SEX DIFFERENCES IN THE BEHAVIORAL EFFECTS OF ACUTE MODERATE ALCOHOL ADMINISTRATION AMONG OLDER ADULTS

By

LAUREN ASHLEY HOFFMAN

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To my brilliant and loving father

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By

Lauren Ashley Hoffman

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A lifestyle of moderate drinking may benefit the health of older men and women. However, essentially no work has been published documenting sex differences in the immediate behavioral effects of acute alcohol administration on older adults. The current project observed the differential behavioral effects of acute moderate/low dose alcohol on older men and women. Dose, sex, and behavioral effects were assessed.

Sixty-two older (ages 55-70) male and female, healthy, moderate drinkers were randomly assigned to dose groups to achieve a peak breath alcohol concentration (BrAC) of 0mg/dL (placebo), 40mg/dL (low), or 65mg/dL (moderate). Subjects (Ss) complete tasks assessing psychomotor performance (Trail Making Test Part-A; i.e. TMT-A), set-shifting (Trail Making Test Part-B; i.e. TMT-B), and working memory (i.e. WMT). The WMT consisted of a remember ‘face condition’ and a remember ‘scene condition’. Time to complete TMT-A&B and accuracy and reaction time for the WMT were recorded.

Results indicate that the low dose facilitated WMT performance relative to the moderate dose. A condition by dose interaction revealed that the low dose group responded more efficiently than the placebo or moderate dose groups under the ‘face

condition'; no significant difference existed between the placebo and active doses. Sex differences revealed that women exhibited better set shifting skills, whereas men responded more efficiently on the WMT.

These data provide new information on sex differences in the immediate behavioral effects of low/moderate dose alcohol among older adults. Further investigation is necessary to determine the effect of sex on acute alcohol consumption and subsequent behavior.

CHAPTER 1
MODERATE DRINKING

In the United States, alcohol is a widely consumed substance that is often underreported in epidemiological studies, with self-reported measures of alcohol use accounting for only 22-32% of the alcohol sold (Kanny et al., 2012). According to the National Survey on Drug Use and Health, 80% of American adults report lifetime use of alcohol and 50.1% report having consumed at least one alcoholic beverage in the past 30 days (Substance Abuse and Mental Health Services Administration, 2006).

The negative consequences of chronic excessive alcohol consumption often affect individuals relatively early in life. Therefore, alcohol is considered the leading risk factor for burden of disease and mortality among individuals aged 15-59 world-wide (World Health Organization, 2004). Furthermore, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) suggests that recurrence of binge drinking behaviors, defined as >5 drinks in a single sitting for men and >4 for women, may lead to negative health consequences (National Institute on Alcohol Abuse and Alcoholism, 2005; Chen et al., 2006).

In response to these issues, the United States Departments of Agriculture and Health and Human Services published guidelines for low-risk drinking (2010). These “Dietary Guidelines for Americans” defined moderate, low-risk drinking as no more than one standard drink per day (i.e. ≤ 7 drinks/week) for women and no more than two drinks per day (i.e. ≤ 14 drinks/week) for men. Additionally, NIAAA suggests that men and women age 65+ should limit their alcohol intake to no more than one drink per day (2005). A single standard drink is defined as 12 ounces of beer containing 5% absolute ethanol, 4-5 ounces of wine containing 12-17% ethanol, or 1.5 ounces of 80-proof spirits

(Dufour et al., 1995; NIAAA, 2010). However, these drinking guidelines are considered liberal for certain populations (e.g. pregnant or breastfeeding women, children and adolescents, or those taking medications that might interact with alcohol, etc.; Dawson & Grant, 2011).

The importance of adhering to the alcohol consumption guidelines is confirmed by several studies that provide detailed information regarding the psychosocial and medical consequences associated with the long-term chronic consumption of alcohol at levels outside the moderate range (e.g. Dawson & Grant, 2001). Chronic excessive alcohol use has been related to over 60 different medical conditions (Room et al., 2005). For example, recurrent binge drinking or heavy drinking (i.e. frequent episodes of binge drinking) is associated with increased risk for unintentional injury or death, liver disease, pancreatitis, cardiovascular disease, and altered brain function (Li, 2008). Moreover, alcohol consumption at a rate of 30-60 g of alcohol per day (~2-4 standard drinks) over the course of ~6 years has been associated with a 41% increase in the risk of breast cancer among women. Interestingly, compared to moderate drinkers, abstainers and heavy drinkers are at greater risk of developing conditions such as coronary heart disease and diabetes mellitus (Room et al., 2005).

Alcohol consumption at moderate levels may benefit certain populations. A moderate drinking lifestyle (i.e. chronic consumption of alcohol at moderate levels) has been associated with reduced risk for cardiovascular disease, osteoporosis, and dementia, among other conditions (Suzuki et al., 2009; Poli et al., 2013). However, the beneficial effects of moderate alcohol consumption are not generalizable to the entire population. Demographics, physical/mental health status, and other important variables

should be accounted for when considering the risks/benefits of moderate alcohol consumption.

Moderate Alcohol's Effects

Alcohol consumption, even at moderate levels, has been shown to affect cognitive functioning, physical health, and mental status. Importantly, acute (i.e. an individual drinking session) and chronic (i.e. drinking moderate levels of alcohol over the lifespan) moderate alcohol consumption may affect the brain and body differently (Nixon, 2009). Whereas many of the effects of chronic alcohol consumption are health related, the effects of acute consumption are often defined by alcohols immediate effects on cognition and performance.

Chronic Moderate Drinking

As noted above, a lifestyle of moderate drinking has been shown to have a protective effect against the development of several diseases and conditions (Suzuki et al., 2009). Specifically, it is shown to reduce the risk for hypertension, upper respiratory infections, gallbladder and renal stones, osteoporosis, age-related macular degeneration and cognitive decline. Furthermore, a moderate drinking lifestyle may defend against autoimmune disorders such as rheumatoid arthritis, overt hypothyroidism, and systemic lupus erythematosus (Carle et al., 2012). The nature of this relationship for select conditions is detailed below.

One of the most well known benefits of light to moderate alcohol consumption is its protective effect against coronary heart disease in middle-aged and older adults. This effect can be best described as a J shaped curve, where those who abstain and those who drink heavily are at greater risk than those who drink moderately (Hvidtfeldt et al.,

2013). These authors also showed that the J shaped curve applies to the relationship between alcohol intake and diabetes mellitus.

The association between alcohol consumption and osteoporosis is best characterized as a U shaped curve (Polli et al., 2013). Chronic heavy drinking and abstinence are associated with the development and progression of osteoporosis. Alternatively, those who consume one to two drinks per day exhibit the greatest bone mineral density and the lowest bone turnover markers. These protective effects exist for both men and women; yet, women seem to experience more benefits with reference to higher bone mineral density (Polli et al., 2013). In a study performed by Rapuri and colleagues (2000), postmenopausal, moderate drinking women had 5-10% greater bone mineral density than abstainers. Although the mechanism is unclear, one theory posits that alcohol stimulates estrogen production and in turn, suppresses the breakdown of bone by osteoclasts, resulting in greater bone mineral density (Tucker, 2009).

Among healthy older adults, low-risk, moderate drinking is thought to stimulate appetite and promote regular digestive functioning. Furthermore, compared to those who abstain, moderate drinkers may experience higher levels of cognitive functioning (Lang et al., 2007). In a review by Verbaten (2009) it was reported that older adult moderate drinkers, aged 60+ years, showed better neurocognitive functioning compared to abstainers. Additionally, Lang and colleagues (2007) revealed a significant positive association between chronic moderate alcohol consumption and performance on tasks assessing recall and numerical reasoning among older male and female moderate drinkers, 60 years of age and older.

Recent evidence has suggested that moderate alcohol intake may delay age associated cognitive decline and protect against late-onset and incident dementia (Gu et al., 2010). Ganguli et al. (2005) observed that adults aged 65 years and older, who consumed moderate amounts of alcohol, had significantly higher levels of cognitive performance and significantly lower levels of cognitive decline compared to abstainers and heavy drinkers. Several theories have been proposed to explain this pattern. One hypothesis is that flavonoids in wine have antioxidant properties, reducing oxidative damage normal to the aging process. Another proposal is that moderate alcohol protects against cognitive decline via its preventative effects for ischemia or stroke (Lobo et al., 2010). At this time, no definitive conclusion exists.

Data imply that light to moderate older adult drinkers (~56+ yrs.) have better overall mental health compared to nondrinkers (e.g. fewer incidents of depression, anxiety, etc.; Green et al., 2004). Declines in physical and cognitive abilities are a part of the normal aging process that may cause older adults to experience an increased prevalence of depressive symptomatology. Depression among older adults has been associated with increased mortality and poorer health outcomes following illness (Fogel, 1991; Lang et al., 2007). However, moderate drinking has been found to have beneficial effects on mood; promoting feelings of happiness and well-being while reducing feelings of stress, tension, and depression. Therefore, older adults may experience mental health benefits from moderate alcohol through the enhancement of emotional well-being (Dufour et al., 1992).

Taken together, the consumption of alcohol at moderate levels may prove beneficial to certain populations. Nevertheless, the advantages of moderate alcohol use

may vary based on individual differences in mental and physical health (e.g. preexisting conditions such as stomach ulcers, diabetes, etc.). Importantly, the beneficial effects of moderate alcohol use are evident, but not equivalent for men and women. Women typically show curves shifted to the left, exhibiting greater health related risk, compared to men, with equivalent amounts of alcohol consumption (Corrao et al., 2000). However, the effects of moderate alcohol consumption on the brain and cognitive function among older adults are relatively underexplored. Even though health professionals do not promote the initiation of drinking in non-drinking older adults, there is evidence for its long-term benefits. However, it is important to note that age groups are inconsistently defined in the alcohol literature. For example, some studies define older adults as 65+ years of age, whereas other studies use populations as young as 50. Consequently, much of the literature addressing alcohol consumption among the older adult population is inconclusive and/or has limited generalizability due to systematic differences in population characterization.

Acute Drinking

Research addressing the immediate, cognitive effects of acute alcohol administration varies by dose. Some acute alcohol studies target BrACs above the legal limit of intoxication for operating a motor vehicle in the US (> 0.08%). Studies addressing acute moderate drinking, intended to mimic social moderate drinking episodes, typically use target breath alcohol concentrations (BrAC) of 0.065% (g/dL) or lower. The acute consumption of alcohol has been repeatedly shown to cause changes in performance for both simple and complex tasks.

Acute drinking: high doses

Studies of acute alcohol administration targeting BrACs above ~0.065%, reveal impairments in several domains including 1) psychophysical abilities; 2) reaction time; 3) memory; 4) cognitive control as evidenced in divided attention or hand eye coordination; 5) attentional set-shifting (an attentional switch from one perceptual dimension, to a novel one; see Chapter 2 for a more thorough definition); and 6) gait and performance in simulated driving scenarios (Holloway, 1994; Lyvers and Maltzman, 1991; Weissenborn & Duka, 2002). Cognitive neuroscience has linked these alcohol induced deficits to particular brain areas through the use of established behavioral tasks. See Table 1-1 for a depiction of these deficits, their structural correlates, and the tasks used to assess them.

One example of these acute alcohol induced deficits is reported in an article by Weissenborn and Duka (2003), in which the authors reported that a mean BrAC of ~0.07% resulted in impaired planning and increased impulsivity. Additionally, Fillmore and colleagues have observed an impaired ability to inhibit a pre-potent response (on the ascending and descending limbs of the BrAC curve) and slowed reaction times in go/no-go tasks at BrACs of ~0.08% (Fillmore and Weafer, 2004; Marczinski and Fillmore, 2003; Weafer and Fillmore, 2012). Taken together, it is evident that frontal lobe functioning is altered with BrACs above ~0.065%, ultimately affecting inhibition, planning, and reaction time.

Furthermore, studies illustrate that impaired frontal lobe functioning due to high dose alcohol administration may be mediated by working memory. Those with poorer working memory are more likely to experience alcohol related impairments on tasks dependent upon the frontal lobes, such as those requiring learning (e.g. button presses,

which stimuli to respond to, etc.; Soderlund et al., 2005). Several memory processes are thought to be impaired by acute high dose alcohol consumption. For example, among a sample of men, BrACs of ~0.08% resulted in alcohol induced impairments in immediate recall on a task modeled after the logical memory subsection of the WAIS-R (Moulton et al., 2005; Wechsler, 1987). Additionally, Weissenborn and Duka (2000) demonstrated that the consumption of alcohol (BrACs ~0.07%) before encoding/retrieval resulted in global impairments in free recall among male and female participants.

