrAC measures taken immediately prior to task administration (r=-0.40, p=0.04; Figure 4-10). This relationship was not observed for N1 latency (p>0.63).

Age and Alcohol Effects on ERP Characteristics

Two [2] (age group: younger vs. older adults) by 2 (alcohol group: placebo vs. active dose) by 3 (repeated: task condition) ANOVA for N1 latency identified a significant main effect of condition ($F_{2,59}$=5.86, p=0.005). Follow-up t-tests for the task condition main effect revealed that across age and alcohol groups, N1 latency was significantly faster under the ‘Remember Face’ condition than the ‘Remember Scene’ condition (M_{face}=173.81±27.48 ms; M_{scene}=183.59±25.40 ms; t_{78}=2.87, p=0.005). A trend-level difference between the passive viewing and ‘Remember Scene’ conditions was also noted, with passive viewing having a faster latency ($M_{passive}$=178.59±24.68 ms;

t_{82}=1.73, p=0.09). The passive viewing and ‘Remember Face’ conditions did not significantly differ (p>0.13). No other significant main effects or interactions were noted for N1 latency (ps>0.25).

A similar analysis was applied to P1 amplitude across task conditions. As for N1 latency, a significant effect of condition was identified ($F_{2,75}$=5.28, p=0.007). Follow-up t-tests indicated that P1 amplitude in the ‘Remember Face’ condition (M_{face}=3.47±2.64 μV) was significantly higher than in the ‘Remember Scene’ condition (M_{scene}=2.78±2.54 μV; t_{85}=3.51, p=0.0007). While the passive viewing and ‘Remember Scene’ conditions did not differ ($M_{passive}$=2.97±2.65 μV; p>.37), a trend-level difference was noted between the ‘Remember Face’ and passive viewing conditions (t_{88}=1.88, p=0.06). No other significant main effects or interactions were noted for P1 amplitude (ps>0.18).

2 (age group) by 2 (alcohol group) by 3 (repeated: task condition) ANOVA revealed a main effect of task condition for P3 amplitude ($F_{2,77}$=15.72, p<0.0001). Follow-up t-tests revealed that P3 amplitude in the ‘Remember Face’ condition (M_{face}=3.28±2.21 μV) was significantly higher than both the ‘Remember Scene’ (M_{scene}=1.78±2.14 μV; t_{85}=6.05, p<0.0001) and passive viewing conditions ($M_{passive}$=2.04±1.92 μV; t_{88}=5.47, p<0.0001), which did not differ from one another (p>0.48). A main effect of age group on P3 amplitude was also observed across task conditions ($F_{1,78}$=5.94, p=0.02), with younger adults having significantly higher P3 amplitude than older adults ($M_{younger}$=2.76±1.87 μV; M_{older}=1.89±1.45 μV; Figure 4-11). No other significant main effects or interactions were noted for P3 amplitude (ps>0.56).

Behavioral Results

Accuracy

2 (age group) X 3 (dose) X 3 (repeated: task condition) ANOVA for accuracy measures detected significant main effects of age group, dose, and task condition ($F_{1,258}$=10.05, p=0.002; $F_{2,258}$=6.17, p=0.002; $F_{2,258}$=67.27, p<0.0001), as well as a dose by task condition interaction ($F_{4,258}$=2.78, p=0.03). All other effects were non-significant (ps>0.11).

Characterization of these main effects revealed that accuracy across task conditions was higher in younger than older adults ($M_{younger}$=93±9.7% vs. M_{older}=88±11.6%; Figure 4-12). This result was confirmed with a t-test for the effect of age group excluding responses from the passive viewing condition was conducted (t_{182}=4.03, p<0.0001). Mean accuracy was significantly lower in the 0.065 g/dL group ($M_{.065}$=87±11.9%) than either the placebo or 0.04 g/dL groups (M_{plac}=92±10.1%, t_{179}=3.00, p=.003; $M_{.04}$=92±9.8%, t_{188}=3.06, p=0.002; Figure 4-13), which did not differ from one another (t_{182}=0.11, p=0.91). In addition, accuracy was significantly higher under the passive viewing task condition ($M_{passive}$=99±1.8%) than the 'Remember Face' (M_{face}=87±10.7%) and 'Remember Scene' (M_{scene}=84±10.4%) conditions (t_{183}=8.89, p<0.0001; t_{183}=10.90, p<0.0001; Figure 4-14). Accuracy under the 'Remember Face' condition was also significantly higher than under the 'Remember Scene' condition (t_{183}=2.00, p=0.05).

Breakdown of the dose by task condition interaction revealed that under placebo, accuracy in the 'Remember Face' condition was significantly greater than in the 'Remember Scene' condition (M_{face}=91±9.1% vs. M_{scene}=83±10.4%; t_{63}=3.19, p=0.002). However, under the 0.04 g/dL (M_{face}=88±10.3% vs. M_{scene}=86.9±9.4%) and 0.065 g/dL

(M_{face}=84±11.3% vs. M_{scene}=81.78±11.1%) doses, accuracy did not differ between these task conditions (ts<1; Figure 4-15).

Reaction Time

2 (age group) X 3 (dose) X 3 (repeated: task condition) ANOVA for reaction time found significant main effects of age group and task condition ($F_{1,258}$=40.78, p<0.0001; $F_{2,258}$=157.00, p<0.0001). A trend towards an age group by task condition interaction was also detected ($F_{2,258}$=2.66, p=0.07). All other main effects and interactions were non-significant (Fs<1).

As expected, reaction time across task conditions was faster in younger than older adults ($M_{younger}$=1018±366 ms vs. M_{older}=1237±467 ms; Figure 4-16). As for accuracy, this age group effect was confirmed with a t-test excluding responses from the passive viewing condition (t_{182}=5.74, p<0.0001). Reaction times were faster in the 'passive viewing' ($M_{passive}$=698±178 ms) condition than either the 'Remember Face' (M_{face}=1329±378 ms, t183=15.01, p<0.0001) or 'Remember Scene' (M_{scene}=1356±317 ms, t_{183}=15.66, p<0.0001) conditions, which did not differ from one another (t_{183}=.65, p=0.52; Figure 4-17).

Breakdown of the age group by task condition interaction revealed that while older adults had significantly slower reaction times than younger adults in both the 'Remember Scene' (M_{older}=1493±301 ms vs. $M_{younger}$=1219±278 ms; t_{90}=4.62, p<0.0001) and 'Remember Face' conditions (M_{older}=1466±427 ms vs. $M_{younger}$=1191±286 ms; t_{90}=4.63, p<0.0001), this difference was diminished in the 'passive viewing' condition (M_{older}=752±165 ms vs. $M_{younger}$=644±175 ms; t_{90}=1.80, p=0.07; Figure 4-18).

Enhancement/Suppression and Behavior

As above, Pearson's r correlation matrices with variables showing significant enhancement or suppression and behavioral outcomes (accuracy and reaction time) were constructed for each combination of age group and alcohol dose. With the exception of a trend-level correlation suggesting a faciliatory influence of P3 amplitude enhancement on reaction time for younger adults receiving placebo ($r=-0.44$, $p=0.07$; Figure 4-19), no significant relationships were detected (all other $ps>0.15$).

Subjective Intoxication, BrAC, and Behavior

Pearson's r correlation matrices were also constructed to characterize the relationship between subjective intoxication, BrAC, and behavioral outcomes for younger and older adults, separated by dose group (placebo vs. active). Because a main effect of task condition was found for both accuracy and reaction time, these relationships were considered separately for each task condition. As noted above, accuracy in the passive viewing condition was very high across age groups and dose levels. Thus, the relationship between subjective intoxication, BrAC, and accuracy under this condition was not considered.

No correlation between subjective intoxication and accuracy or reaction time was detected for younger adults under placebo for either the 'Remember Face' or 'Remember Scene' task condition ($ps>0.23$). A significant relationship between BrAC at 25 minutes post-beverage and subjective intoxication was noted for younger adults ($r=0.37$, $p=0.03$; Figure 4-20) under active doses. However, no relationships between subjective intoxication, BrAC, and reaction time were found under any task condition for younger adults receiving alcohol ($ps>0.18$).

Older adults receiving a placebo beverage showed no relationship between subjective intoxication and accuracy or reaction time under any task condition (ps>0.32). However, significant negative relationships between BrAC at 60 minutes post-beverage and both accuracy and reaction time were found for older adults receiving an active alcohol dose under the 'Remember Face' (r=-0.46, p=0.02 and r=0.40, p=0.04; Figure 4-21) condition. This relationship was also detected for accuracy, but not reaction time, in the 'Remember Scene' condition (r=0.-40, p=0.04; p>0.23; Figure 4-22). Notably, correlations between BrAC measurements and subjective intoxication were non-significant for older adults (ps>0.10).

Results Summary

Enhancement/Suppression

Results indicated that younger, but not older, adults showed significant enhancement and suppression of early- and middle-components of the ERP under both placebo and active alcohol (Figures 4-4 - 4-6). In contrast, older adults showed some evidence of enhancement, but not suppression (Figures 4-7 and 4-8). Regression analyses revealed an interaction of age group and alcohol dose accounted for 8% of the variance in N1 latency enhancement. When characterized, we found that N1 latency enhancement in younger but not older adults was disrupted by active alcohol doses (Figure 4-9).

BrAC, Subjective Intoxication, and Enhancement/Suppression

BrAC, but not subjective intoxication, was negatively correlated with the degree of P3 amplitude enhancement in older, but not younger, adults (Figure 4-10). Degree of enhancement did not correlate with behavioral measures in older adults. Younger adults

receiving placebo showed a trend-level correlation between greater P3 amplitude enhancement and faster reaction times (Figure 4-19).

Behavioral Outcomes

Expected age group and dose effects for behavioral outcomes were found, with older adults having lower accuracy and slower reaction times across task conditions (Figures 4-11 and 4-15). Task condition by dose and task condition by age group interactions were identified for accuracy and reaction time, respectively. No interactions of dose by age group were found. Breakdown of these interactions revealed that a) accuracy in the 'Remember Face' condition was higher than the 'Remember Scene' condition under placebo, but not under either active alcohol dose (Figure 4-14); and b) age group differences in reaction time were greater under the 'Remember Face' and 'Remember Scene' conditions than in the passive viewing condition (Figure 4-17).

BrAC, Subjective Intoxication, and Behavior

Although a significant positive relationship between BrAC and subjective intoxication was found for younger Ss (Figure 4-20), older Ss showed no such relationship. Neither measure predicted accuracy or reaction time for younger Ss. In contrast, BrAC and subjective intoxication were differentially correlated with behavior for older Ss, with BrAC being negatively correlated with accuracy and reaction time in the 'Remember Face' condition (Figure 4-21), and accuracy in the 'Remember Scene' condition (Figure 4-22). No relationship between subjective intoxication and behavior was noted for older Ss.

Table 4-1. Demographic and affective variables.

	Younger Ss			Older Ss		
	Placebo N=19 Mean SD	0.04 g/dL N=16 Mean SD	0.065 g/dL N=17 Mean SD	Placebo N=13 Mean SD	0.04 g/dL N=13 Mean SD	0.065 g/dL N=14 Mean SD
Age (years)	27.84 2.67	29.00 3.25	27.29 2.37	61.85 4.34	58.85 2.85	61.93 4.55
Education (years)*	16.84 1.26	17.00 1.10	16.41 1.18	16.00 1.58	15.77 1.54	17.21 1.19
BMI (kg/m^2)	25.90 4.94	26.12 6.06	23.28 3.14	25.66 4.29	24.77 4.51	26.56 6.20
Verbal Age[a]	18.05 1.00	18.18 1.01	18.34 1.33	19.04 1.65	18.88 1.01	19.26 1.06
MMSE	-	-	-	29.00 0.91	29.54 0.66	29.36 0.63
HVLT	-	-	-	27.31 4.35	25.15 4.18	24.29 3.97
BDI-II	2.32 2.75	2.63 2.92	3.29 2.31	-	-	-
GDS[&]	-	-	-	2.77 2.09	0.92 1.19	2.07 2.34
STAI[b]	39.95 5.23	41.56 3.58	41.18 5.74	44.38 5.75	43.69 8.04	43.54 6.33

[a]Significant effect of age group ($F_{1,91}$=12.79, p=0.0006; older > younger). [b]Significant effect of age group ($F_{1,91}$=5.51, p=0.02; older > younger). *Significant dose group effect in older Ss ($F_{2,37}$=3.97, p=0.03); 0.065 g/dL > .04 g/dL or placebo (t_{26}=2.61, p=0.03; t_{26}=2.19, p=0.08, respectively). [&]Trend dose group effect in older Ss ($F_{2,37}$=2.99, p=0.06); 0.04 g/dL > placebo (t_{26}=2.41, p=0.05).