Planning, inhibition, reaction time, and memory are some of the most commonly studied domains affected by high dose alcohol administration (BrACs > 0.065%). Whereas the effects of higher doses of acute alcohol consumption are widely noted, low dose acute alcohol has been less frequently explored.

Acute drinking: low doses

Literature addressing acute moderate/low dose alcohol (i.e. BrAC ≤ 0.065%) has been somewhat inconsistent. However, low doses of alcohol have been associated with a host of impairments in various domains of cognitive functioning.

Deficits in psychomotor skills such as hand-eye coordination and simple reaction time begin to emerge at BrACs as low as 0.04% (Eckardt et al., 1998; Field et al., 2010). Additionally, low dose alcohol consumption has been shown to affect recognition memory. Bisby et al. (2009) reported significant impairments in verbal recognition memory at BrACs as low as 0.059%. Studies have found that doses resulting in BrACs as low as 0.02% can cause individuals to falsely remember significantly more items on recognition memory tasks, compared to placebo doses (Milani & Curran, 2000).

Impairments on tasks engaging the frontal lobes may be particularly sensitive to low dose alcohol administration (Field et al., 2010). Acute low dose alcohol consumption can impair executive functioning important for planning, working memory (i.e. ability to store and manipulate information as it is being presented), cognitive flexibility (i.e. ability to mentally switch between concepts despite schedules of reinforcement), and complex behavioral control (see Chapter 2 for a more thorough definition of these concepts; Oscar-Berman & Marinkovic, 2007). A review by Fillmore (2007) reveals consistent deficits in executive function as a result of low dose alcohol administration. Impairments are reliably observed at BrACs below 0.065% for tasks assessing top-down (controlled and effortful; see Chapter 2) attention and multitasking abilities. For example, Schulte et al. (2001) found that a BrAC of ~0.06% increased reaction times and number of errors on a task that required participants to attend to and identify irregularities in visual and auditory stimuli. Furthermore, low dose alcohol consumption may increase impulsivity. de Wit and colleagues (2000) observed increased levels of impulsivity on a stop-signal task at BrACs as low as ~0.06% (compared to placebo).

Another important function affected by acute low dose alcohol is cognitive flexibility, which can be assessed by one's ability to set-shift. Set-shifting is the capability to switch between thinking about two different concepts and to display flexibility when schedules of reinforcement are altered (Field et al., 2010). Lyvers and Maltzman (1991) assessed this ability among moderate social drinkers using the Wisconsin Card Sorting Test. They demonstrated that those with BrACs of ~0.05% were significantly more impaired than those who received the placebo; ultimately making more errors indicative of inappropriate implementation of a sorting strategy that was

previously reinforced but no longer suitable. This impairment demonstrates one of the many detrimental effects that acute low doses of alcohol have on frontal (executive) function. Therefore, alcohol administration at low and moderate doses may significantly impair executive functioning dependent upon the frontal lobes, such as attention, working memory, and inhibition, without an observable global impairment in cognitive functioning (Field et al., 2010).

Older Adults & Acute Moderate Drinking

Much of the acute alcohol literature is derived from studies of younger adults (e.g. Fillmore, 2008) and high doses of alcohol (i.e. BrACs ≥ 0.065%; e.g. Vogel-Sprott, 1984). Therefore, relatively little is known about the neurocognitive effects of low dose alcohol (i.e. BrACs ≤ 0.065%) consumption on older adults (i.e. adults aged 50+). Research conducted in our laboratory suggests that older and younger adults might experience the acute effects of moderate alcohol on cognition and behavior differently.

General deficits in attentional processing (e.g. covert visual attention and set-shifting) have been observed among older adults (age ~50-74) at BrACs as low as 0.04% (Gilbertson et al., 2010; Gilbertson et al., 2009). Recent work has found that older adults show speed/accuracy tradeoffs (measured by efficiency: % accuracy/ average reaction time) at BrACs of 0.05% when performing the Posner paradigm, a covert visual attention task (Sklar et al., 2012). Additional research from our laboratory has revealed that older adults (mean age 57±6.8) show impairments in psychomotor and set-shifting performance on the Trail Making Test (TMT; Reitan and Wolfson, 1993) at BrACs of ~0.05% (Gilbertson et al., 2009).

However, inconsistent findings have emerged from acute low-dose alcohol studies. Using a different sample of older moderate drinkers aged 55-70, our laboratory

demonstrated a facilitative effect on psychomotor performance with the TMT at target BrACs of ~0.04% (compared to placebo and ~0.065%; Boissoneault et al., under review). The faciliatory effects of this concentration have also been observed for tasks assessing working memory. Older adults have been shown to more accurately recognize previously presented face stimuli in a remember/ignore task at a BrAC of ~0.04% compared to ~0.065% and placebo (.0%). In tasks assessing reaction time and efficiency, older adults are shown to exhibit the longest reaction times and the least efficiency at ~0.065% (compared to placebo and 0.04%; Boissoneault et al., under review). However, further investigation and replication of these findings is necessary to fully understand the effects of acute low dose alcohol consumption on older adults.

Alcohol Metabolism

The BrAC obtained following ethanol consumption varies depending on the rate of alcohol absorption (from the gastrointestinal tract to the bloodstream), the volume of alcohol distribution (determining alcohol bioavailability), and the rate of elimination (in the liver; Mumenthaler et al., 1999). Although not the focus of the current project, we present an overview of alcohol metabolism in the interest of completeness.

Alcohol absorption is dependent upon the concentration of alcohol consumed, the amount and type of food in the stomach, and the rate of action in the gastrointestinal tract. Alcohol passes from the stomach and small intestine into the blood, a process referred to as absorption. The rate of gastrointestinal absorption will determine the amount of alcohol in the main circulatory system and the resulting BrAC. A greater amount of food in the stomach will slow gastrointestinal absorption and cause a slowly rising BrAC. Alcohol that has gone through the absorption process then travels to the liver via the portal vein where it is converted to acetaldehyde by alcohol dehydrogenase.

There, other enzymes convert acetaldehyde to acetate, which is eventually metabolized into carbon dioxide and water.

Notably, acetaldehyde is poisonous when presented to the body in large quantities. Therefore, the liver may reach maximum performance (i.e. maximum levels of acetaldehyde), resulting in a small portion of alcohol to be distributed among the body water content in the bloodstream and in fluid in and between cells. This small quantity of unmetabolized alcohol allows one to measure alcohol concentration in breath and urine (see Mumenthaler et al., 1999 for a more thorough overview). Importantly, the intake of medications metabolized by the liver may alter the capacity of the liver to metabolize alcohol. Therefore, the consumption of other substances should be considered, especially among populations that typically consume prescription and over-the-counter medications, such as older adults.

Older adults and alcohol metabolism. As the body ages, body fat content increases and body water content decreases. Because alcohol solubility is heavily dependent upon body water, these changes are thought to result in an increased sensitivity to alcohol (i.e. higher BrACs; Dufour et al., 1995). Therefore, a smaller volume of distribution will result in a higher BrAC in an older adult compared to a younger adult who received an equivalent dose of alcohol (Dufour et al., 1995; Davies and Bowen, 2006). Importantly, studies addressing the effects of alcohol on older and younger adults can control for these differences in metabolism and achieve equivalent BrACs by administering alcohol doses that account for height, weight, sex, and age (e.g. Sklar et al., 2012).

Sex Differences in Moderate Alcohol Consumption

Although the general mechanisms of alcohol are comparable between men and women, alcohol's metabolism, its effects on cognition, and its health related consequences may be dependent upon sex. However, the influence of sex remains somewhat unclear and alcohol's differential effects on men and women remain largely underexplored in the literature. It has been long thought that when administered equivalent amounts of alcohol, adjusted for body weight, women reach higher BrACs compared to men (e.g. Jones and Jones, 1976; Niaura et al., 1987). Additionally, previous research has suggested that women may be more susceptible to the impairing effects of alcohol on cognitive functioning (e.g. worse performance on tasks assessing immediate and delayed recall, divided attention, and visual scanning compared to men; Miller et al., 2009). Nonetheless, recent evidence may indicate otherwise, emphasizing the importance of the task and alcohol dose administered when observing apparent sex differences (see Weissenborn and Duka, 2003 and Nixon et al., in press).

Biology & Pharmacokinetics

Differences in alcohol metabolism among men and women are complex and many of the topics surrounding alcohol metabolism remain controversial. However, research hints at mechanisms that may contribute to sex differences in alcohol metabolism. Importantly, the following is not meant to be a comprehensive review of the literature. A narrow range of topics will be discussed in an effort to draw awareness to some of the biological differences that exist between men and women and that may affect alcohol consumption (see Thomasson, 1995 and Holmila & Raitasalo, 2005 for a more thorough review).

Research has previously demonstrated that women have increased bioavailability (i.e. degree of alcohol availability to target tissues), faster disappearance rates (i.e. the rate at which BrACs decrease), and slightly decreased gastric alcohol dehydrogenase activity (i.e. breakdown of alcohol in the gastric system) than men, when consuming equivalent amounts of alcohol. Furthermore, the proportion of body fat to water content is higher in women compared to men, at equivalent body weights. Therefore, women are thought to reach higher BrACs compared to men when equivalent amounts of alcohol are consumed and when doses are body weight dependent (Mumenthaler et al., 1999). Importantly, higher peak BrACs are not consistently observed among women (see Weissenborn and Duka, 2003; Marczinski et al., 2008).

Differences in alcohol metabolism and disappearance have been attributed to hormonal differences. For example, some studies suggest that dihydrotestosterone, a male reproductive hormone, may inhibit alcohol dehydrogenase in the liver, resulting in a slower alcohol disappearance rate (Mumenthaler et al., 1999).

Though largely inconclusive, research demonstrates that fluctuating female hormones, (i.e. estrogen and progesterone), may influence alcohol dehydrogenase activity. For example, animal studies have demonstrated that administration of supplemental steroid hormones (e.g. estrogen) affects hepatic alcohol dehydrogenase activity. Estrogen administration resulted in significantly increased hepatic alcohol dehydrogenase activity (i.e. quicker breakdown of alcohol and lower resulting alcohol levels), whereas the combination of estrogen and progesterone resulted in significantly increased alcohol concentrations (Mumenthaler et al., 1999). Therefore, it is suggested

that varying hormonal levels between and within sexes may differentially influence alcohol metabolism and the resulting BrAC. However, many of the studies assessing the effects of hormonal fluctuations on alcohol metabolism are conflicting. Despite evidence that biological differences associated with sex impact alcohol's effects, these complex mechanisms are not yet fully understood.

Alcohol, Cognition, and Health

Studies conducted over three decades suggest that sex differences in cognitive performance after acute alcohol administration are largely dependent upon the task and dose administered (Nixon et al., under review). As an illustration, Mumenthaler et al. (2009) provides a comprehensive review of acute alcohol administration at various doses, revealing several similarities and differences in cognitive functioning among men and women. In this paper the authors conclude that, when sexes are matched for target BrAC, men and women perform equivalently on tasks assessing simple reaction time, simple psychomotor abilities, simple information processing, hand steadiness, and body sway.

Conversely, sex differences are observed in tasks requiring divided attention and those assessing long-term memory, decision making, and recall. Women exhibit slower short-term memory recall, slower retrieval from long-term memory, and more impairment on tasks requiring divided attention. Additionally, it is proposed that women may experience greater negative effects on complex motor skills (e.g. driving) from acute alcohol consumption (Miller et al., 2009).

Niaura and colleagues (1987) demonstrated alcohol induced sex differences in memory by administering a short-term memory task to men and women under the influence of low dose alcohol. The authors revealed that women recovered short-term

working memory significantly more slowly than did men. Additionally, Jones and Jones (1976) revealed that women and men performed similarly on tasks assessing immediate recall, but that delayed recall was more so impaired among women given a moderate dose of alcohol (BrAC = 0.072%). Miller and colleagues observed acute alcohol induced sex differences in complex motor coordination and information processing speed and capacity, such that women showed greater impairment in all three behavioral domains compared to men at equivalent BrACs. Other studies suggest that women may be more susceptible to the effects of alcohol on global cognitive functioning and may report higher levels of subjective intoxication compared to men with equivalent BrACs (Miller et al., 2009).

Although altered cognitive function as a result of a single moderate dose does not always significantly differ between men and women, repeated administration of alcohol at moderate doses may result in greater cognitive and motor impairments in women (Dougherty et al., 1998; Mumenthaler et al., 2009). For instance, Dougherty et al. (1998) administered a rotary pursuit task to participants, for which they were to maintain the tip of a wand they held over a rotating light source. They found that women who were repeatedly administered alcohol over a series of sessions performed significantly worse than men with equivalent BrACs. Additionally, the same study reported that men developed a slight tolerance to alcohol's negative effects on task performance, while women became more sensitive to the effects of alcohol on performance across sessions. These inconsistencies suggest that systematic methodologies must be applied across studies.

Alcohol consumption has different implications for mental and physical health related consequences among men and women. For example, moderate drinking women have a greater risk of injury when consuming alcohol, compared to men (Nolen-Hoeksema, 2004). Research indicates that women who binge drink (5 drinks in 1 episode) are more likely to experience negative consequences (e.g. hangover, performing poorly in school, experiencing alcohol related memory loss) from chronic alcohol consumption than men (White, 2003). Women who engage in chronic alcohol consumption are more likely to experience health related complications, such as increased risk of cardiovascular disease and mortality. Whereas the alcohol literature suggests that, on average, men can consume ~9 drinks per day before they are at increased risk for coronary heart disease, women may experience the same level of risk when alcohol is consumed at a rate of ~4 drinks per day (Corrao et al., 2000). Moreover, heavy drinking is 4 times more likely to result in mortality for woman than men (Nolen-Hoeksema and Hilt, 2006).

The beneficial effects of moderate alcohol consumption on physical health also differ between men and women. For example, moderate drinking is more effective in benefiting bone mineral density in women compared to men. The NHANES III study revealed 4% greater bone mineral density in women who consume moderate alcohol, whereas male moderate drinkers showed 2% greater bone mineral density, relative to nondrinkers (Tucker, 2009). Women may experience alcohol's protective effects against diabetes mellitus more so than men as well (Poli et al., 2013). Further investigation is needed to fully characterize the longitudinal effects of chronic moderate alcohol consumption among men and women, independently.

Sex Differences & Older Adults

Studies concerning sex differences among older moderate drinkers are almost nonexistent in the alcohol literature. Although research addressing the differential effects of moderate alcohol consumption on men and women provides some information on adult populations, few to no studies have used an older adult sample. Therefore, little is known regarding the interaction between cognition, sex, and moderate alcohol consumption among older adults. The current study addresses the differential behavioral effects of acute low dose alcohol administration on older men and women.

Older Adults & Moderate Alcohol: Considerations

When addressing moderate alcohol consumption among the older adult population, there are several modulating variables that must be considered. Some of these variables are common to all age groups and others are more specific to the aging population.

Recreational and illicit drug use/abuse, a modulatory variable among all adult age groups, can increase the risk of health complications even when combined with low doses of alcohol. For example, drugs use among older adults (e.g. cocaine and marijuana) can have advanced detrimental effects on the cardiovascular system. According to the National Survey on Drug Use and Health (2011), ~4.8 million adults age 50 and over have consumed an illicit drug in the past year. Some of the most commonly consumed drugs among older adults, other than alcohol, are marijuana and nonmedical use (i.e. not used as prescribed or abused) of prescription drugs. Of those adults aged 50 or older who reported the consumption of an illicit drug in the past year,

31.5% recounted nonmedical use of prescription drugs (National Survey on Drug Use and Health, 2011).

Furthermore, older adults are generally faced with more health ailments and require the use of more medications (Berardi et al., 2006). Over-the counter (OTC) and prescription drug use is extremely common among American adults age 65 and older. It is estimated that this group consumes 40 % of all OTC medications and 25-30% of all prescription medications (National Institute on Drug Abuse, 2005). Some OTC medications such as those that treat allergies, the common cold, and osteoarthritis may interact with alcohol, proving potentially dangerous and compromising overall health (Neafsey et al., 2002). Of the most common medications prescribed to older adults, ~77% have pharmacological interactions with alcohol.

Common neurobehavioral consequences of alcohol and prescription/OTC drug interactions include excessive drowsiness, CNS depression, and dizziness which may exacerbate drug side-effects (Smith, 2009). For example, the majority of benzodiazepines affect brain functions in the same way that alcohol does. Alone, these substances can affect problem solving, emotional response, and general cognitive functioning (Room et al., 2005). When benzodiazepines are used in conjunction with alcohol, these effects are amplified, sometimes resulting in extreme drowsiness, depressed heart functions, or trouble breathing. The interaction between benzodiazepines and alcohol is of particular concern among older adults, as this aging population demonstrates an increased response to these drugs. Additionally, acute alcohol consumption can prolong the sedative effects of benzodiazepines (NIAAA,

1995). Therefore, older adults should be cautious when ingesting alcohol with other substances in order to avoid adverse effects.

Prescription, OTC, and illicit drug consumption are just a few of the considerations that should be addressed when moderate alcohol is consumed. Individual differences in health and demographics should always be taken into account before one engages in alcohol consumption.

Discussion

Alcohol is a commonly consumed substance in the United States. Although acute moderate alcohol consumption results in more immediate, and usually, detrimental effects on cognitive function, chronic consumption may protect against specific diseases and conditions, including cardiovascular disease, osteoporosis, and mood disorders for particular populations. However, the implications of age and sex are not yet fully defined, complicating our understanding of alcohol's acute effects on cognition, behavior, and health. Despite the fact that USDA and NIAAA moderate drinking guidelines are available for the older adult population (no more than one drink/day for men and women age 65+), the acute alcohol literature concerned with older adult moderate drinkers is relatively limited. Currently, the alcohol literature has provided little data characterizing the differential effects of acute low dose alcohol on older men and women.

Table 1-1. Cognitive Domains, Structural Correlates, and Task Assessment

Cognitive Domain	Main Structural Correlates	Assessment Examples
Psychomotor Ability: Hand-eye Coordination, Balance, Reaction Time[a]	Cerebellum, Basal Ganglia, Premotor Cortex, Parietal Cortex, Supplementary Motor Area, Cingulate Motor Cortex, Primary Motor Cortex	Finger Tapping, Trail Making Test Part-A , Rotary Pursuit Task
Working Memory[b]	Frontal Lobes, Prefrontal Cortex, Parietal Lobes, Anterior Cingulate Cortex	Gazzaley Remember/Ignore Task, Location Span Task, Digit Span Task, Brown-Peterson Task, N-back
Recall[c]	Anterior/Posterior Cingulate Cortex, Globus Pallidus, Thalamus, Left Cerebellum, Prefrontal Cortex, Hippocampal and Parahippocampal Regions (Medial Temporal Lobe), Right inferior Parietal Cortex	Logical Memory Subsection of the WAIS-R, Word List Memory Task, Cued Recall Tests (Stimulus/Response Tasks), Free Recall Tests (image and word stimuli)
Recognition[d]	Anterior/Posterior Cingulate Cortex, Left Cerebellum, Prefrontal Cortex, Hippocampus (Medial Temporal Lobe), Perirhinal Cortex, Right inferior Parietal Cortex	Old-new Recognition Task (yes/no), Forced Choice Recognition (multiple choice), Continuous Visual Word Recognition Paradigm
Attention: Top-down Attention, Covert Visual Attention, Set-shifting[e]	Frontal Lobes, Prefrontal Cortex, Lateral Intraparietal Area (Parietal Cortex), Superior Colliculi, Anterior Cingulate Cortex	Gazzaley Remember/Ignore Task, Posner Paradigm, Trail Making Test Part-B
Gait[f]	Brainstem, Cerebellum, Basal Ganglia, Primary Motor Cortex, Premotor Cortex, Supplementary Motor Area, Prefrontal Cortex	Examination of Walking Patterns, Turning Procedures, Sit to Stand tasks, Multitasking (Walk & Talk Tasks)
Executive Function: Planning, Cognitive Flexibility, Set-shifting, Behavioral Control, Inhibition, Decision Making[g]	Frontal Lobes, Dorsolateral Prefrontal Cortex, Orbitofrontal Cortex, Anterior Cingulate Cortex	Go/no-go Tasks, Stop-Signal Task, Trail Making Test Part-B, Wisconsin Card Sorting Task, Stroop Color Word Interference Task

[a]Hicks & Birren, 1970, [b]Muller & Knight, 2006, [c,d]Cabeza et al., 1997, [e]Filley, 2002, [f]Sanders & Gillig, 2010, [g]Alvarez & Emory, 2006. [a-g]These are primary references for cognitive domains and some of their structural correlates.

CHAPTER 2
OLDER ADULTS AND COGNITION

Normal aging is often associated with sub-clinical cognitive changes in attentional suppression, inhibition, processing speed, and cognitive efficiency (a sensitive measure of cognitive integrity taking into account speed and accuracy measures; Nixon, 1999; Gazzaley et al., 2005a; Rypma et al., 2006; Carriere et al., 2010). Therefore, it is important to understand cognition in reference to age related decline, independent of alcohol.

Though age related decline is highly variable, cognitive function is typically thought to plateau or slightly improve until the mid fifties, at which point cognitive abilities begin to decline, with evident subclinical deficits by the mid seventies (Seattle Longitudinal Study, 1956; Schaie et al., 1989). The 'frontal aging' and 'inhibitory control' hypotheses were proposed to partially explain these sub-clinical declines seen in normal aging. They posit that the cognitive deficits associated with aging are, in part, due to inefficient processes (e.g. lack of appropriate inhibition) mediated by the frontal lobe (West, 1996; Raz et al., 1997; Greenwood, 2000). Age related declines in information processing speed are thought to have a negative effect on cognitive performance when a task requires speed, ultimately accounting for general cognitive slowing and poorer performance on demanding tasks (Lockenhoff, 2011; Salthouse, 2010).

For the purposes of this review, four aspects of neurocognitive function will be addressed: psychomotor performance, set-shifting abilities, working memory, and top-down attentional control processes. Importantly, the following will focus on healthy

aging. Age-related neuropathologies such as Alzheimer's, Parkinson's disease, and conditions associated with acute events such as stroke will not be discussed.

Psychomotor Performance and Set-shifting Abilities

The phenomenon of psychomotor slowing as a result of age-related decline is well documented (e.g. Houx & Jolles, 1993; Keyes & White, 2000). Studies assessing age-related slowing in psychomotor abilities are typically consistent when influential variables such as health, education, and major life-events are controlled for. Pure measures of psychomotor performance (e.g. finger tapping) allow for the reliable, direct assessment of age-related changes in psychomotor ability (i.e. without the influence of executive functioning, memory, etc.). For example, Gunstad and colleagues (2006) performed a study in which participants, ages 50-82, were required to tap a circle on a touch screen with their index finger as quickly as possible for 60 seconds. They demonstrated age related declines in psychomotor speed using a simple motor tapping task.

The more complex the task, the easier it is to determine age-related differences in psychomotor skills (Houx & Jolles, 1993). For example, Salthouse (1984) observed a significant age-related decline in psychomotor abilities on tasks requiring typing skills with older adults showing longer choice reaction times and slower tapping rates than younger adults (note that no age-related deficit was observed for typing proficiency suggestive of age related differences in character anticipation). Studies assessing general processing speed show age-related decrements in psychomotor skills regardless of the level of expertise particular to a task (e.g. pianist playing the piano). Furthermore, Keyes and White (2000) found that increased age correlated with slower psychomotor speed on tasks such as the TMT Part A (i.e. TMT-A). These findings were

observed for young-old (age 56-75) and old-old (age 75-82) adults. Importantly, Keyes and White noted that psychomotor impairments observed among older adults contributed heavily to the impairments seen in executive performance. Nonetheless, age significantly influenced executive functioning beyond that accounted for by psychomotor speed, suggesting independent impairments in both independent and interaction effects in these domains.

Set-shifting, the ability to display cognitive flexibility when switching between instructional sets, is compromised with increased age. Attentional set-shifting is commonly assessed with the TMT Part B (i.e. TMT-B), a measure used to evaluate cognitive flexibility, visual scanning, and visual-motor tracking (Perry et al., 2009). Age-related deficits in set-shifting ability are widely associated with neuropathological changes in frontal lobe structures and deteriorating prefrontal function, important for executive function (Keyes & White, 2000). Older adults have been shown to recruit brain regions that younger adults do not, presumably to compensate for brain regions that are less active (due to age-related decline) and to successfully complete a task. Specifically, age-related increases in neural activity are prominent in the prefrontal cortex (Cabeza & Dennis, 2012). Importantly, greater activity is not always associated with better cognitive performance (Cabeza & Dennis, 2012).