Table 4-2. Alcohol-use related variables.

	Younger Ss			Older Ss		
	Placebo N=19	0.04 g/dL N=16	0.065 g/dL N=17	Placebo N=13	0.04 g/dL N=13	0.065 g/dL N=14
	Mean SD	Mean SD	Mean SD	Mean SD	Mean SD)	Mean SD
QFI* (oz. absolute ethanol/day)	0.35 0.25	0.41 0.25	0.42 0.35	0.55 0.39	0.22 0.20	0.28 0.23
MaxQFI[a] (oz. absolute ethanol)	4.02 2.15	4.22 1.72	3.78 1.55	2.18 1.15	1.80 0.97	1.78 1.00

[a]Significant effect of age group ($F_{1,91}$=42.31, p<0.0001; younger > older). *Significant dose group effect in older Ss ($F_{2,37}$=4.70, p=0.01. Placebo > 0.04 g/dL and 0.065 g/dL (t_{26}=2.87,p=0.02; t_{26}=2.39, p=0.06, respectively).

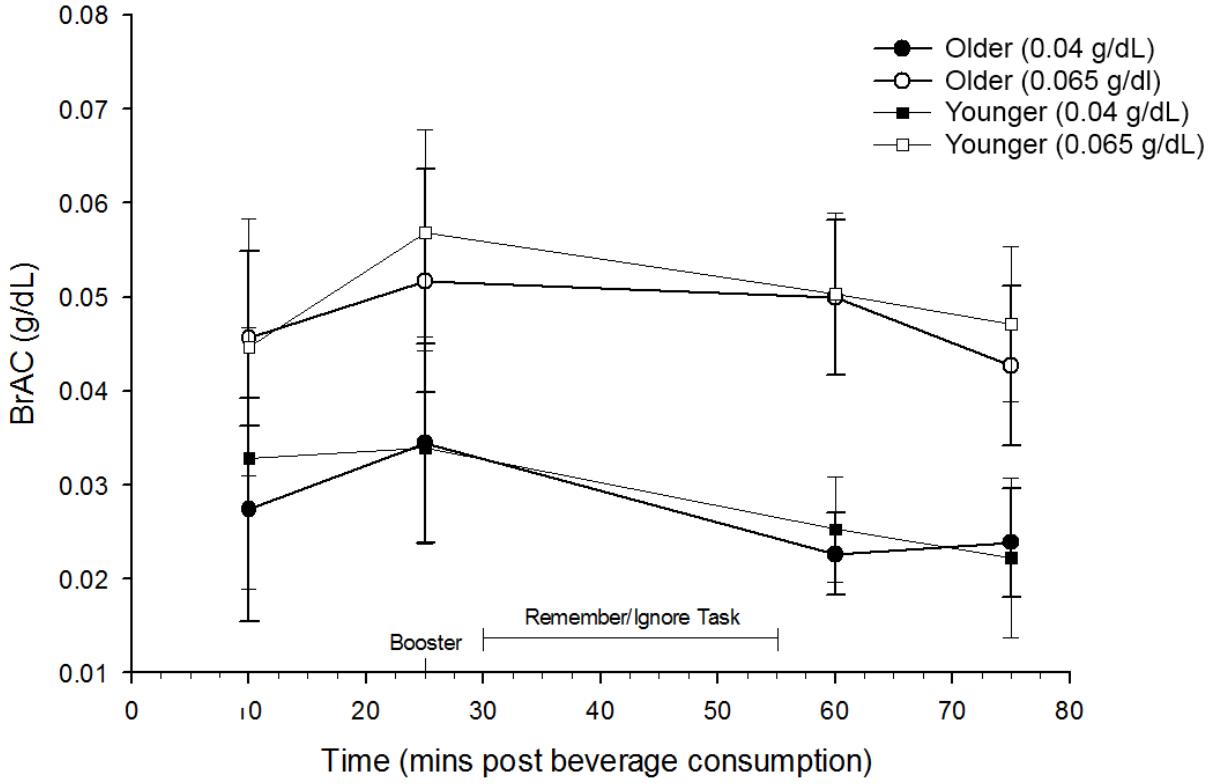

Figure 4-1. BrACs for Age and Active Dose Groups.

No differences were noted between younger and older Ss for either dose at any time point (ps>0.40). Error bars depict standard deviations.

Younger Adults: Grand Average Waveforms by Task Condition (Placebo)

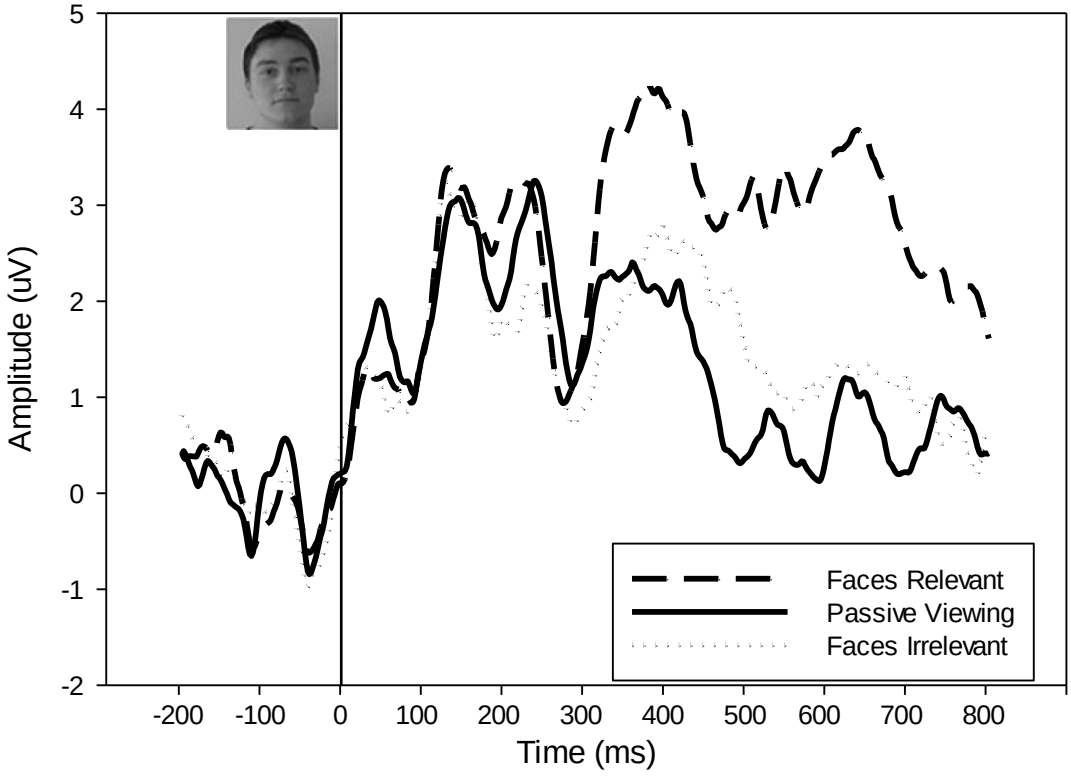

Figure 4-2. Grand Average Waveforms Associated With 'Face' Cue Stimuli by Task Condition in Younger Ss.

Older Adults: Grand Average Waveforms by Task Condition (Placebo)

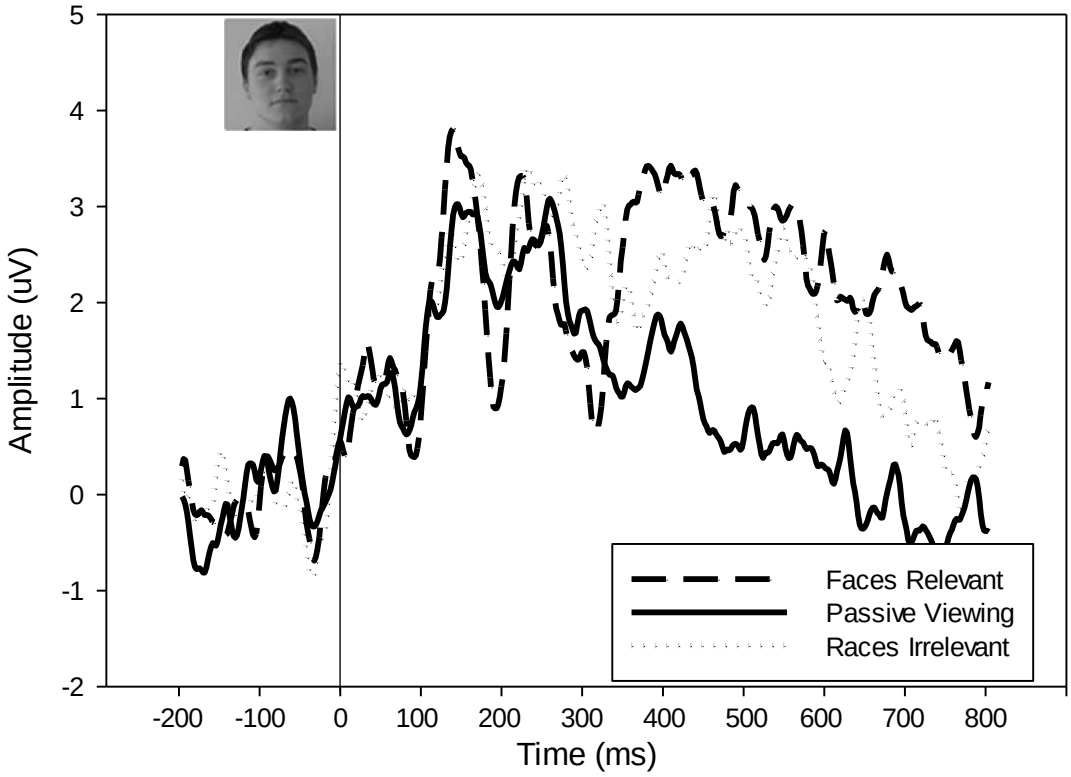

Figure 4-3. Grand Average Waveforms Associated with 'Face' cue Stimuli by Task Condition in Older Ss.