Impairments in executive functioning observed among older adults vary considerably across task. Results are highly dependent upon task complexity, participant age, level of education, and previous experience (Jurado & Rosselli, 2007). Illustrating this conclusion, Crawford and Channon (2002) reported that older adults performed better on executive functioning tasks that required real-life problem solving

but performed more poorly on tasks such as the Wisconsin card-sorting task (WCST) and the TMT-B (see Table 1-1) relative to younger adults. Although the tasks listed above are meant to assess executive functioning, some may rely more heavily on the strategy implemented to complete the task than pure executive ability and implementation of compensatory tactics may produce varying results (Jurado & Rosselli, 2007). For instance, some individuals may rely on cues from the researcher or their environment, yielding a false assessment of executive function. Regardless, Wecker et al. (2005) found impairments on the TMT-B even when controlling for visual scanning, motor speed, perceptual speed, and other skills required by the task that do not directly target executive functioning. Therefore, with a more complex task, such as the TMT-B (e.g. Wecker et al., 2005), one can control for certain variables and target set-shifting impairments independent of other cognitive skills (Jurado & Rosselli, 2007).

Taken together, psychomotor and set-shifting performances are impaired with age and rely heavily on the sample of interest and the structural changes that occur with the aging process. Importantly, discrepancies exist concerning the age at which impairments in set-shifting abilities begin to emerge, possibly due to methodological differences in task selection, ability to address individual differences other than age, and study design (e.g. age as a continuous vs. categorical variable; Jurado & Rosselli, 2007). Therefore, additional research is required to clarify when and to what extent these age-related impairments occur.

Top-down Attention & Working Memory

Top-down attention is the voluntary, effortful, controlled attention to stimuli in the environment (Connor et al., 2004). Working memory refers to the temporary storage and manipulation of information necessary to complete a cognitive task. The ability to

recall and manipulate a series of temporarily stored numbers (e.g. reorganizing a verbal list of numbers into numerical order after a short period of time) is one example of working memory (Baddeley, 1992). Top-down attention and working memory processes, required in set-shifting tasks, are highly dependent upon frontal lobe activity, which is thought to have different activation patterns for older and younger adults (Glisky, 2007; Cabeza et al., 2004). A study performed by Cabeza et al. (2002), assessing verbal and non-verbal episodic memory recall and recognition, revealed greater bilateral prefrontal cortical activation among older adults than younger adults whose activation was largely restricted to the right lateral hemisphere. This pattern suggests the recruitment of additional neural units to successfully complete a memory task. Importantly, the prefrontal cortex is specifically implicated in attentional inhibition and working memory performance (Nielson et al., 2002; Reuter-Lorenz et al., 2000). Therefore, age-related deficits in directed remembering tasks (Gazzaley et al., 2008) or tasks demanding top-down attentional inhibition, where older adults are less able to ignore irrelevant stimuli, may be due to less discriminant attentional networks (Andres et al., 2006; Drag and Bieliauskas, 2010).

Top-down Attention

Top-down modulation of attention allows one to selectively attend to relevant stimuli and ignore irrelevant stimuli. Directed attending and ignoring may be referred to as the enhancement or suppression of attention, respectively (Gazzaley et al., 2005b). The assessment of enhancement (under remember conditions) and suppression (under ignore conditions) of attention has been widely explored in the literature. Gazzaley et al. (2011) used a remember/ignore paradigm to observe top-down attentional control and its impact on working memory in older adults. Top-down attention has specific

processes that researchers can probe using basic behavioral measures such as reaction time and accuracy. Older adults have shown slower reaction times and lower levels of accuracy compared to younger adults on remember/ignore tasks. It is proposed that these impairments, indicative of inefficient attentional modulation, are not due to processing speed deficiencies (i.e. overall slowing) but to prefrontal cortical dysfunction (i.e. poorer attentional processes; Bollinger et al., 2011). Positive correlations have been observed between attentional suppression of irrelevant stimuli and working memory performance (Gazzaley et al., 2005a). Therefore, attentional suppression and enhancement are critical for ideal working memory performance and prevention of working memory capacity overload (Gazzaley, 2011).

Working Memory

Memory and its relation to normal aging has been widely noted throughout the literature. Specific types of memory (e.g. episodic memory) are thought to show linear decline across the adult lifespan beginning as early as age 20, though others remain relatively intact (e.g. semantic memory; Hedden & Gabrieli, 2004). With normal aging, short-term memory (the ability to maintain small amounts of information for short periods of time; Puckett & Stockburger, 1980) and familiarity-based memory are thought to remain reasonably unimpaired. Working memory relies on several systems to ensure optimal performance and requires the simultaneous storage and processing of information. Furthermore, working memory is thought to probe the central executive system, implicated in attentional control (Baddeley, 1992).

It is well established that working memory is susceptible to age-related decline. Studies indicate that, although more prominent in spatial tasks, age-related declines in working memory are also observed in verbal tasks. In reference to spatial task

performance, Myerson and colleagues (1999) demonstrated that older adults performed significantly worse than younger adults on tasks where participants were required to reproduce a sequence of locations (location span task) or the combination of both locations and digits in the order that the series previously appeared (combined span task). Studies assessing verbal working memory with the Brown-Peterson task, in which participants are asked to remember a very small set of letters while their attention is focused elsewhere, yield conflicting results. These studies have shown equivalent and worse performance by older adults compared to younger adults (e.g. Craik et al., 1977; Inman et al., 1983; Floden et al., 2000).

However, when older adults are assessed in divided groups based upon performance, it is theorized that high performing older adults, unlike low performers, counteract age-related decline in working memory through plastic reorganization of neurocognitive networks. Using tasks such as the n-back, in which participants are presented with a sequence of stimuli and must indicate when the current stimulus matches the one from n steps earlier in the sequence, researchers have demonstrated age-dependent alterations in prefrontal cortical activation. Although younger adults show greater activation of the right prefrontal cortex (PFC) than the left PFC on tasks requiring memory and attention, middle aged and older adults show equivalent activation in the right and left PFC (Dixit et al., 2000). As discussed previously, older adults that recruit right and left PFC bilaterally may exhibit better working memory than those who do not (Cabeza et al., 2002). However, behavioral differences observed between high and low performing older adults are less noticeable in young-old populations (≤ 70 years old).

Generally, memory tasks that demand self directed strategies (e.g. ignoring irrelevant information or categorizing lists) are more difficult to perform as one ages. One of the most important processes contributing to optimal memory is attention and where attention is allocated during memory tasks to complete targeted goals. Older adults show consistent impairments in both keeping task-relevant information in mind (enhancement of attention), and ignoring task-irrelevant information (suppression of attention; Mather et al., 2010). Taken together, attentional processing and memory-based functions rely heavily upon one another and healthy age-related alterations in brain function may disrupt both systems, directly and indirectly.

Cognition & Older Adults: Sex Differences

Sex differences in cognitive performance among older adults are relatively underexplored in the literature. For instance, studies assessing sex differences in psychomotor and set-shifting abilities among older adults are almost non-existent. However, the few studies that are available offer insight into some of the possible sex differences in normal cognitive decline. Generally, men are thought to maintain higher levels of spatial orientation throughout the aging process and women are thought to preserve higher levels of word fluency (Avolio and Waldman, 1994). Sex differences in tasks assessing episodic memory have been previously documented among the older adult population. Similar to the findings of younger participants, older women have been shown to recall the placement of objects in a room better than their older male counterparts (Lewin et al., 2001). Furthermore, studies of episodic memory suggest that older women show significantly better recall of life events and are more specific in their description (Pillemer et al., 2003). In contrast, older studies assessing deficits in the

ability to ignore irrelevant information, an attentional suppression deficit, found no significant main effect of sex in a population of older adults (Hoyer et al., 1979).

Despite research assessing sex differences in cognitive function among the general adult population, less attention concerning this topic has been directed toward the older adult population. A small number of publications have begun to address the similarities and differences between older men and women, but many cognitive domains associated with altered performance in normal aging have yet to be assessed by sex. Therefore, further investigation is needed to characterize differences in cognitive ability among older men and women.

Conclusions & The Current Study

By 2015, over 46 million Americans will be 65 years of age or older (US Census Bureau, 2008). Although normal cognitive aging has been well characterized in many domains (e.g. deficits in memory and attention), studies inconsistently define the older adult population. Despite evidence that sub-clinical cognitive changes can be observed in healthy adults as young as 50 years of age, research concerned with the older adult population is largely focused on those 70+ years of age. Furthermore, cognitive function among older adults after acute low dose alcohol administration has been largely ignored in the literature.

The majority of studies addressing acute moderate alcohol consumption are concerned with younger, college aged adults and higher doses of alcohol resulting in BrACs above the legal limit of intoxication for motor vehicle operation (e.g. Vogel-Sprott, 1984; Fillmore, 2008). Furthermore, virtually no information is available concerning sex differences among older moderate drinkers. The effects of sex and acute low dose alcohol administration on age related deficits in psychomotor performance, set-shifting

abilities, attention, and working memory needs thorough documentation. Ultimately, these data have implications for moderate drinking guidelines and government policy. However, at this time, the extent to which acute alcohol intake differentially affects older men and women is unknown.

Although moderate drinking as a lifestyle may be beneficial to the older adult population, there is a need to study the immediate, acute effects of low/moderate dose alcohol on cognition. Therefore, the current study is an attempt to identify low dose alcohol's acute, differential effects on cognition for older male and female moderate drinkers. We posit one hypothesis and ask three empirical questions: Hypothesis 1) Subjects administered the moderate alcohol dose (0.065% g/dL) will perform worse on tasks assessing psychomotor, set-shifting, and working memory performance, than those administered the low dose (0.04% g/dL) or placebo (0.0% g/dL), Empirical Question 1) Will administration of the low dose facilitate performance (compared to the placebo and moderate dose) on psychomotor, set-shifting, or working memory tasks, Empirical Question 2) Will older men and women perform differently on tasks assessing psychomotor abilities, set-shifting, or attention mediated working memory, Empirical Question 3) Will there be a dose by sex interaction on any of the behavioral tasks?

CHAPTER 3
METHODS

This section details the current study, including a description of the participants, experimental procedures, data acquisition and analysis. A 3 (Breath Alcohol Concentration Level: placebo; low [40mg/dL]; moderate [65mg/dL]) X 2 (Sex: Male; Female) double blind, placebo-controlled factorial design was used. All procedures were approved by the University of Florida Health Science Center Institutional Review Board (protocol #403-2010).

Participants

Sixty-two older (ages 55-70) male (n=26) and female (n=36), healthy, moderate drinkers from North Central Florida communities were recruited. Moderate drinking was defined per U.S. Department of Agriculture / Health and Human Services guidelines. The age range was chosen to be consistent with the current literature on alcohol and aging populations, including the published work in our laboratory (Sklar et al., 2012; Gilbertson et al., 2009). Persons over the age of 70 were not included in the study because the experimental objective was not to study aging effects, per se, but rather to study the differential effects of alcohol on older men and women. Participants were primarily Caucasians (~91%). African-Americans (~ 2%) and Hispanics (~ 3.5%) were also represented, as were individuals endorsing 'other' group identification (~ 3.5%).

Subjects (Ss) who contacted the laboratory (via public advertisements) were informed of basic inclusionary criteria. Candidates had 12-18 years of completed education and considered themselves to be in good physical health. Ss who met basic criteria and showed continued interest were invited to complete two in-laboratory screening sessions to determine eligibility.

As part of the initial screening, Ss completed self-report measures and cognitive testing via paper-and-pencil assessment (Table 3-1). Questionnaires addressed a) participant demographics, b) verbal ability (Shipley Institute of Living Scale – Verbal (SILS-V) [Zachary, 1986]), c) alcohol (Quantity Frequency Index (QFI) [Cahalan et al., 1969]) and substance use histories, d) levels of state anxiety (Spielberger State Anxiety Inventory (STAI) [Spielberger, 1983]), e) depressive symptomatology (Geriatric Depression Scale (GDS) [Yesavage et al., 1982]) and f) mild cognitive impairment (Mini Mental Status Exam (MMSE) [Folstein et al., 1975]; Hopkins Verbal Learning Test (HVLT) [Benedict et al., 1998]). See Table 3-1 for paper-pencil screening measures and exclusionary cutoffs.

Ss who continued to qualify participated in the second screening session during which height and weight were recorded, vision was evaluated (20/40 or better corrected vision was required to ensure task feasibility), and a self-reported medical history was obtained. Axis-I psychiatric disorders (e.g. depression, anxiety disorders, schizophrenia) were assessed using a computerized diagnostic interview schedule, version IV (c-DIS-IV), consistent with the Diagnostic and Statistical Manual-IV criteria for Axis-I diagnoses (Robins et al., 2000; American Psychiatric Association Task Force on DSM-IV., 1994). Ss were excluded from the study if they met criteria for 1) a current Axis-I disorder, 2) current or lifetime diagnosis of alcohol dependence, 3) current nicotine dependence, 4) lifetime diagnosis of any psychotic disorder, or 5) a current diagnosis of major depressive disorder (or lifetime diagnosis if treated with electroconvulsive therapy). Ss who 6) suffered from a chronic medical condition or were taking a medication which contraindicated alcohol consumption, 7) had a diagnosis of epilepsy, HIV/AIDS, or

uncontrolled Type II diabetes, 8) had a body-mass-index indicating obesity, 9) were not fluent in English, 10) or had a past incidence of powerful electric shock and/or head trauma were also excluded. Qualifying Ss were stabilized (≥ 3 months) on prescription and / or over-the-counter medications common to aging. Per IRB protocol, Ss who reported suicidal or homicidal intent were to be discontinued and provided clinical referral/assistance, as appropriate. No suicidal or homicidal reports were made in the current study.

Ss provided written informed consent prior to participating in the screening and testing sessions. Those Ss who completed the first screening session (~one hour) were compensated $15.00 and those who completed the second session (~two hours) were compensated an additional $37.50.

Pre-Testing Participant Guidelines

Ss were instructed not to consume alcohol or sleep aids 24 hours prior to testing. Additionally, Ss were told to avoid sinus/allergy medications on the day of testing and fast at least four hours prior to their scheduled session. Ss were allowed their usual morning medications and one caffeinated drink before testing (to avoid caffeine withdrawal). Ss who completed the laboratory testing session were compensated $120.00.

Pre-Testing Procedures

Ss were transported to the laboratory between 8:00 and 10:00 AM. Research personnel reviewed recent medication and caffeine intake with the participant and obtained a blood pressure reading. Ss were administered a urine toxicology screen to test for illicit substance use, including opioids, tetrahydrocannabinol, cocaine, methamphetamine, benzodiazepines, and barbiturates. Thereafter, a breath sample

was taken to test breath alcohol concentration (BrAC). Individuals testing positive for the urine/breath tests mentioned above were discontinued and driven home. One hour prior to beverage administration, Ss consumed a ~240 calorie breakfast-bar to ensure an equivalent amount of food in the stomach of all participants before alcohol administration. Prior to testing, Ss were re-administered the GDS and STAI to assess current mood.

Alcohol / Beverage Administration

Alcohol administration procedures were performed to achieve a randomly assigned, desired peak BrAC of either 0mg/dL (placebo), 40mg/dL (low), or 65mg/dL (moderate). Alcohol dosing calculations were determined using a modified Widmark calculation (taking into consideration the age, sex, height, and weight of the individual, as appropriate) to reach the desired BrAC level (Watson et al., 1981; Widmark, 1932). Beverages were mixed by trained laboratory personnel, according to standard procedure (e.g. Fillmore et al., 2008). The task administrator and Ss were blind to the assigned dose. Alcoholic beverages each consisted of 183 mL of chilled, sugar free, caffeine free, lemon-lime soda and a varied amount of 100% medical grade alcohol. Beverages containing 0mg/dL (placebo) consisted only of the vehicle solution (183 mL) and a small amount of surface alcohol. Both the placebo and alcoholic beverages were misted with alcohol to enhance placebo effectiveness. Ss were given five minutes to consume two beverages. BrAC measurements were taken by an unblinded researcher 10, 25, 60, and 75 minutes post beverage consumption. Thirty minutes after initial consumption, Ss were administered a booster beverage that contained either alcohol or placebo content, in order to sustain the desired peak BrAC. Ss in the placebo group received a placebo booster beverage. If Ss who were administered an active alcohol

dose had a BrAC ≥ half the desired peak BrACs then they were administered a placebo booster. Those Ss who had a BrAC < half of the desired peak BrACs were administered the active alcohol booster. The active booster, totaling 180 mL, consisted of 1/2 of the original alcohol dose and the vehicle. Ss received a microwaveable healthy choice meal (~325 calories) after the completion of testing and were transported home by laboratory personnel when BrACs were at 0.0%.

Cognitive Testing

The cognitive test battery consisted of the Trail Making Test Parts A and B (TMT-A & TMT-B, respectively; Reitan and Wolfson, 1993) and a working memory task (WMT) established by Gazzaley and colleagues (2005). Ss completed the TMT-A and TMT-B fifteen minutes after initial beverage consumption. Ss were administered the TMT-A first, followed by the TMT-B. The WMT was administered thirty minutes after initial beverage consumption. Participants were told to complete each task “as quickly and accurately as possible”. All testing took place in a private, sound-attenuated booth.

TMT A & B

TMT-A & TMT-B (Figure 3-1), subtests of the Halstead Reitan Battery (Russell et al., 1970), are a measure of psychomotor (TMT-A) and set shifting (TMT-B) abilities, and require Ss to essentially “connect the dots”. For TMT-A, Ss were prompted to connect numbered dots (1-25) without lifting their pen. For TMT-B, Ss were instructed to connect alternating numbers and letters (i.e. 1 to A to 2 to B, up to 13). Prior to each part of the TMT, subjects completed a shortened practice version to ensure a thorough understanding of the instructions. TMT-A typically takes less than 1 minute to complete and TMT-B can take up to 3 minutes. If a mistake was made, Ss were made aware and

directed back to the last correct connection made. The dependent variable of interest was the time to completion and errors were accounted for in this measure.

WMT

The WMT is a two-part, remember/ignore, computerized battery that assesses working memory and recognition. The task consisted of two blocks of grey-scale stimuli, and twenty trials per block. Each trial consisted of two neutral faces and two scenes, presented in a pseudo-random order, to avoid participant expectation. In one block, Ss were instructed to remember the faces and ignore the scenes (i.e. 'face condition'). In the other, Ss were instructed to remember the scenes and ignore the faces (i.e. 'scene condition'). Blocks were counterbalanced between Ss such that the order in which instructional sets were presented (i.e. block 1: remember the faces, ignore the scenes; block 2: remember the scenes, ignore the faces) and the specific stimuli within each block were randomly assigned. Each stimulus was presented for eight-hundred milliseconds (ms), followed by a two-hundred ms interstimulus interval, indicated by a blank screen.

After nine seconds of delay, for which a fixation cross (+) was presented, a probe stimulus appeared at which point Ss were to indicate whether or not the probe stimulus was in the preceding set of cue stimuli using a response pad (Figure 3-2). Ss were instructed to use the index finger of their dominant hand to press the right button if the response stimulus was present in the preceding set, or the left button if the stimulus was absent. Trials were separated by a red 'X' in the center of the screen. This task took ~ 33 minutes to complete. Dependent variables of interest were accuracy, reaction time (for accurate trials), and efficiency ratios (% accurate / average reaction time for accurate trials).

Breath Measures

Breath Alcohol Concentrations (BrAC) were measured using a standard breathalyzer (Intoxylizer® 400PA; CMI, Inc., Owensboro, KY). After testing was completed, breaths were taken ~ every 15 minutes. Once levels had declined to 0.0% (g/dL), Ss were transported home as noted above. When obtaining BrAC, the subject would inhale, hold their breath, and exhale into the tube provided. The resulting BrAC displayed was hidden from the Ss view and recorded by the unblinded researcher. After each beverage administration, Ss rinsed their mouths with water and spit into a provided container to assure there would be no left over residue from the alcohol consumed (placebo groups also rinsed and spit).

Subjective Intoxication

Subjective intoxication was assessed using a modified questionnaire (Harrison et al., 2007). The 10-point Likert scale survey was administered before (i.e. pre-test) and after (i.e. post-test) TMT-A & TMT-B, and before the first block and after the last block of the WMT. Placebo effectiveness was assessed at the completion of the study using a basic questionnaire on which Ss indicated whether they felt they had received alcohol. If Ss indicated that they had not received alcohol, they reported the approximate time at which they came to that conclusion.

Statistical Analyses

All statistical analyses were performed using SAS Version 9.1 (SAS Institute, Inc., Cary, NC). Statistical significance was defined as $p \leq .05$.

Participant Characteristics

Participant demographics, affective measures, and substance use data were analyzed for differences with two (Sex) X three (Dose) general linear model analysis of

variance (GLM). As a conservative measure, uncorrected t-tests were conducted to further explore interactions when appropriate. The relationship between demographic variables (e.g. age, education) and dependent variables (e.g. accuracy & reaction time) were assessed with Pearson's r correlation matrices.

Behavioral Analyses

Time to complete TMT-A & B, as well as reaction time, accuracy, and efficiency (% accuracy / average reaction time) for both instructional sets of the WMT were recorded. In order to be included in statistical analyses for accuracy and efficiency of the WMT, Ss were required to accurately respond to at least 50% of the trials.

A 2 (active doses) X 2 (sex) GLM was performed for time to complete (TMT-A & B), accuracy, reaction time, and efficiency (WMT) to determine whether the active alcohol doses could be collapsed. Primary results of interest for the GLM performed were the dose main effect and the dose by sex group interaction. Tukey's familywise error correction was applied to follow-up analyses, where appropriate. Results indicated a trend level difference between active doses for the dependent variable of time to complete TMT-A ($F_{1,37}$=3.20, p=0.08), suggesting that the low dose (40 mg/dL) was associated with a quicker time to complete TMT-A than the moderate dose (65 mg/dL). No significant or trend level difference between the active doses was detected for TMT-B.

A significant effect of dose was identified for reaction time to face stimuli ($F_{1,33}$=5.17, p=.03) with the low dose being associated with quicker reaction times than the moderate dose. A main effect of dose was also identified for accuracy to face stimuli ($F_{1,33}$=7.41, p=.01) which suggested that the low dose was associated with better accuracy as compared to the moderate dose. Reaction time to scene stimuli yielded no

significant difference between the active doses, while accuracy for scene stimuli yielded trend-level differences between doses ($F_{1,32}$=3.65, p=.07). The low dose was associated with greater accuracy for scene stimuli than the moderate dose. Efficiency under the scene condition yielded no significant difference between active doses. However, efficiency under the face condition yielded significant results that suggested that the low dose was associated with greater efficiency as compared to the moderate dose ($F_{1,33}$=10.75, p=0.003). No (active) dose X sex group interactions were detected for any of the dependent variables (p's>.26). Because active doses were not consistently similar or dissimilar across the dependent measures of interest, active doses were not collapsed for any of the variables of interest in order to better assess their effects.

Thus, to assess behavioral outcomes for TMT-A & B, separate 2 (sex group) X 3 (dose group) GLMs were conducted. 2 (sex group) X 3 (dose group) X 2 (repeated: task condition; 'Face Condition', Scene Condition') GLM was performed for the WMT behavioral data (reaction time, accuracy, and efficiency). Significant interactions were further explored with simple main effect analyses.

Correlational Analyses: Subjective Intoxication, BrAC, and Performance

The potential relationship between measures of subjective intoxication (pre-test and post-test for the TMT A&B and WMT), BrAC measures, and behavioral performance was assessed separately for older men and women using Pearson's r correlation matrices. Due to the differences in instructional set (i.e. 'face condition' vs. 'scene condition'), performance on the WMT was assessed separately for the two conditions. Importantly, active dose groups (i.e. 40 mg/dL & 65 mg/dL) were collapsed for the assessment of correlational analyses due to the continuous nature of the BrACs, subjective intoxication measures, and the dependent measures of interest.