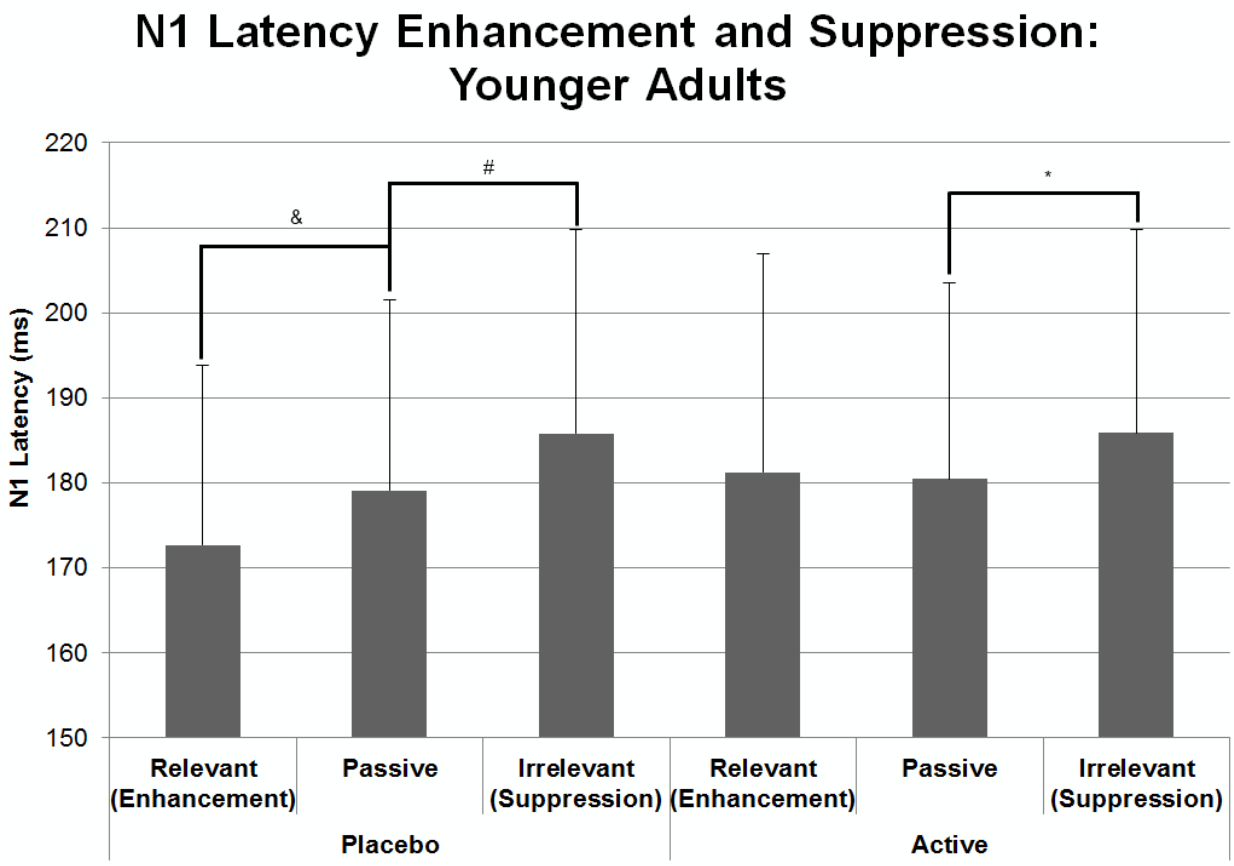

Figure 4-4. N1 Latency Enhancement and Suppression: Younger Adults

Younger adults demonstrated both enhancement and suppression of N1 latency under placebo, and suppression under active alcohol. Error bars depict standard deviations.[&]: t_{14}=2.06, p=0.06; #: t_{15}=2.18, p=0.04; *: t_{28}=2.58, p=0.02.

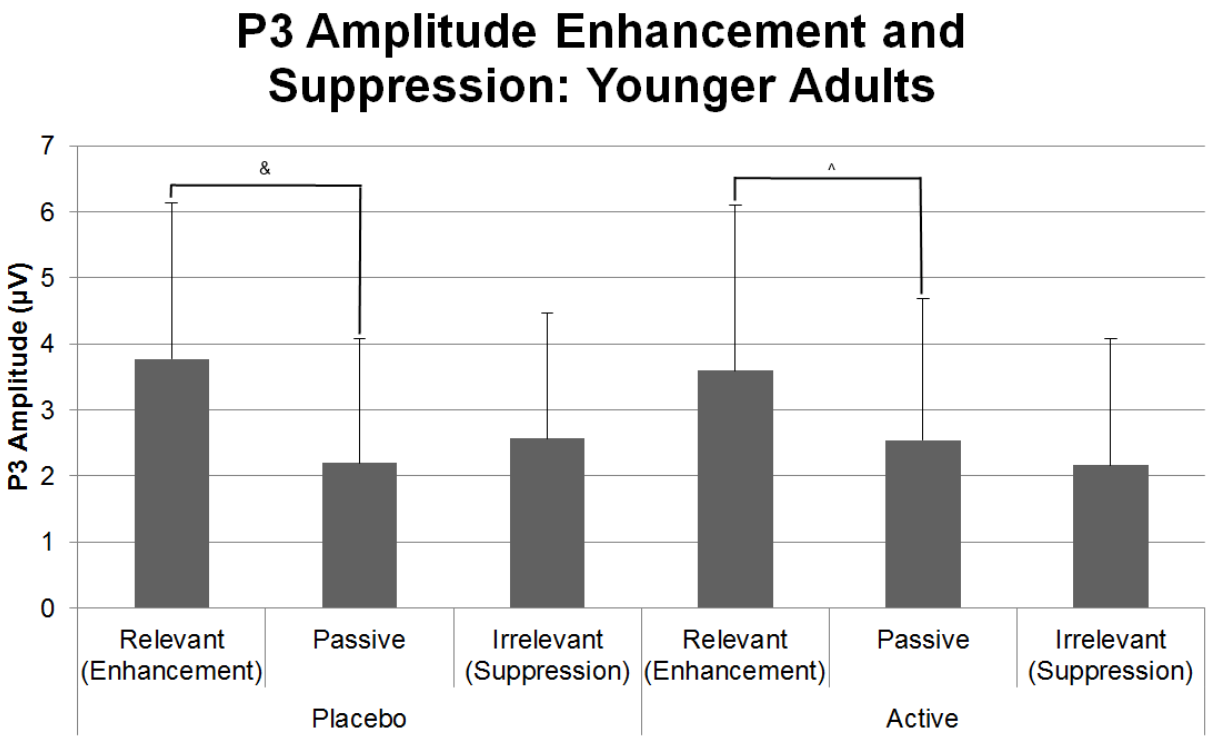

Figure 4-5. P3 Amplitude Enhancement and Suppression: Younger Adults

Younger adults demonstrated significant enhancement of P3 amplitude under both placebo and active alcohol doses. However, suppression of P3 amplitude was not noted in either condition. Error bars depict standard deviations. $^{\&}$: $t_{18}=3.35$, $p=0.004$; ^: $t_{30}=2.71$, $p=0.01$.

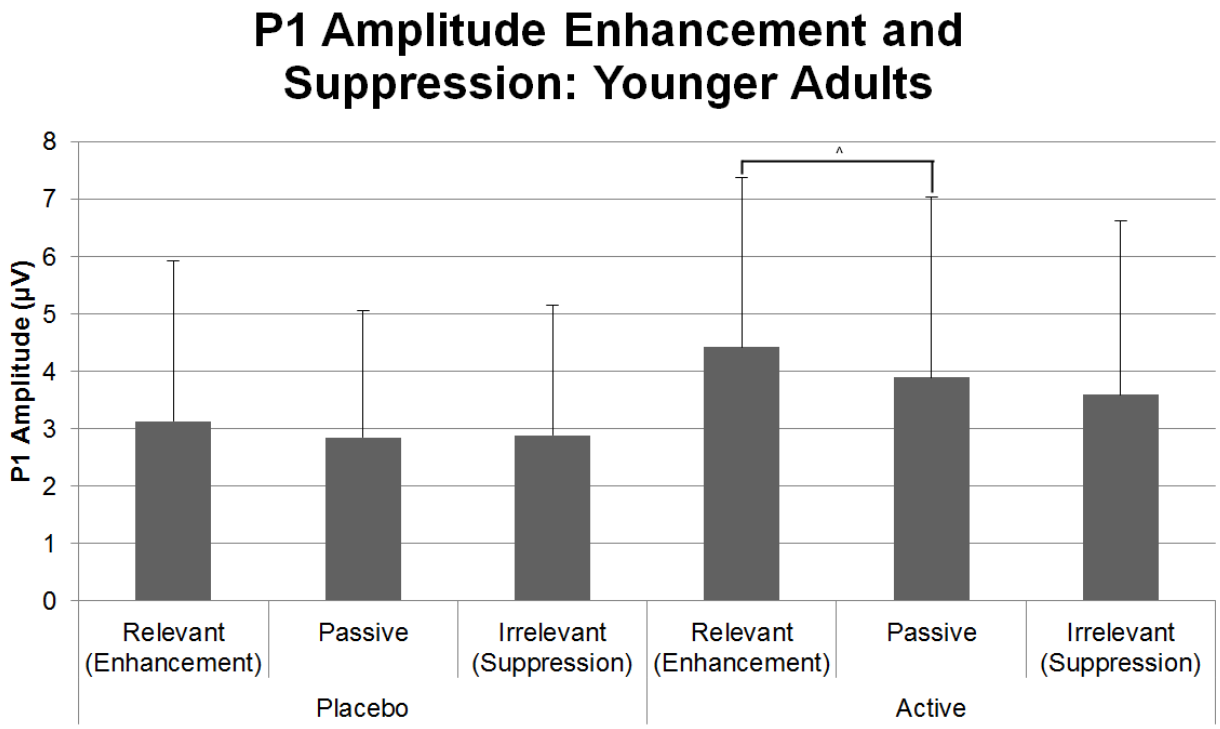

Figure 4-6. P1 Amplitude Enhancement and Suppression: Younger Adults

Younger adults showed neither enhancement nor suppression of P1 amplitude under placebo. Under active alcohol doses, however, they showed a trend toward P1 amplitude enhancement (t_{29}=1.95, p=0.06). Error bars depict standard deviations.

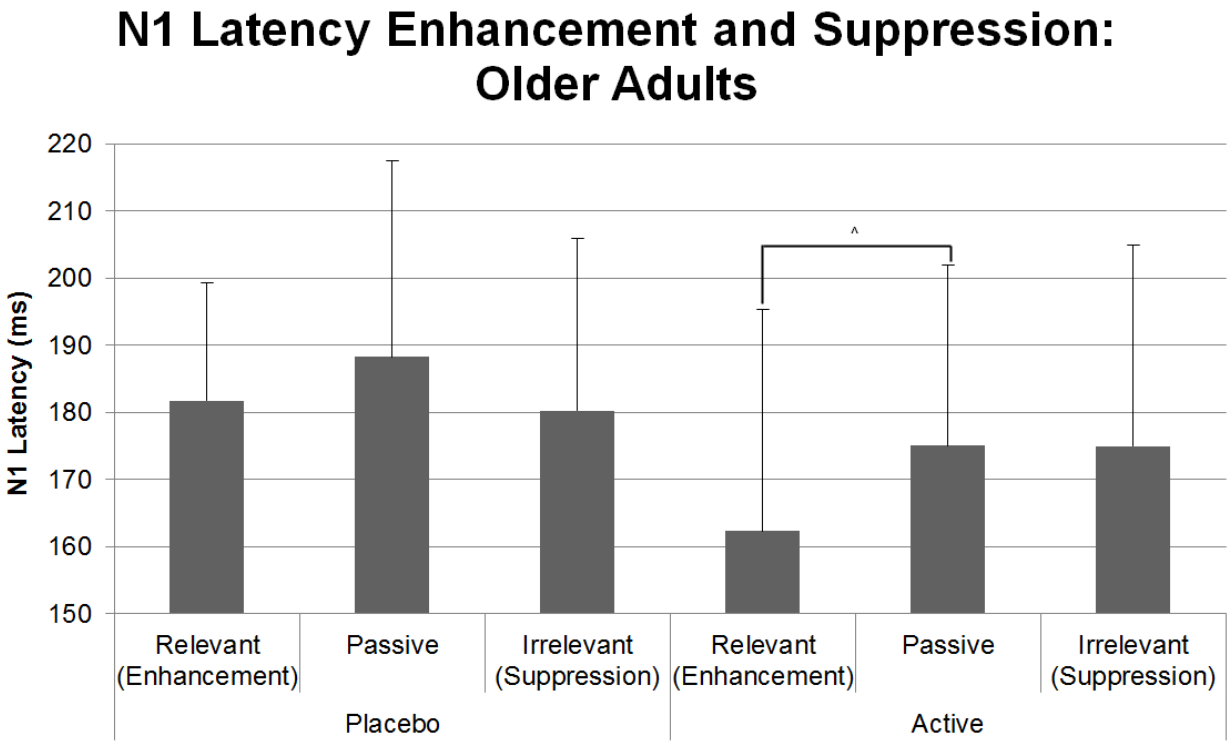

Figure 4-7. N1 Latency Enhancement and Suppression: Older Adults

Older adults given an active dose of alcohol showed significant enhancement of N1 latency. This effect was not seen under placebo. Older adults did not show suppression of N1 latency under either treatment. Error bars depict standard deviations. ^: t_{23}=3.16, p=0.004.

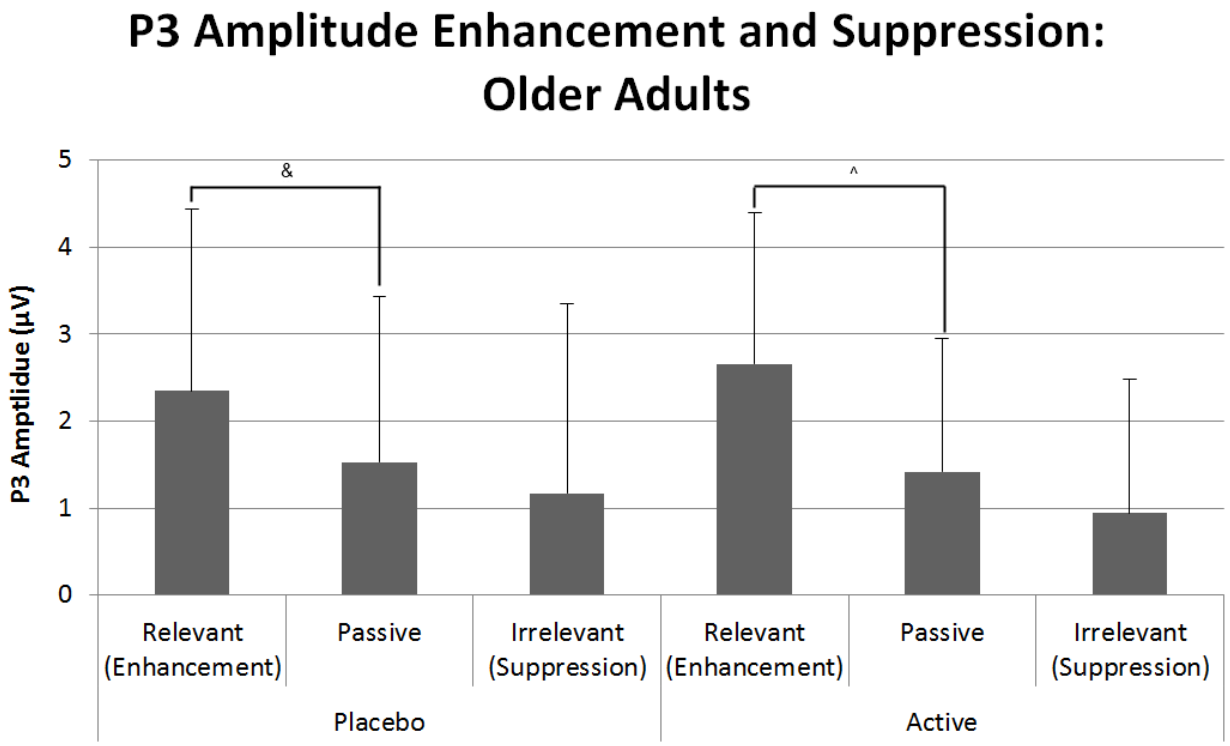

Figure 4-8. P3 Amplitude Enhancement and Suppression: Older Adults

Older adults showed significant enhancement of P3 amplitude under active doses of alcohol, but only non-significant enhancement under placebo. Error bars depict standard deviations. *: $t_{24}=3.58$, $p=0.002$; $^{\#}$: $t_{11}=1.67$, $p=0.12$.

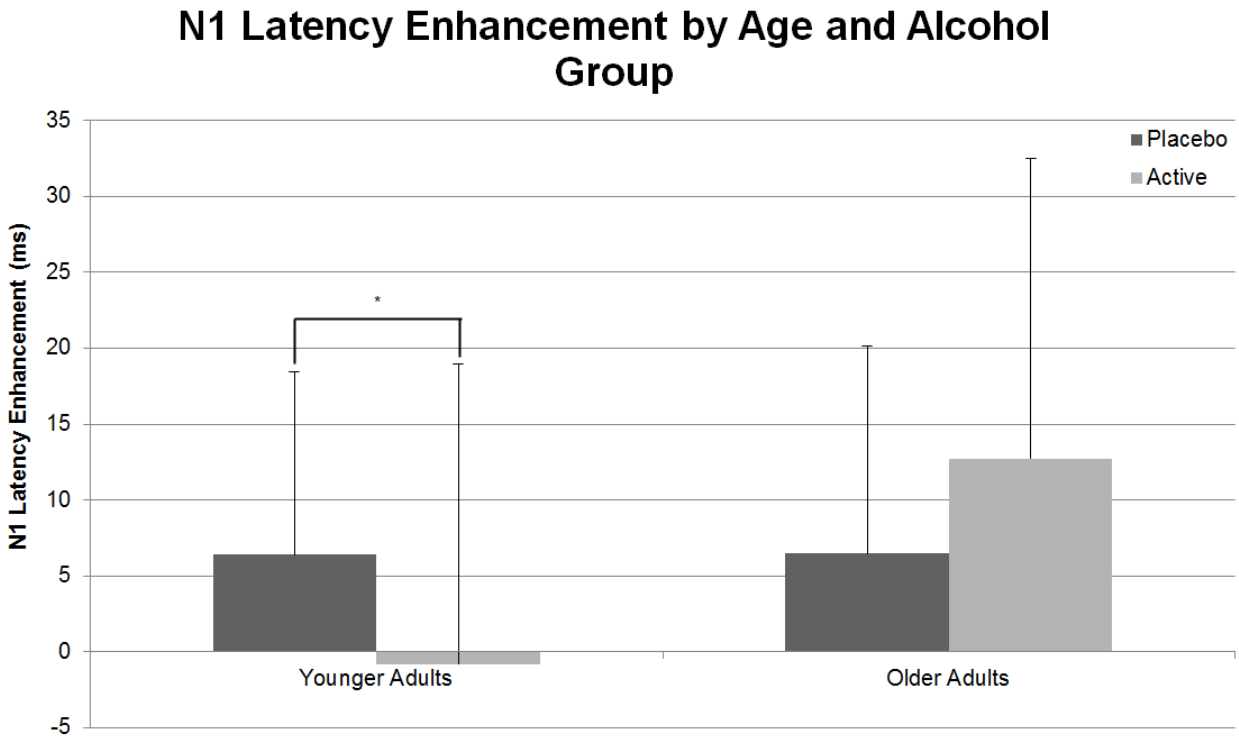

Figure 4-9. N1 Latency Enhancement by Age and Alcohol Group

Regression analysis identified a significant age group by alcohol group interaction ($F_{1,73}$=6.30, p=0.01, R^2=0.08; Figure 4.9). Follow-up analyses indicated active alcohol doses trended towards disruption of N1 latency enhancement for younger (t_{41}=1.71, p=.09) but not older Ss (t_{30}=0.77, p=0.44). Error bars depict standard deviations.

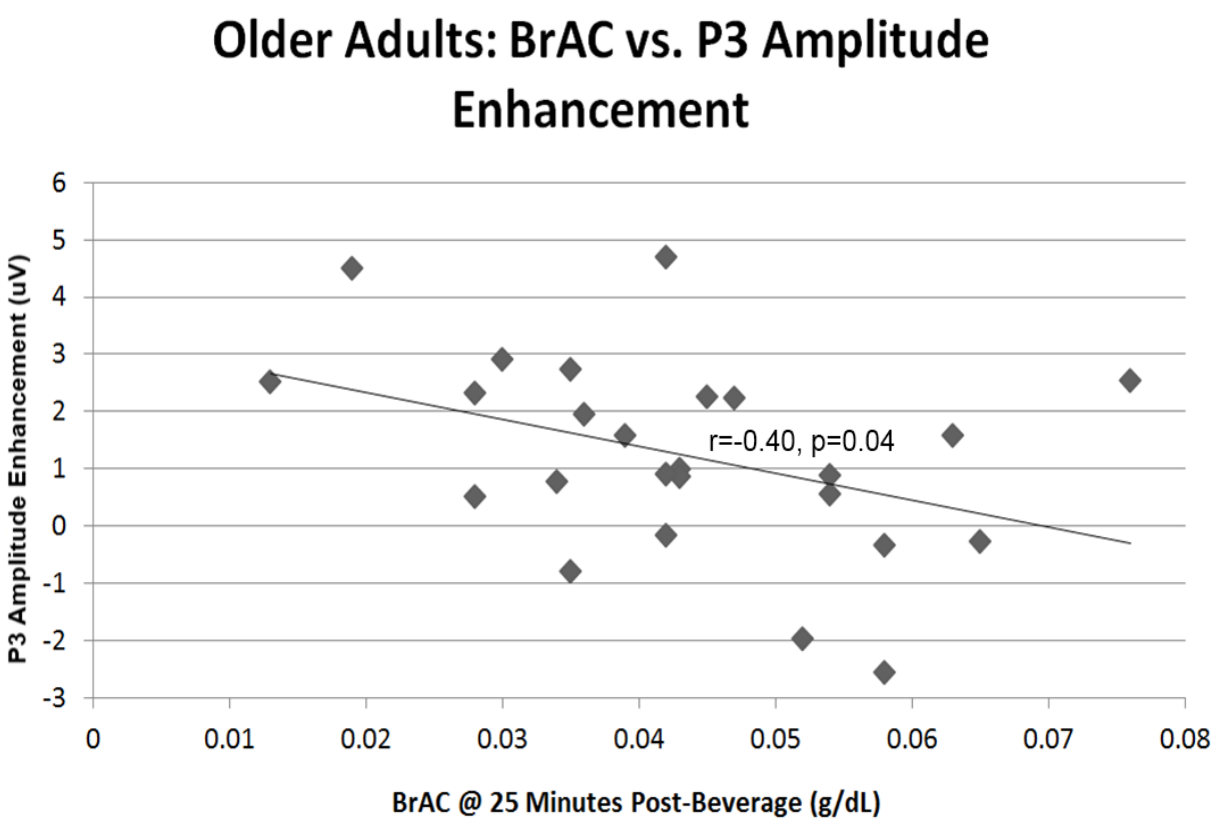

Figure 4-10. Older Adults: BrAC vs. P3 Amplitude Enhancement

Older Ss showed a negative relationship between BrAC measurements taken 25 minutes post-beverage and P3 amplitude enhancement (r=-0.40, p=0.04). This relationship was not observed for N1 latency enhancement in older Ss (p>0.60) or for any enhancement/suppression measure in younger Ss (ps>0.33).

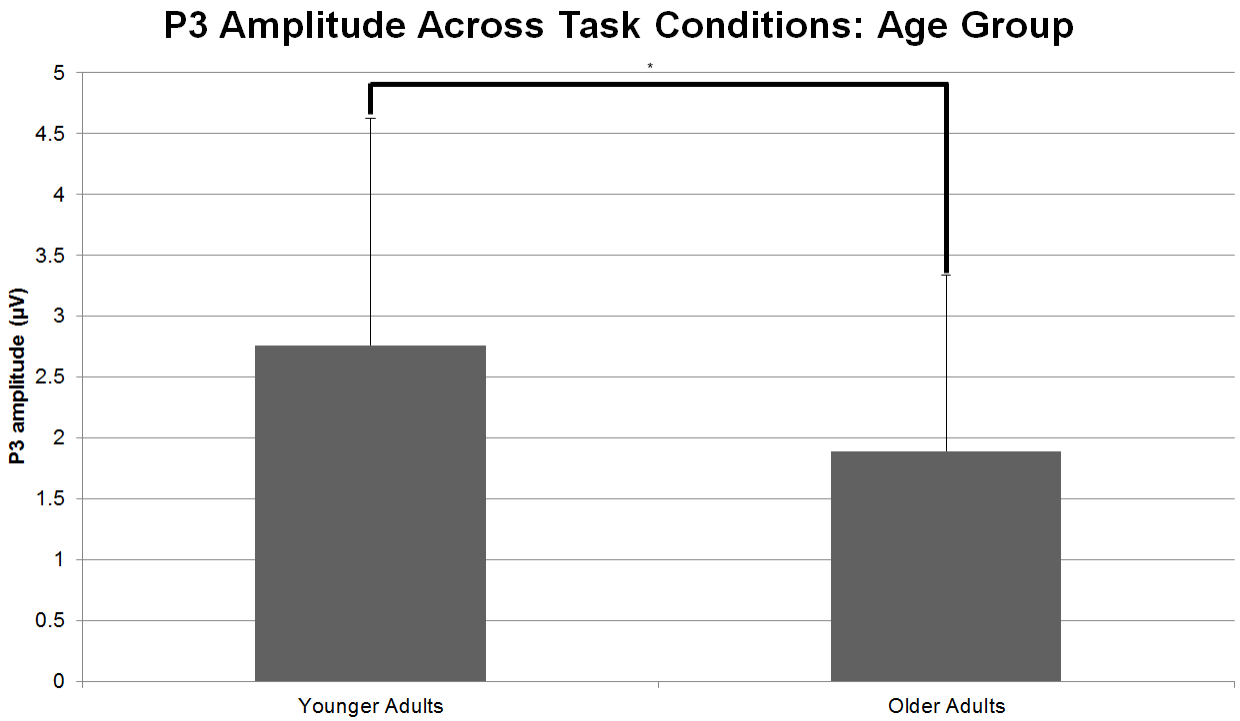

Figure 4-11. P3 Amplitude Across Task Conditions: Age Group

A main effect of age group was detected for P3 amplitude across task conditions, with amplitudes being significantly higher in younger than older Ss ($F_{1,78}$=5.94, p=0.02). Error bars depict standard deviations.