Table 3-1. Screening measures and exclusionary cutoffs

Screening Measure	Assessment	Exclusionary Cutoff
Geriatric Depression Scale (GDS)[a]	Depressive Symptomatology	≥ 11
State Anxiety Inventory (STAI)[b]	State Anxiety	Not exclusionary
Shipley Institute of Living Scale – Verbal (SILS-V)[c]	Verbal Ability	< 12.9
Quantity Frequency Index (QFI)[d]	Average Alcohol consumption over past 6 months	>2 drinks/day (men) >1 drink/day (women)
Hopkins Verbal Learning Test (HVLT)[e]	Verbal Memory	<16
Mini-mental State Examination[f]	Mental Status	<27

[a] Yesavage et al., 1982, [b] Spielberger, 1983, [c] Zachary, 1986, [d] Cahalan et al., 1969, [e] Benedict et al., 1998, [f] Folstein et al., 1975

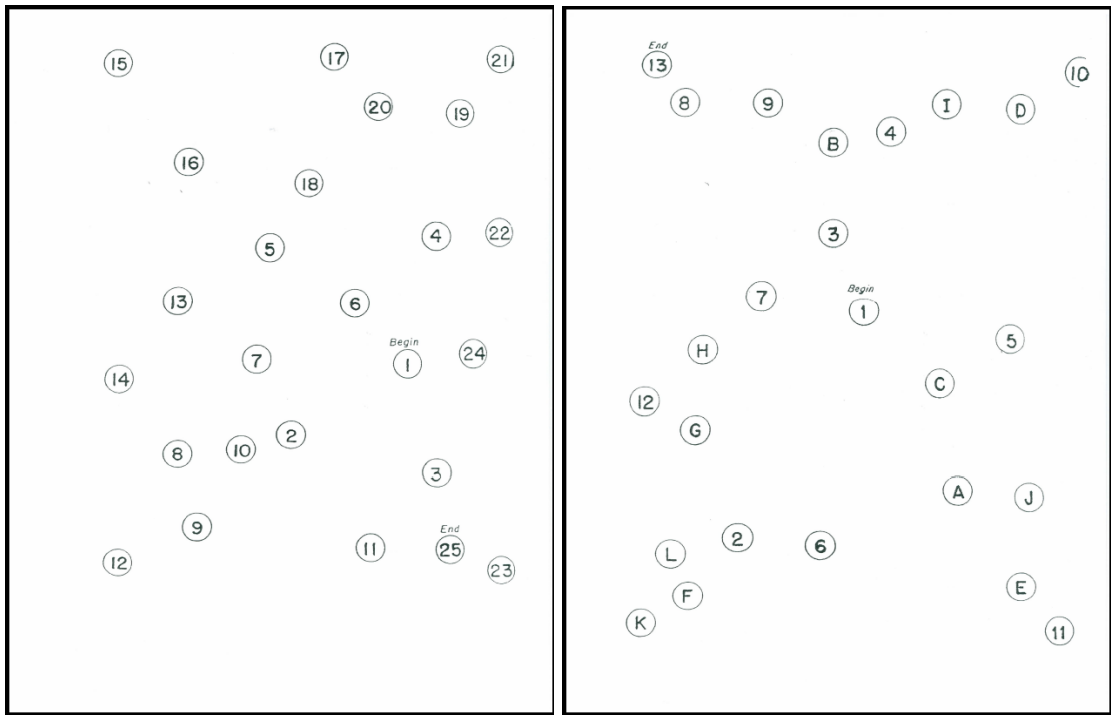

Figure 3-1. Trail Making Test A & B. For TMT-A, subjects draw a line connecting the circles in numeric order as quickly and accurately as possible. For TMT-B, subjects are instructed to draw a line connecting the circles, switching from numeric to alphabetical order (i.e. 1, a, 2, b, 3, c, etc.) as quickly and accurately as possible. The dependent variable of interest is time to complete the task. See text for more detail. Taken from the Halstead Reitan Battery (Russell et al., 1970).

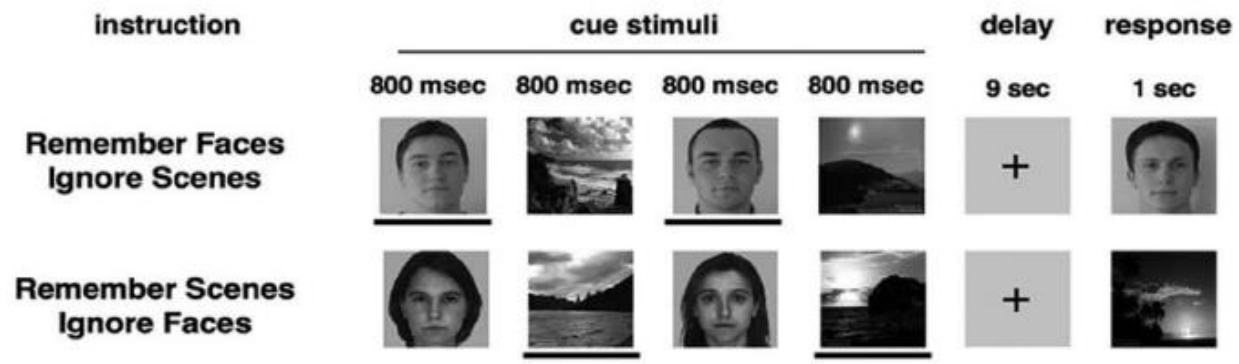

Figure 3-2. Working Memory Task. Face and scene stimuli were individually presented. Underlines indicate which images subjects were told to remember in a given instructional block. Cue stimuli were presented within trails in pseudo-random order. Subjects reacted to probe stimuli with a button-press method, ultimately assessing short-term recall and working memory. See text for additional description. Adapted from Gazzaley, A., Clapp, W., Kelley, J., McEvoy, K., Knight, R.T., & D'Esposito, M. (2008). Age-related top-down suppression deficit in the early stages of cortical visual memory processing. Proc Natl Acad Sci U S A, 105, pg. 13123, Figure 1.

CHAPTER 4
RESULTS

Descriptive Variables

As noted in Chapter 3, a conservative approach was used to detect potential age and dose group differences. Means and standard deviations for demographic, affective, and alcohol related variables by sex and dose group are presented in Table 4-1. No significant difference between dose groups or sexes existed for age, education, verbal age (SILS-V), GDS, or QFI. A significant main effect of sex was identified for the STAI for which women reported slightly higher state anxiety levels (M_{women}=44.86± 6.87; M_{men}=41.45± 5.16; $F_{1,56}$=4.32, p=0.04). However, both sexes reported levels non-indicative of significant distress. STAI did not significantly correlate with the dependent variables of interest (rs<.32, ps>.08). Placebo effectiveness was relatively high among Ss (~74%), with 75% of the men and 73% of the women reporting that they had received alcohol when a placebo dose was administered (no significant difference between sexes, χ^2(1, N=19)=0.01, p=0.40).

BrAC Results

Peak BrACs by sex and active dose are shown in Figure 4-1. As expected, mean BrACs significantly differed between active dose levels at every time point (all $Fs_{1,25}$>18, ps<0.0003). No significant sex difference for BrAC was noted at any given time point for any dose group (all ts<1, ps>0.40).

Behavioral Results

TMT

TMT-A

2 (sex) X 3 (dose) GLM for time to complete TMT-A yielded no significant main effects of sex or dose ($F_{1,56}$=0.00, p=1.00; $F_{2,56}$=1.53, p=0.23). Additionally, no sex by dose interaction was observed ($F_{2,56}$=0.95, p=0.39).

TMT-B

2 (sex) X 3 (dose) GLM for time to complete TMT-B detected a significant main effect of sex ($F_{1,55}$=6.74, p=0.01). No significant main effect of dose or sex by dose interaction was observed ($F_{2,55}$=1.82, p=0.17; $F_{2,55}$=1.35, p=0.27). Characterization of the main effect for sex revealed that men (M=86.22± 36.66 sec) took significantly longer to complete TMT-B compared to women (M=66.79± 22.60 sec; Figure 4-2), independent of the alcohol dose administered. Note that one female subject was not included in TMT-B analysis due to exceptional deviation from the average time to complete (>6 standard deviations from the mean).

WMT

Accuracy

2 (sex) X 3 (dose) X 2 (repeated: task condition) GLM for accuracy measures yielded a significant main effect of dose ($F_{2,51}$=5.23, p=0.009). All other between subjects effects (sex & sex X dose) were non-significant (ps>.61). Detailed characterization of the dose main effect revealed that the low dose group (M=87.22± 5.62% correct) was significantly more accurate than the moderate dose group (M=79.47± 8.15% correct; t_{35}=3.27, p=0.005; Figure 4-3). No significant differences between placebo and the low or moderate doses were observed (ps>0.16). Within

subjects analyses yielded no significant effect of condition ('face condition' vs. 'scene condition') or its interaction with sex or dose (ps>0.20).

Reaction time

2 (sex) X 3 (dose) X 2 (repeated: task condition) GLM for reaction time yielded no significant effect of sex, dose, condition, or their interactions (all Fs<2.52, ps>0.11).

Efficiency

2 (sex) X 3 (dose) X 2 (repeated: task condition) GLM for efficiency ratios (% accurate / mean reaction time for accurate trials) revealed a significant main effect of dose group ($F_{2,51}$=4.42, p=0.02) and a trend for sex ($F_{1,51}$=3.63, p=0.06). The sex X dose interaction term was not significant (p>0.90). Characterization of the dose main effect revealed that the low dose group (M=0.67± 0.15) responded more efficiently than the moderate dose group (M=0.54± 0.14; t_{35}=2.82, p=0.02; Figure 4-4). No significant differences between placebo and the low or moderate doses were observed (ps>0.26).The trend for sex suggested that men (M=0.64± 0.19) responded more efficiently than did women (M=0.57± 0.11; t_{55}=1.83, p=0.07; Figure 4-5).

Within subjects analyses yielded a main effect of condition ($F_{1,51}$=8.27, p=0.006) and a dose X condition interaction ($F_{2,51}$=4.46, p=0.02). All other within subjects terms were non-significant (all Fs<2.48, ps>0.09). Analysis of the condition main effect revealed that Ss responded more efficiently under the 'face condition' (M= 0.63± 0.18) compared to the 'scene condition' (M= 0.58± 0.14; t_{56}=2.30, p=0.03; Figure 4-6). Further investigation of the dose X condition interaction revealed that the low dose group (M=0.75± 0.20) responded more efficiently than the placebo group (M=0.62± 0.13; t_{36}=2.46, p=0.04) and the moderate dose group (M=0.55± 0.17; t_{36}=3.68, p=0.002; Figure 4-7) under the 'face condition'. No significant difference was detected between

the placebo and moderate dose groups under the ‘face condition’ ($p>0.39$). No significant difference between dose groups was detected under the ‘scene condition’ ($ps>0.28$).

Continuous Relationships: Subjective Intoxication, BrAC, and Behavior

Pearson’s r correlation matrices were constructed to characterize the relationship between subjective intoxication, BrAC, and behavioral measures for the active dose groups. Separately, the relationship between subjective intoxication and behavioral outcomes was assessed for men and women in the placebo group.

TMT

No correlation between subjective intoxication and time to complete TMT A or B was detected for men or women under the placebo dose ($rs<0.18$, $ps>0.67$). Additionally, no correlation between subjective intoxication or BrAC and time to complete TMT A or B was detected for men or women under the active doses ($rs<0.34$, $ps>0.11$).

Exploratory analyses were performed, for the active dose groups, to assess the relationship between BrAC and subjective intoxication. For women who received an active dose, a significant relationship was observed between BrAC at 10 minutes post beverage consumption ($BrAC_{10}$) and pre-test subjective intoxication ($r=0.47$, $p=0.02$). Additionally, a significant relationship between BrAC at 25 minutes post beverage consumption ($BrAC_{25}$) and post-test subjective intoxication was noted for the women ($r=0.41$, $p=0.05$). No relationship between subjective intoxication and BrAC was noted for men who received an active dose ($rs<0.37$, $ps>0.14$).

WMT

No significant correlations between subjective intoxication, accuracy, reaction time, or efficiency, for either face or scene conditions, under the placebo dose was observed among women ($rs<0.50$, $ps>0.09$). However, a significant relationship between pre-test subjective intoxication and scene reaction time was noted for men under the placebo condition ($r=0.72$, $p=0.04$; Figure 4-8). Additionally, a trend level relationship was observed between pre-test subjective intoxication and efficiency for men who received placebo under the scene condition ($r= -0.67$, $p=0.07$; Figure 4-9). No other significant relationships were observed for the placebo dose under the face or scene conditions.

For women who received an active dose, a significant relationship was observed between pre-test subjective intoxication and face condition reaction time ($r=0.43$, $p=0.04$; Figure 4-12) and between pre-test subjective intoxication and face condition efficiency ($r=-0.41$, $p=0.05$; Figure 4-13). No other significant relationships were noted for pre or post-test subjective intoxication. A trend level correlation was observed between $BrAC_{25}$ and face condition efficiency measures ($r=-0.38$, $p=0.08$; Figure 4-14). Additionally, a significant relationship was noted between $BrAC_{60}$ and face condition reaction time ($r=0.54$, $p=0.008$; Figure 4-15), and between $BrAC_{60}$ and face condition efficiency ($r=-0.59$, $p=0.003$; Figure 4-16). No other significant relationships were observed for women administered an active dose.