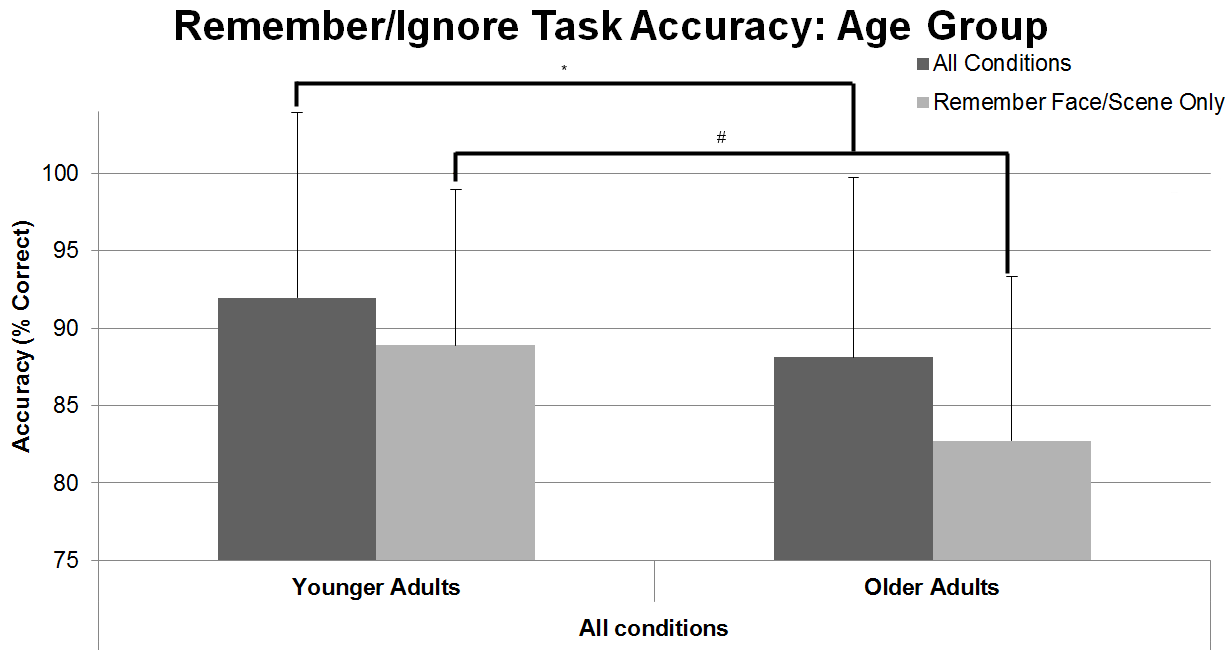

Figure 4-12. Remember/Ignore Task Accuracy: Age Group

2 (age group) X 3 (repeated: task condition) ANOVA revealed that accuracy across task conditions was significantly higher among younger than older Ss. T-tests showed this pattern was consistent when only those from the 'Remember Face' and 'Remember Scene' conditions were considered. Error bars depict standard deviations. *: $F_{1,258}$=10.05, p=0.002; #: t_{182}=4.03, p<.0001.

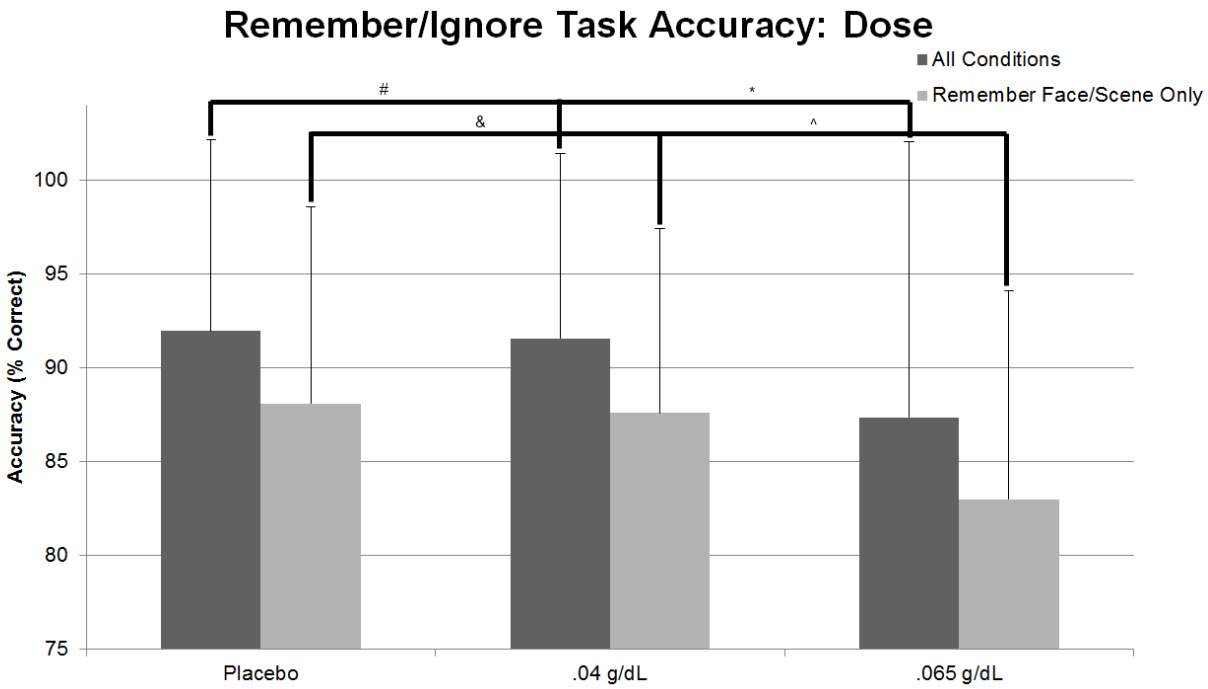

Figure 4-13. Remember/Ignore Task Accuracy: Dose

Accuracy in the 0.065 g/dL dose group was significant lower than both the placebo and 0.04 g/dL dose groups. This pattern was consistent when only responses from the 'Remember Face' and 'Remember Scene' conditions were considered. Error bars depict standard deviations. *: $t_{188}=3.06$, $p=0.002$; $^{\#}$: $t_{179}=3.00$, $p=0.003$; &: $t_{124}=2.66$, $p=0.009$; ^: $t_{118}=2.39$, $p=0.02$.

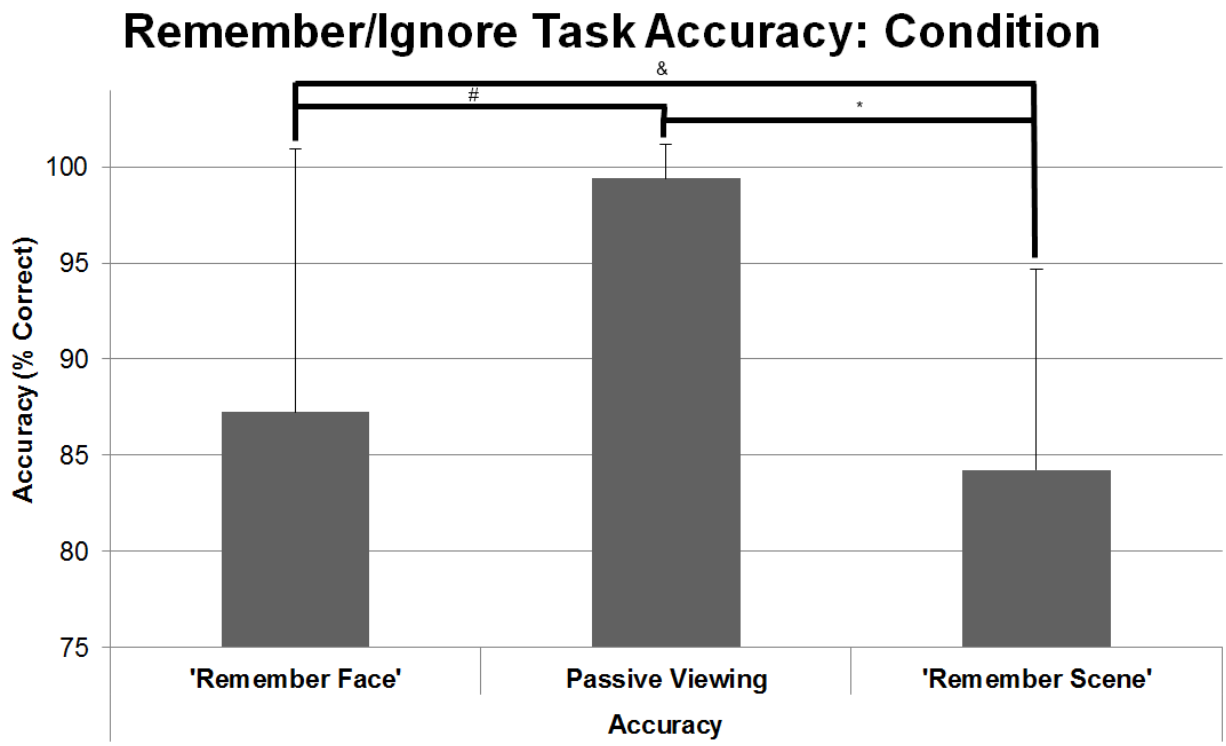

Figure 4-14. Remember/Ignore Task Accuracy: Condition

Accuracy under the Passive Viewing condition was significantly higher than the 'Remember Face' or 'Remember Scene' task conditions. Additionally, accuracy in the 'Remember Face' condition was significantly higher than in the 'Remember Scene' condition. Error bars depict standard deviations. *: $t_{183}=10.90$, $p<0.0001$; $^{\#}$: $t_{183}=8.89$, $p<0.0001$; $^{\&}$: $t_{183}=2.00$, $p=0.05$.