For men who received an active dose, a significant relationship was observed between pre-test subjective intoxication and face condition accuracy ($r=-0.64$, $p=0.01$; Figure 4-10) and between post-test subjective intoxication and face condition accuracy ($r=-0.58$, $p=0.02$; Figure 4-10). Additionally, a significant negative correlation was noted

between BrAC at 60 minutes post beverage consumption ($BrAC_{60}$) and face condition accuracy (r=-0.53, p=0.05; Figure 4-11). No other significant relationships were noted for men administered an active dose.

Exploratory analyses were performed, for the active dose groups, to assess the relationship between BrAC and subjective intoxication. No significant relationships were noted for either women or men, immediately before or after administration of the WMT.

Results Summary

Summary: TMT A & B

TMT-A yielded no significant effect of sex, dose, or their interaction. However, a main effect of sex for TMT-B was observed, with men taking longer to complete the task (Figure 4-2).

Summary: WMT

A significant effect of dose was revealed for accuracy, with the low dose (40 mg/dL) group performing more accurately than the moderate dose (65 mg/dL) group (Figure 4-3). No effect of sex, sex X dose, or condition was observed for accuracy measures.

No significant effect of sex, dose, condition, or their interactions were observed for reaction time.

A main effect of dose and a sex trend was observed for efficiency (Figures 4-4 & 4-5). Results indicate that the low dose group responded more efficiently than the moderate dose group. Additionally, the sex trend suggests that men responded more efficiently than women. No sex X dose interaction was found. However, a main effect of condition suggested that participants performed more efficiently under the face condition than the scene condition (Figure 4-6). Furthermore, a dose X condition

interaction revealed that the low dose group performed more efficiently than the placebo or moderate dose groups under the face condition, whereas no significant difference between doses was observed under the scene condition (Figure 4-7).

Summary: Continuous Relationships

A significant positive relationship was observed between $BrAC_{10}$ and subjective intoxication and between $BrAC_{25}$ and subjective intoxication, for women. However, men did not show this association.

Women showed a positive relationship between $BrAC_{25}$ and efficiency under the face condition (Figure 4-14). Furthermore, women showed a significant positive relationship between $BrAC_{60}$ and face condition reaction time (Figure 4-15) and a negative relationship between $BrAC_{60}$ and face condition efficiency (Figure 4-16). While men did not exhibit these relationships, they did show a negative relationship between $BrAC_{60}$ and accuracy under the face condition (Figure 4-11).

Men showed significant relationships between subjective intoxication and 1) face condition accuracy (Figure 4-10), 2) scene condition reaction time (Figure 4-8), and 3) scene condition efficiency (Figure 4-9). Women revealed a significant relationship between subjective intoxication and 1) face condition reaction time (Figure 4-12) and 2) face condition efficiency (Figure 4-13). All reported relationships were in the expected direction such that greater subjective intoxication was correlated with lower accuracy, increased reaction times, and lower efficiency scores.

Table 4-1. Descriptive variables

	Men			Women		
	Placebo N=8 Mean SD	40mg/dl N=9 Mean SD	65mg/dl N=9 Mean SD	Placebo N=12 Mean SD	40mg/dl N=11 Mean SD	65mg/dl N=13 Mean SD
Age (years)	62.13 5.14	59.89 5.01	62.22 3.63	61.92 4.17	60.36 3.01	62.23 5.36
Education (years)	15.63 1.85	15.67 1.87	16.89 1.36	16.08 1.51	16.18 1.17	16.38 1.61
Verbal Age[1]	19.00 1.45	18.60 1.08	19.36 0.61	18.74 1.72	19.29 1.07	19.34 1.18
GDS[2]	2.13 2.64	2.56 2.24	1.78 2.54	2.42 2.27	0.82 1.25	2.31 1.93
STAI[3a]	41.25 5.97	42.78 4.55	40.33 5.27	43.83 4.73	44.73 8.74	46.85 6.72
QFI[4]	0.45 0.29	0.31 0.28	0.29 0.22	0.39 0.25	0.24 0.15	0.23 0.20

[1]Shipley Institute of Living Scale-Verbal (SILS-V; Zachary, 1986), [2]Geriatric Depression Scale (Yesavage et al., 1982), [3]State Anxiety Inventory (Spielberger, 1983), [4]Quantity Frequency Index (Cahalan et al., 1969), [a]Significant effect of sex [$F_{1,56}$=4.32,p=.04; women (M=44.80) >men (M=41.45)].

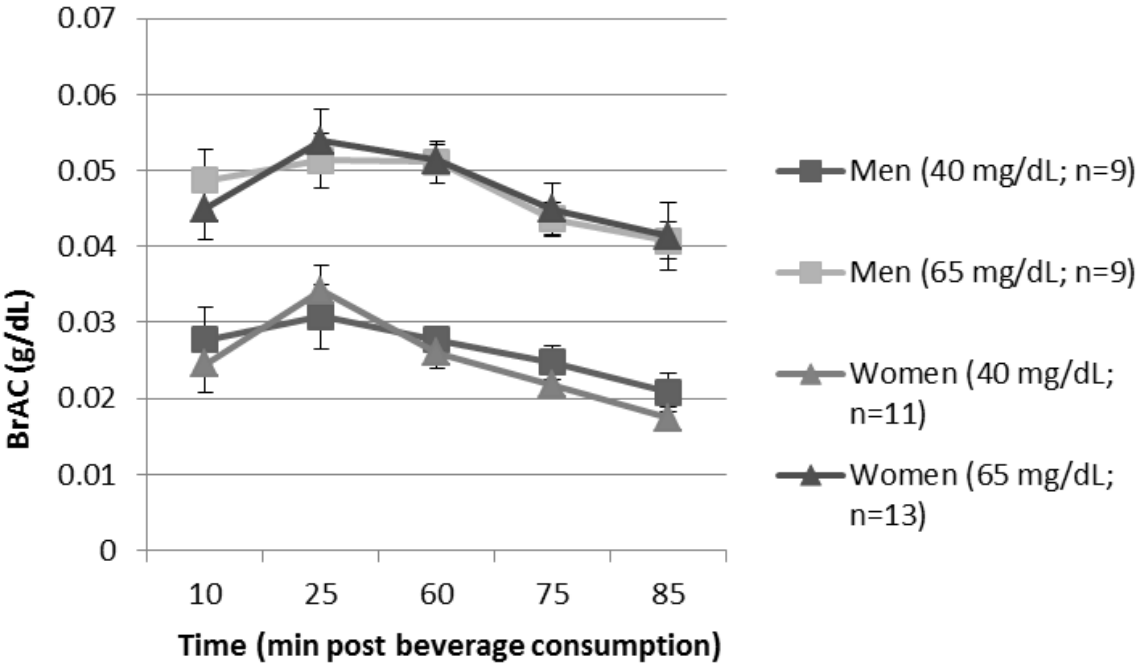

Figure 4-1. BrACs for Sexes and Active Dose Groups. No differences were noted between male and female Ss for either dose at any time point (ps > 0.40). Error bars depict standard error.

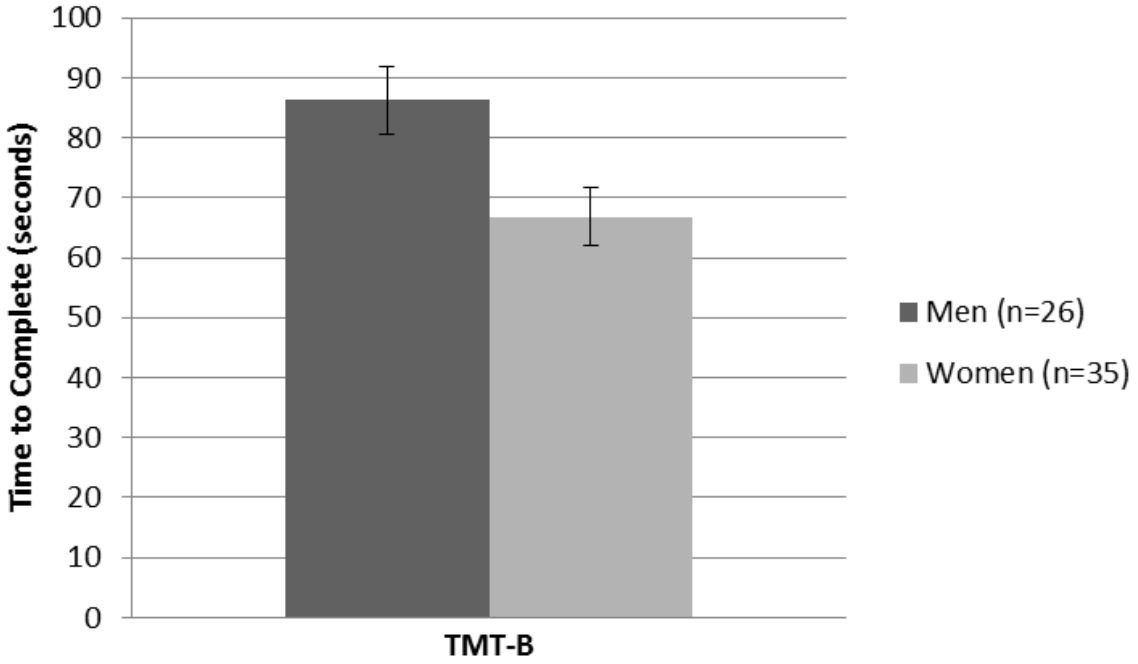

Figure 4-2. Trail Making Test B: Sex Main Effect. 2 (sex) X 3 (dose) GLM revealed that time to complete TMT-B across all dose conditions was significantly longer among men relative to women. Error bars depict standard error. $F_{1,55}=6.74$, $p=0.01$

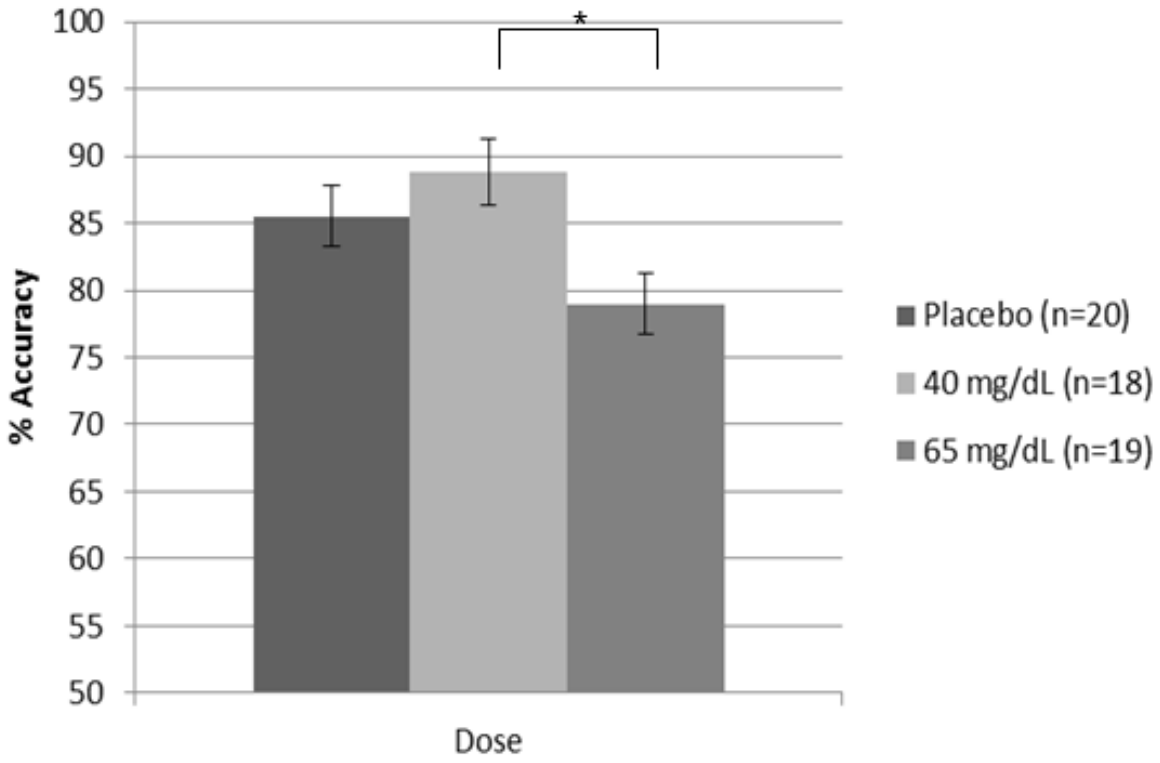

Figure 4-3. Accuracy: Dose Main Effect. 2 (sex) X 3 (dose) X 2 (repeated: task condition) GLM revealed that % accuracy in the working memory task was significantly higher among the low dose group compared to the moderate dose group. Error bars depict standard error. $F_{2,51}=5.23$, $p=0.009$, $*t_{35}=3.27$, $p=0.005$