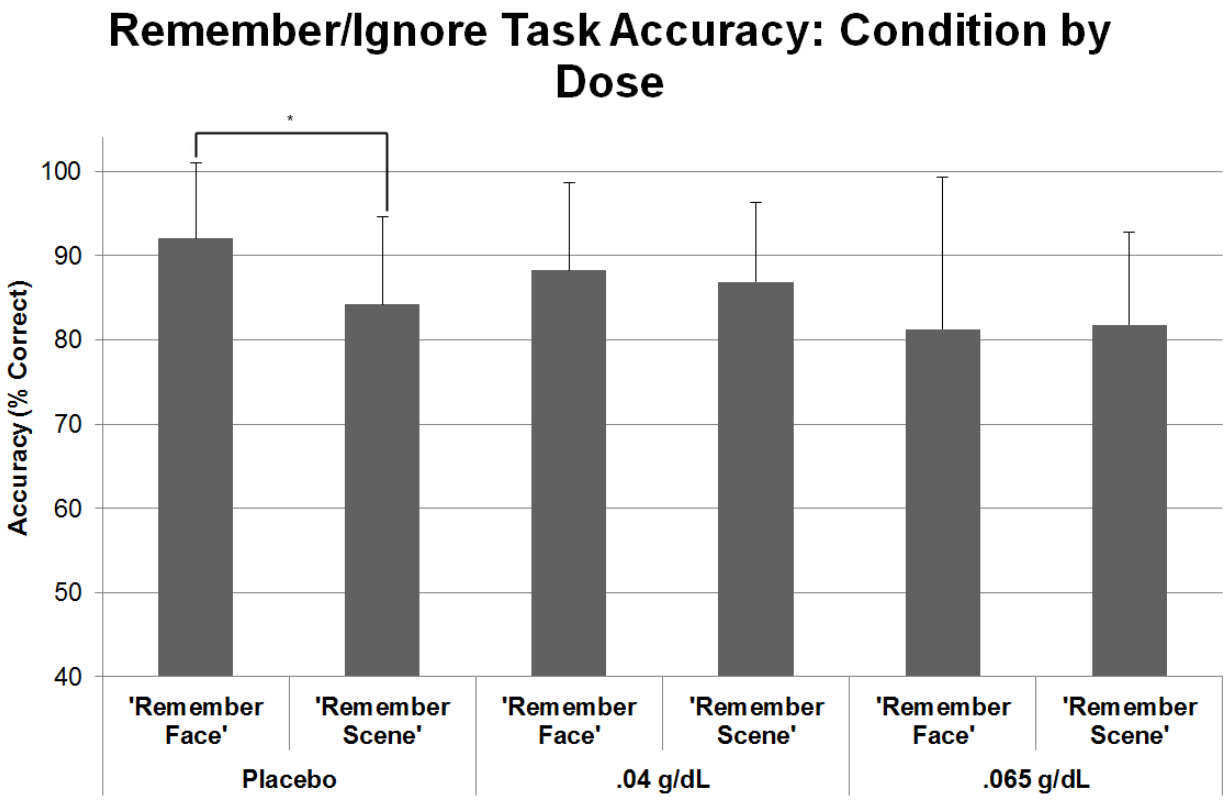

Figure 4-15. Remember/Ignore Task Accuracy: Condition by Dose

Under placebo, accuracy in the 'Remember Face' condition was significantly greater than in the 'Remember Scene' condition. However, this difference was lost under both active doses of alcohol. Error bars depict standard deviations. *: t_{63}=3.19, p=0.002.

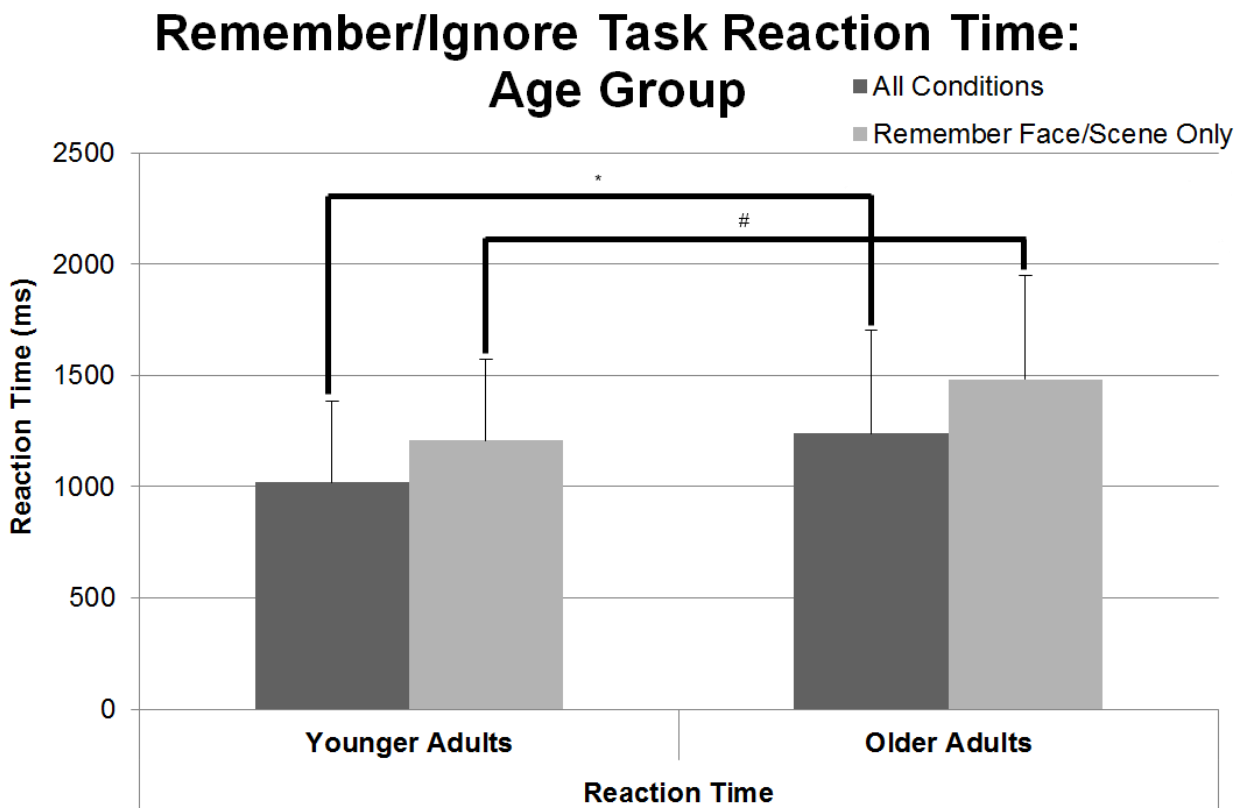

Figure 4-16. Remember/Ignore Task Reaction Time: Age Group

2 (age group) X 3 (repeated: task condition) ANOVA revealed younger adults had significantly faster reaction times than older Ss across task conditions. T-tests confirmed this effect remained when only responses from the 'Remember Face' and 'Remember Scene' task conditions were considered. Error bars depict standard deviations. *: $F_{1,258}=40.78$, $p<0.0001$; #: $t_{182}=5.74$, $p<0.0001$.

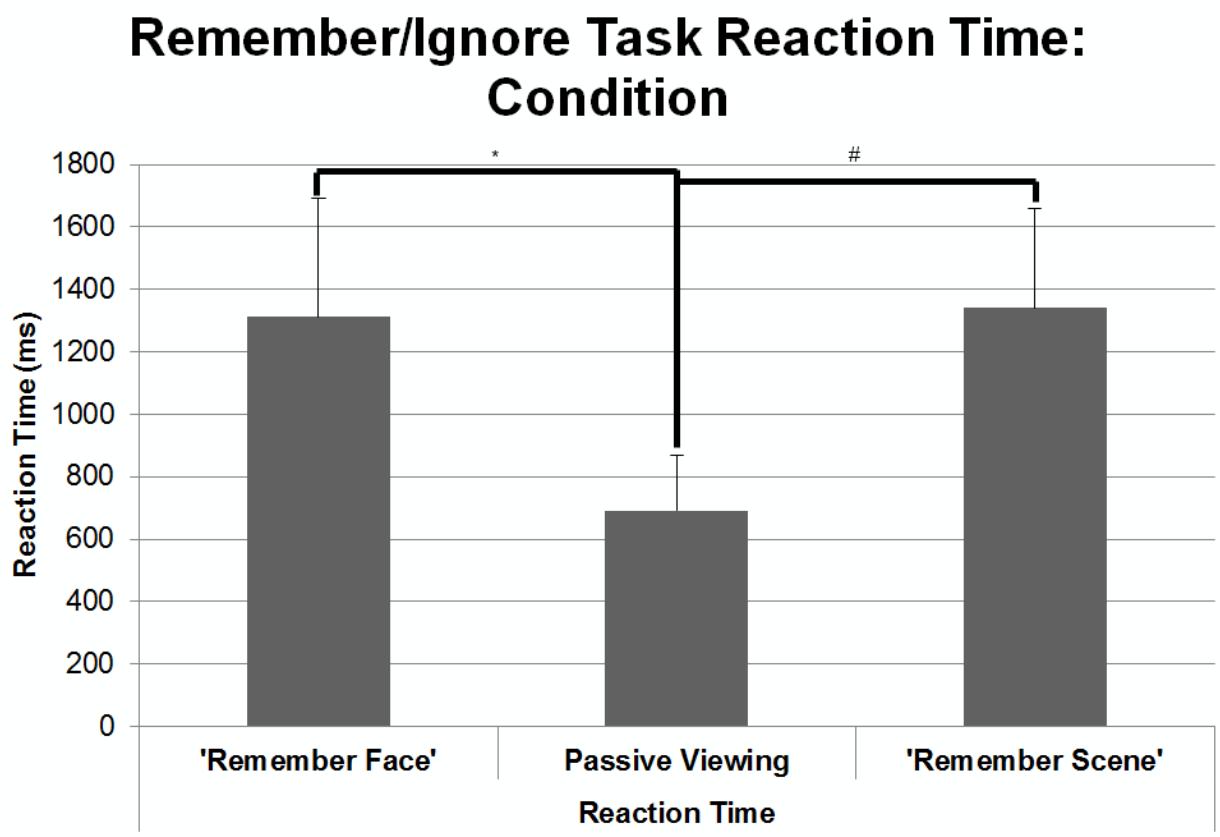

Figure 4-17. Remember/Ignore Task Reaction Time: Condition

Reaction times in the passive viewing task condition were significantly faster than either of the other task conditions, which did not differ from one another (t_{183}=0.65, p=0.52). Error bars depict standard deviations. *: t_{183}=15.01, p<0.0001; #: t_{183}=15.66, p<0.0001.

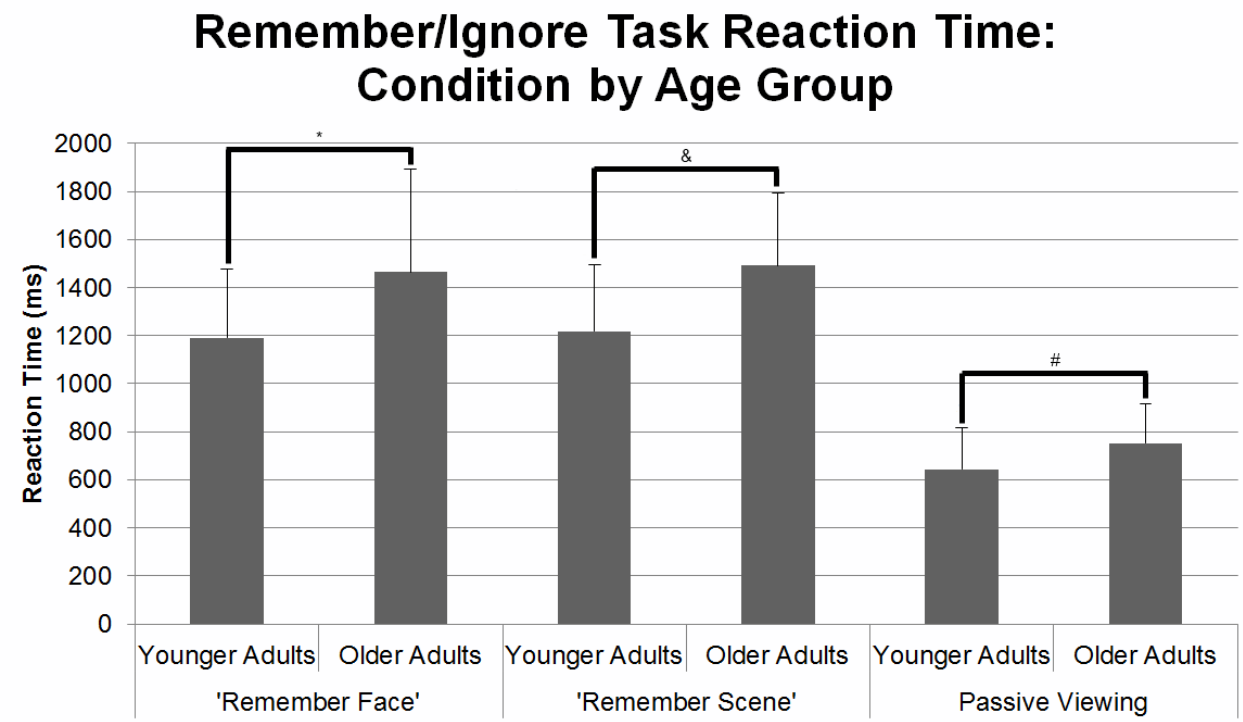

Figure 4-18. Remember/Ignore Task Reaction Time: Condition by Age Group

In the 'Remember Face' and 'Remember Scene' conditions, younger Ss had significantly faster reaction times than older Ss. While still trend-level, this difference was lessened in the Passive Viewing condition. Error bars depict standard deviations. *: $t_{91}=4.62$, $p<0.0001$; $^{\&}$: $t_{91}=4.63$, $p<0.0001$; $^{\#}$: $t_{91}=1.80$, $p=0.07$.

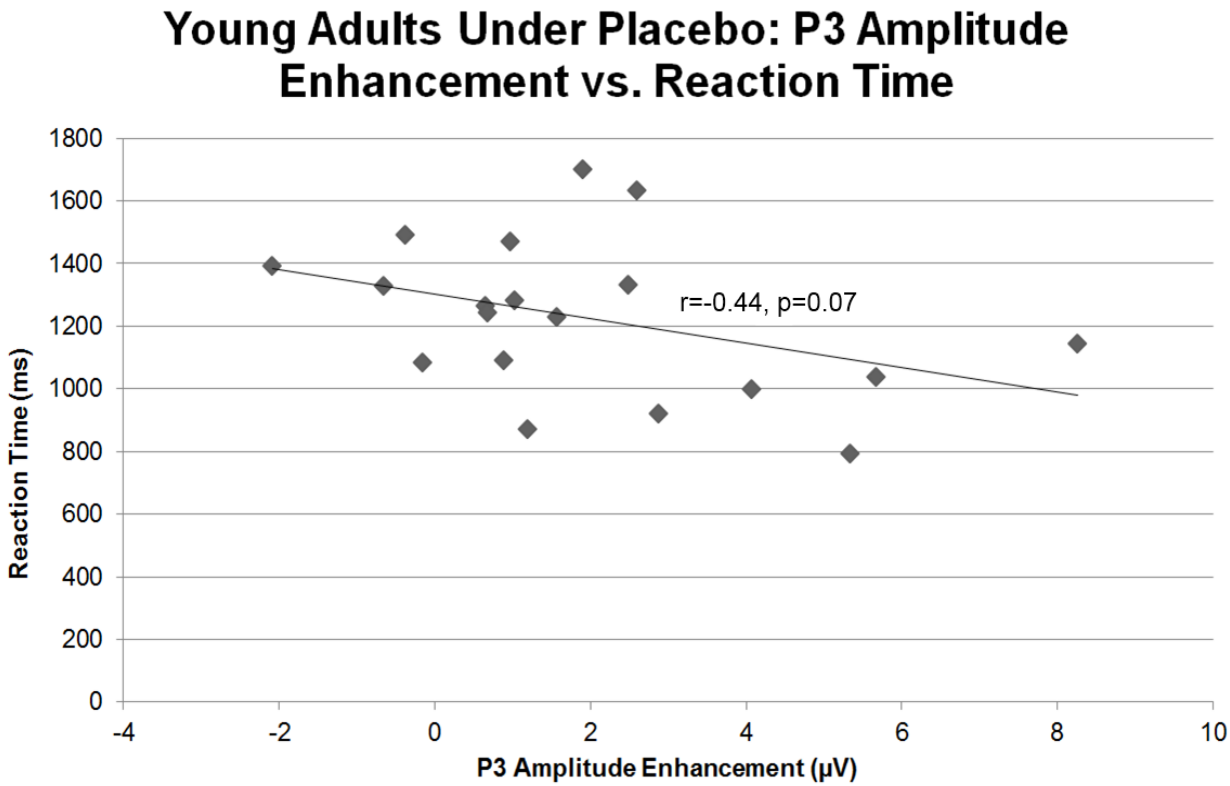

Figure 4-19. Young Adults Under Placebo: P3 Amplitude Enhancement vs. Reaction Time

A trend-level correlation between greater P3 amplitude enhancement and faster reaction time was noted for younger adults receiving a placebo beverage (r=-0.44, p=0.07). This relationship was not noted for other any other age or dose group (ps>0.15).

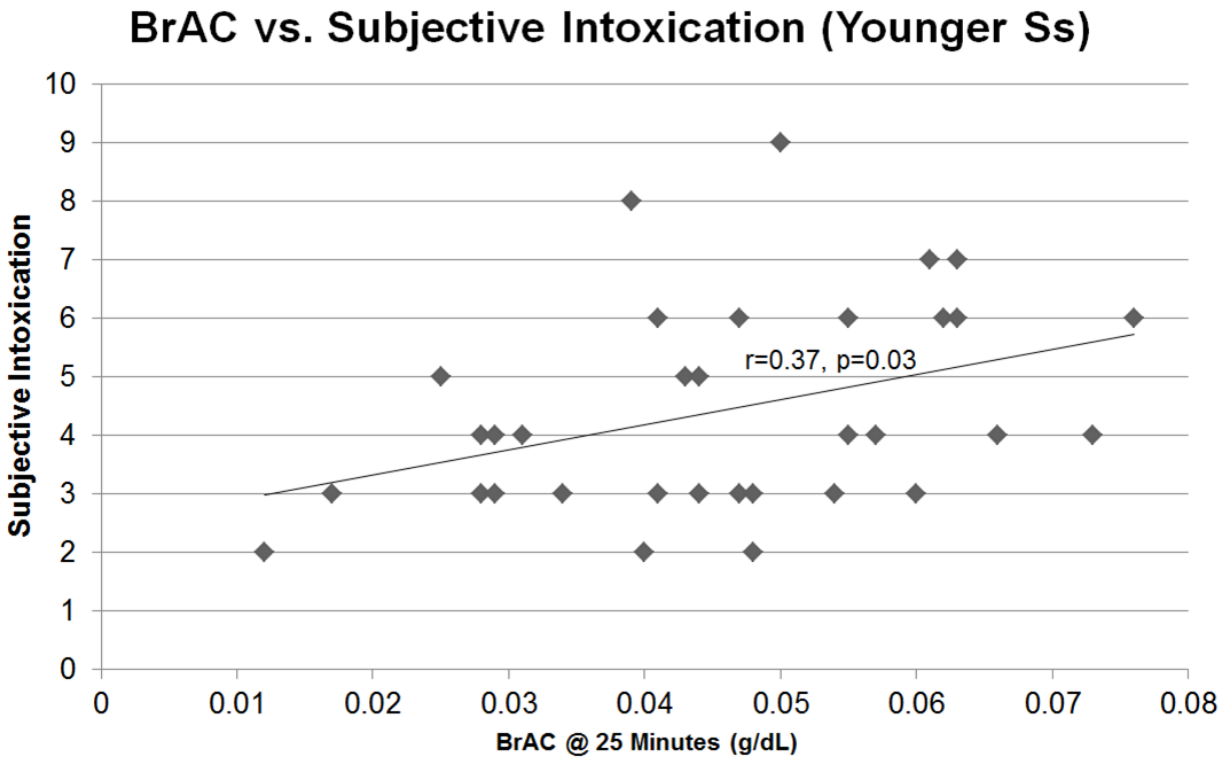

Figure 4-20. BrAC vs. Subjective Intoxication in Younger Ss.

Correlational analyses revealed that for younger but not older Ss, BrAC measures at 25 minutes were significantly associated with higher subjective intoxication (r=0.37, p=0.03).

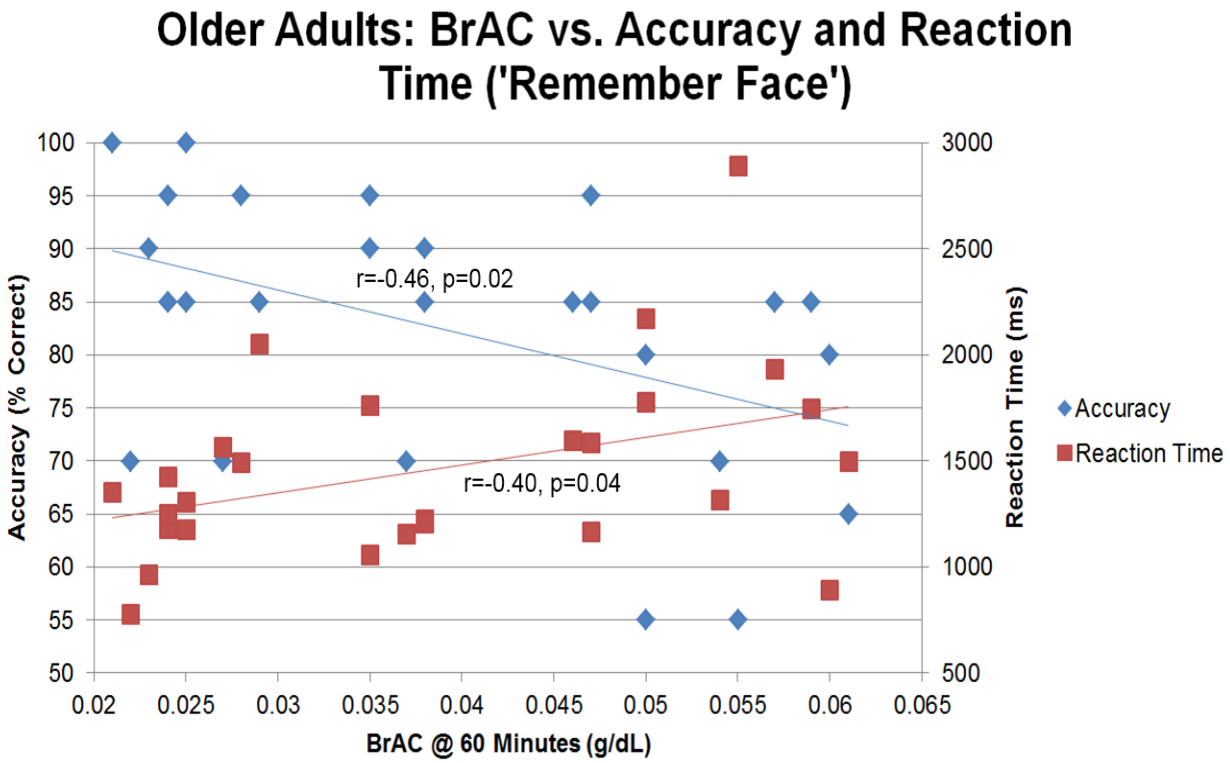

Figure 4-21. Older Adults: BrAC vs. Accuracy and Reaction Time ('Remember Face')

Correlation analyses revealed that BrAC measurements at 60 minutes post-beverage were significantly negatively correlated with accuracy (r=-0.46, p=0.02) and positively correlated with reaction time (r=0.40, p=0.04) in the 'Remember Face' task condition for older but not younger adults (ps>0.18).

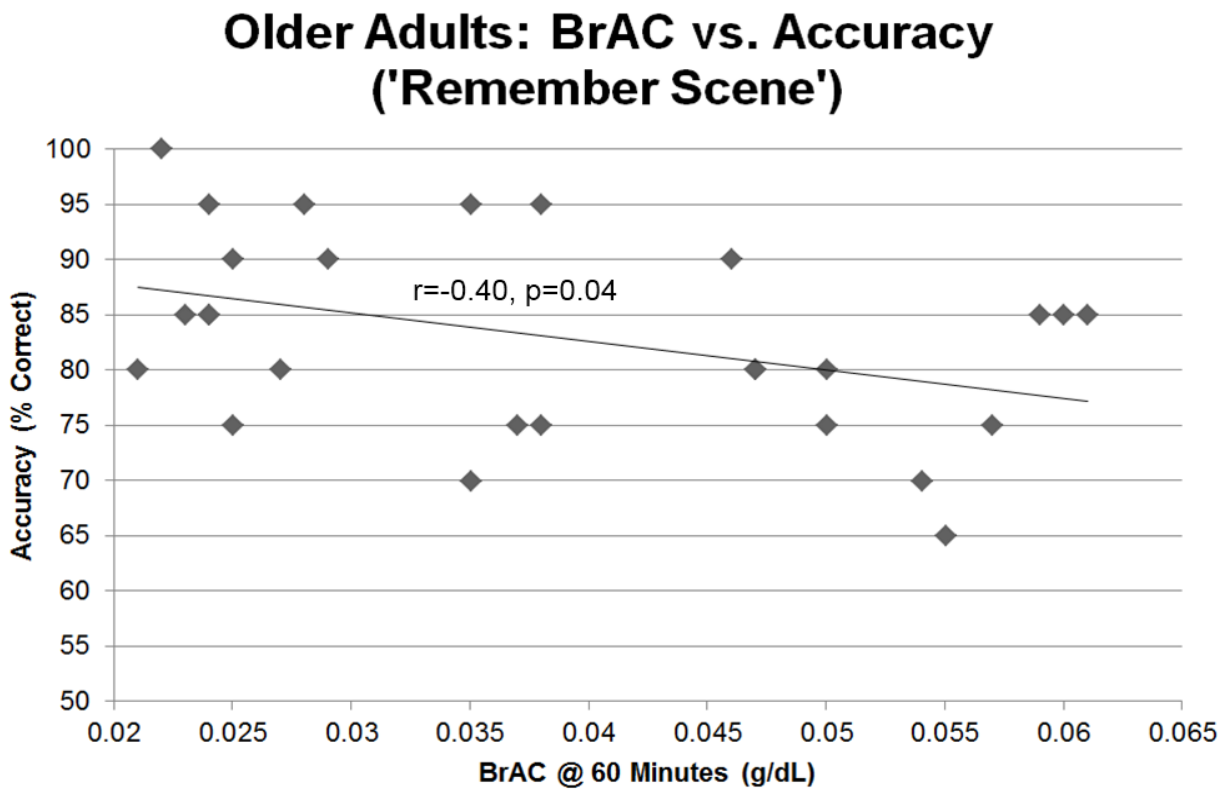

Figure 4-22. Older Adults: BrAC vs. Accuracy ('Remember Scene')

As in the 'Remember Face' task condition, BrAC measurements taken at 60 minutes post-beverage correlated with poorer accuracy in older, but not younger, Ss (r=-0.40, p=0.04).

CHAPTER 5
DISCUSSION AND CONCLUSIONS

Top-Down Attention

Findings pertaining to the effects of age and alcohol on suppression and enhancement are discussed first due to this study's focus on top-down attention. Because results indicated differences in patterns of alcohol and age effects on suppression and enhancement, these components of top-down attention are addressed separately.

Suppression

Consistent with our hypothesis, older Ss did not show suppression of any ERP measure regardless of alcohol condition. In contrast, younger Ss showed suppression of N1 latency under both placebo and active alcohol. These results are similar to those reported by Gazzaley et al. (2008). Despite similarities, some discrepancies were found. For example, Gazzaley and colleagues reported that younger Ss showed suppression for each ERP measure surveyed. Our sample of younger Ss did not show P3 or P1 amplitude suppression under either alcohol condition.

The reason for this discrepancy is unclear. Initial review suggested age was similar between samples, but other demographic details were not readily available for comparison. Because P1/P3 amplitude suppression were not apparent under placebo, our alcohol manipulation is unlikely to account for these differences.

We also predicted older Ss would be particularly susceptible to alcohol-induced disruption of suppression. Regression analyses provided no evidence supporting either an alcohol main effect or an interaction with age group on suppression. However, older Ss did not show suppression under either alcohol condition, and younger Ss showed

suppression under both. Therefore, it is not surprising that alcohol administration did not predict individual participants' degree of suppression.

Enhancement

Contrary to our prediction that enhancement would be less affected by alcohol and/or age than suppression, regression analysis indicated that alcohol administration disrupted enhancement in younger Ss. Unexpectedly, alcohol administration appeared to increase enhancement in older Ss. We suggest that moderate alcohol consumption may have resulted in 'alcohol myopia', or increased attentional focus on contextually relevant stimuli, in older Ss (Steele and Josephs, 1990).

Correlation of Top-down Attention with BrAC and Subjective Intoxication

Review of the relationship between alcohol levels and enhancement produced unexpected results; BrAC (but not subjective intoxication) correlated negatively with P3 amplitude enhancement in older Ss. This correlation was initially counterintuitive when considered in the context of alcohol myopia for older adults noted above; the negative relationship between alcohol level and enhancement suggests enhancement in older Ss was potentiated at low BrACs but disrupted at higher concentrations.

Correlation of Top-Down Attention with Working Memory Performance

Correlations between physiological indices of enhancement and suppression and working memory performance (accuracy and reaction time) produced mixed results. Results indicated a moderate, trend-level positive correlation between P3 amplitude enhancement and reaction time for younger adults receiving placebo. No other enhancement or suppression measure correlated with either behavioral outcome for either dose or age group. The absence of a significant positive correlation between enhancement and working memory performance in older Ss is interesting when

considered in the context of findings that alcohol increased enhancement for older Ss. Together, these findings that suggest although low-to-moderate alcohol intake may increase neurophysiological indicators of enhancement in older adults, corresponding behavioral effects are not observed.

ERP Characteristics

Although not of primary interest in this study, we expected age and alcohol would have effects on ERP characteristics irrespective of task condition. We also predicted that older Ss would be differentially sensitive to effects of alcohol on ERP characteristics. Unexpectedly, the active alcohol doses used in this study were not associated with decreased amplitude or increased latency of any examined ERP component. Furthermore, although evidence for the expected age-related reduction in P3 amplitude was detected, no age group by alcohol group interaction was noted. These findings contradict previous reports from our laboratory that older adults were particularly susceptible to disruption of P3 amplitude and latency by low doses of alcohol in a covert attention task (Lewis et al., in revision). It is possible that working memory processes tapped by the remember/ignore task used in the current study are relatively unaffected by the low-to-moderate levels of alcohol used in this study. Additional work is needed to characterize this discrepancy.

Working Memory Performance

We examined indicators of working memory performance (accuracy and reaction time) in order to determine whether behavioral consequences of moderate alcohol consumption were particularly evident for older Ss. Potential age-dependent correlations between working memory performance, BrAC, and subjective intoxication were also of interest.

Age and Alcohol Effects

Hypothesized age-related decrements in accuracy were detected; older Ss were less accurate than younger Ss across task conditions. In addition, accuracy under the 0.065 g/dL dose was significantly lower than both the placebo and 0.04 g/dL dose, suggesting a threshold effect of acute alcohol intake on working memory performance irrespective of age group. However, results did not reflect the predicted interaction of alcohol administration and age group.

Exploratory analyses revealed a hierarchy of difficulty for task condition, with the 'Remember Scene' condition being the most difficult, followed by the 'Remember Face' and passive viewing conditions. Task difficulty interacted with alcohol dose. Under placebo, accuracy in the 'Remember Face' condition was significantly higher than the 'Remember Scene' condition. Accuracy was equivalent between conditions under either active dose. This interaction suggests that across age groups, alcohol administration increased the functional difficulty of the 'Remember Face' task condition.

Predictably, younger Ss had faster reaction times than older Ss. However, this difference was mitigated in the passive viewing condition.

Correlation with BrAC and Subjective Intoxication

Earlier work led us to hypothesize that older Ss would demonstrate alcohol-related behavioral impairments uncorrelated with self-assessments of intoxication. As predicted, BrAC correlated with poorer working memory performance in older Ss. No such effect was detected for subjective intoxication measures. These data complement results from previous research showing that older Ss given a moderate dose of alcohol rated themselves as not intoxicated on the ascending limb, when impairments on a simple psychomotor task were apparent. However, on the descending limb, when

behavioral impairments were not detected, older Ss rated themselves as significantly intoxicated (Gilbertson et al., 2009).

Self-Assessment of Intoxication and Placebo Effectiveness

As noted in Specific Aim 2, potential age group differences in the ability to accurately judge one's level of intoxication were of interest. We hypothesized older Ss would experience dissociation between BrAC and self-assessments of intoxication. Our data supported this prediction, with older Ss showing no correlation between these measures. Younger Ss, in contrast, demonstrated a significant positive relationship between BrAC measures and subjective intoxication.

Preliminary analyses indicated that placebo effectiveness in this study was very high for older Ss (85%). High rates of placebo effectiveness for older adults have been previously reported (63%; Gilbertson et al., 2010). In contrast, we found that significantly fewer younger Ss receiving placebo reported having received alcohol (42%), a proportion consistent with previous literature examining placebo effectiveness in young adults (40%; Sayette et al., 1994).

The behavioral implications of placebo effectiveness for older Ss (e.g., Gilbertson et al., 2010, Fillmore and Vogel-Sprott, 1998) deserve further consideration. Because of the very high rate of placebo effectiveness for older Ss in this study, we were unable to appropriately examine this issue. However, subject accrual for this dissertation's parent project is ongoing. Therefore, this analysis may be reconsidered after additional older Ss have completed the laboratory session.

Study Caveats and Limitations

Age Range

We restricted ages for younger and older Ss to 25-35 and 55-70 years of age, respectively, in order to recruit two distinct populations with no overlap and because of our particular interest in the interaction between age and alcohol administration. As a result of this design, our data do not address alcohol effects on attentional function or working memory performance for adults between 35 and 55 years of age, or for those over 70. To address this limitation, future studies should include additional age groups.

Dose Range

Due to our interest in the effects of alcohol concentrations associated with moderate drinking events and to improve the feasibility of the study, we used two active dose levels: 0.04 g/dL and 0.065 g/dL. Additional work utilizing dose levels both above (≥0.08 g/dL) and below (~0.02 g/dL) would provide useful information about dose dependent effects of alcohol on attentional function and how these thresholds may differ between younger and older Ss.

Sex Differences

As reviewed in Chapter 2, physiological differences between men and women underlie a greater vulnerability of women to alcohol-related health consequences. It is poorly understood whether physiological differences between sexes may also drive a differential effect of acute moderate alcohol on attentional function and working memory performance. Thus, the potential interaction of sex with alcohol administration and age is of interest. Limitations of the current sample prevent meaningful analysis of sex effects and interactions. However, this study's parent project is powered to address this concern.

Task Limitations

Because of this project's focus on attentional function and subsequent working memory performance, only data from the remember/ignore task were considered in the current analysis. Results suggested important differences in the effects of low-to-moderate alcohol administration on attentional function between older and younger adults. However, further work with additional tasks is needed to characterize whether age and moderate alcohol use have similar effects on other aspects of neurocognitive function.

Cross-sectional Design

Finally, although results of this dissertation suggest that age-related deficits in top-down attention may be present in a group of older Ss around 60 years of age, its cross-sectional design does not provide information regarding the age-related trajectory of these deficits.

Overall Summary

In addition to providing partial replication of age-related deficits in top-down attention (Gazzaley, 2011), this study provides critical information regarding the effect of acute low-to-moderate alcohol intake on performance in both older and younger adults. Alcohol did not appear to affect younger Ss' ability to modulate top-down attention, and those young Ss receiving placebo who enhanced attention to relevant stimuli tended to have better working memory performance.

In contrast, older Ss who received alcohol were able to enhance attention to contextually relevant stimuli but did not show corresponding improvement of behavioral performance. Although interesting, the explanation for this differential effect of alcohol

on neurophysiological measures as opposed to behavior is unclear. Older Ss also appeared unable to effectively judge their level of alcohol-related intoxication.

Taken together, these data provide new information about the acute effects of alcohol concentrations typical of moderate drinking events on attentional function and working memory performance in older adults. It is unknown if older adults are at higher risk for moderate alcohol-induced injury or health-related consequences as a result of these effects. Further investigation to address this possibility involving a greater number of participants and including complex behavioral tasks is underway.

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BIOGRAPHICAL SKETCH

Jeffrey Boissoneault was born in 1985 in Gainesville, FL. He graduated from Eastside High School in 2003 and earned a Bachelor of Arts degree in biology from New College of Florida in 2007. During his undergraduate education, he developed an interest in the intersection of neurobiology and substance use which has only grown during the process of earning his Ph.D. in biomedical science with a concentration in cognitive neuroscience.

Upon completion of his Ph.D., Jeffrey plans to continue in Dr. Nixon's laboratory as a Post-Doctoral Associate and to pursue funding for additional training in neuroimaging techniques. Outside of the laboratory, he is an avid rock climber and weight lifter and enjoys spending time with friends and family.