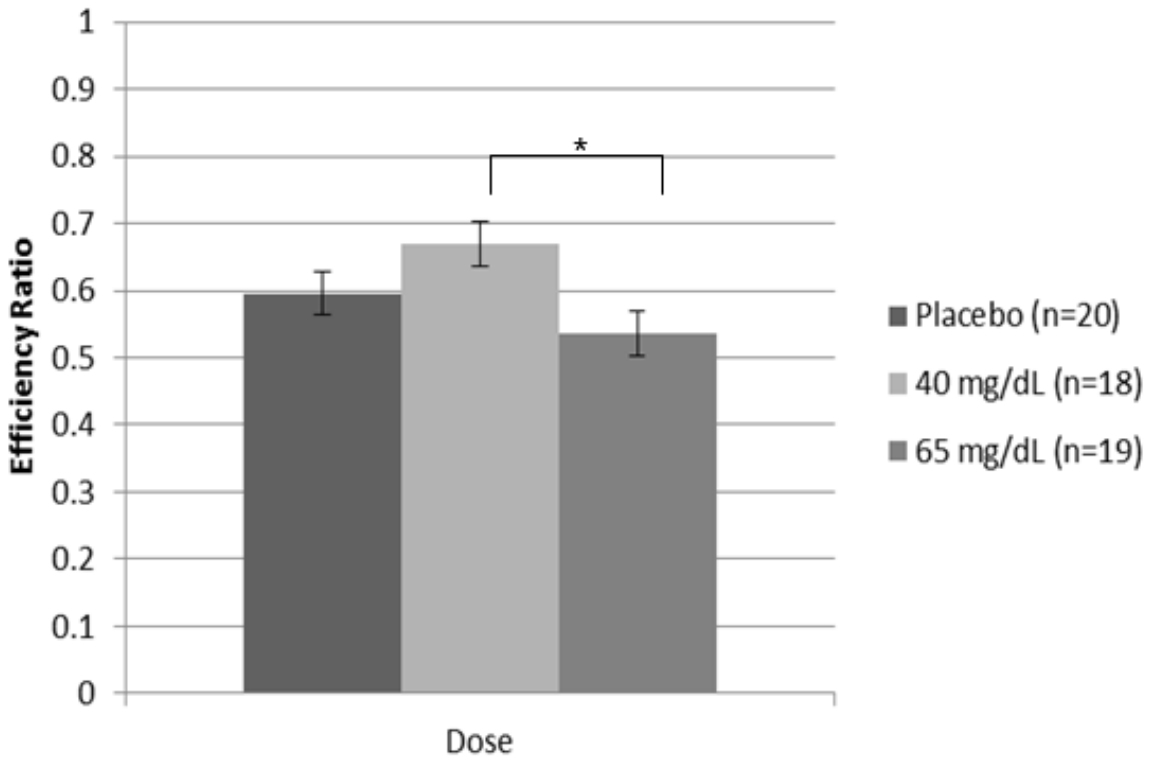

Figure 4-4. Efficiency: Dose Main Effect. 2 (sex) X 3 (dose) X 2 (repeated: task condition) GLM revealed that the low dose group was more efficient (% accuracy/mean reaction time) than the moderate dose group for the working memory task. Error bars depict standard error. $F_{2,51}=4.42$, $p=0.02$, $*t_{35}=2.82$, $p=0.02$

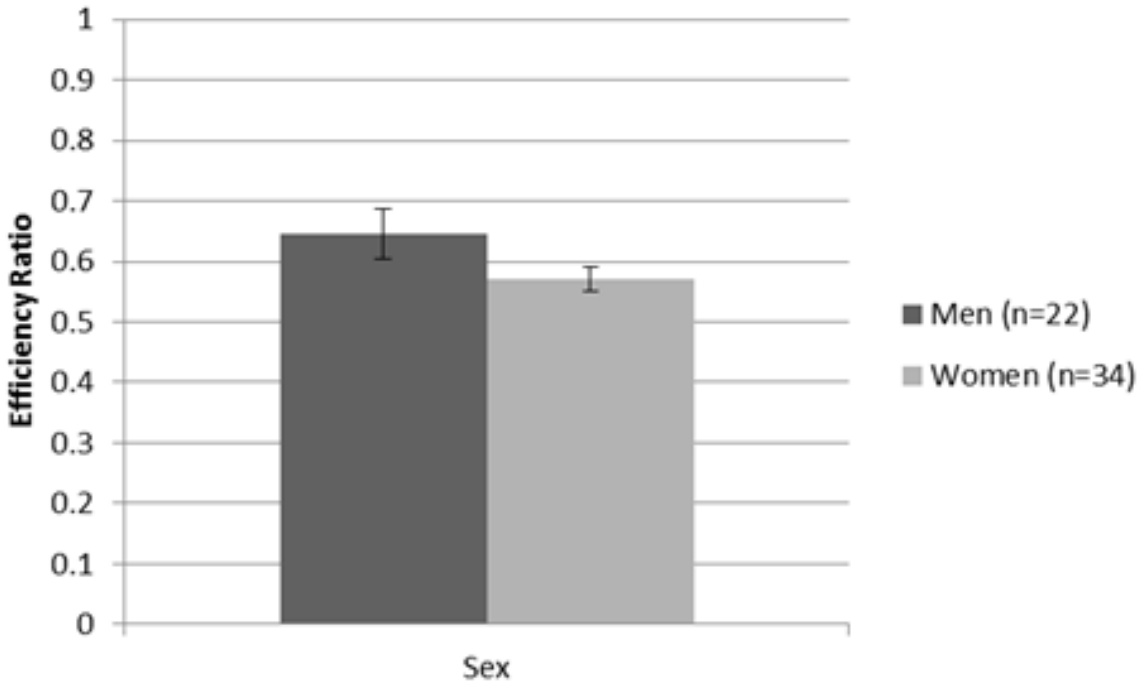

Figure 4-5. Efficiency: Trending Sex Main Effect. 2 (sex) X 3 (dose) X 2 (repeated: task condition) GLM revealed that older men performed more efficiently (% accuracy/mean reaction time) for the working memory task than did the older women. Error bars depict standard error. $F_{1,51}=3.63$, $p=0.06$

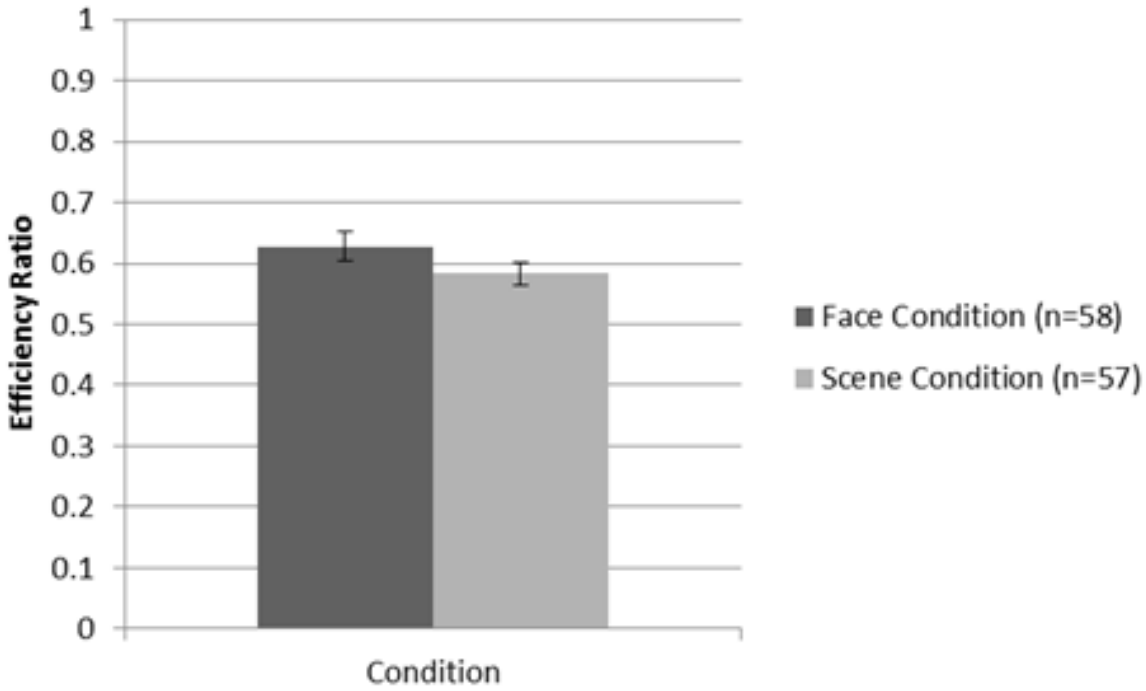

Figure 4-6. Efficiency: Condition Main Effect. 2 (sex) X 3 (dose) X 2 (repeated: task condition) GLM revealed that participants responded more efficient (% accuracy/mean reaction time) under the face condition than the scene condition. Error bars depict standard error. $F_{1,51}=8.27$, $p=0.006$

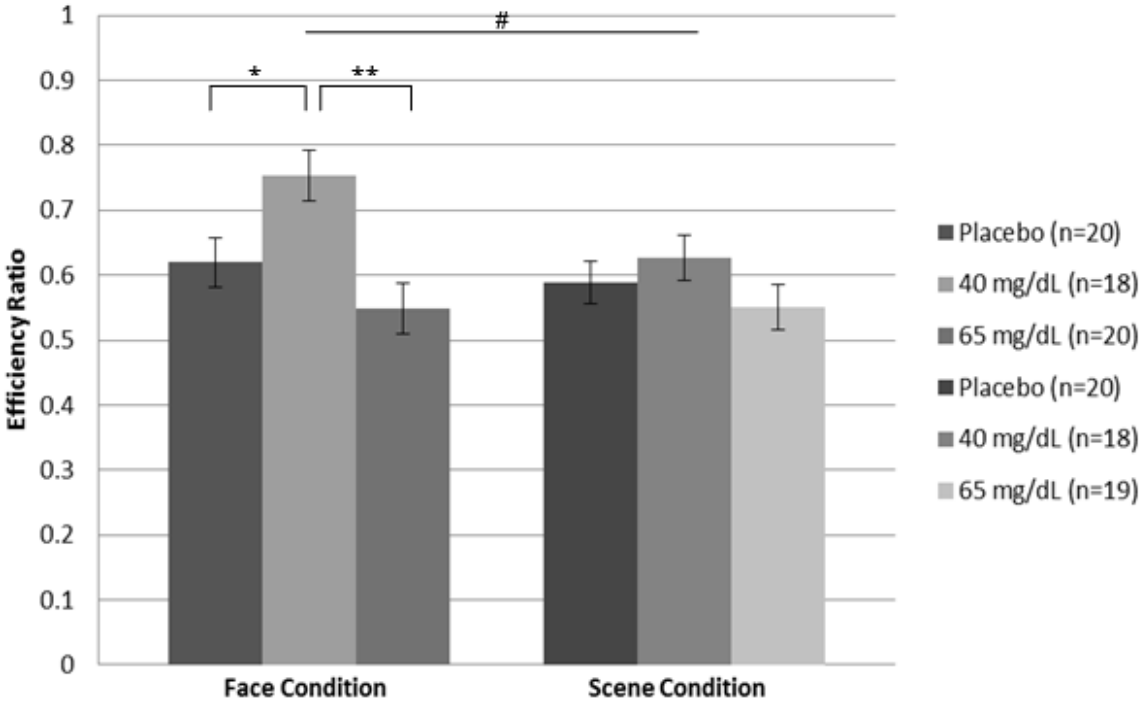

Figure 4-7. Efficiency: Condition X Sex Interaction. 2 (sex) X 3 (dose) X 2 (repeated: task condition) GLM revealed that the low dose group responded more efficient (% accuracy/mean reaction time) than the placebo or moderate dose group under the face condition. No significant difference between dose groups was observed under the scene condition. Error bars depict standard error. #$F_{2,51}$=4.46, p=0.02, *t_{36}=2.46, p=0.04, **t_{36}=3.68, p=0.002

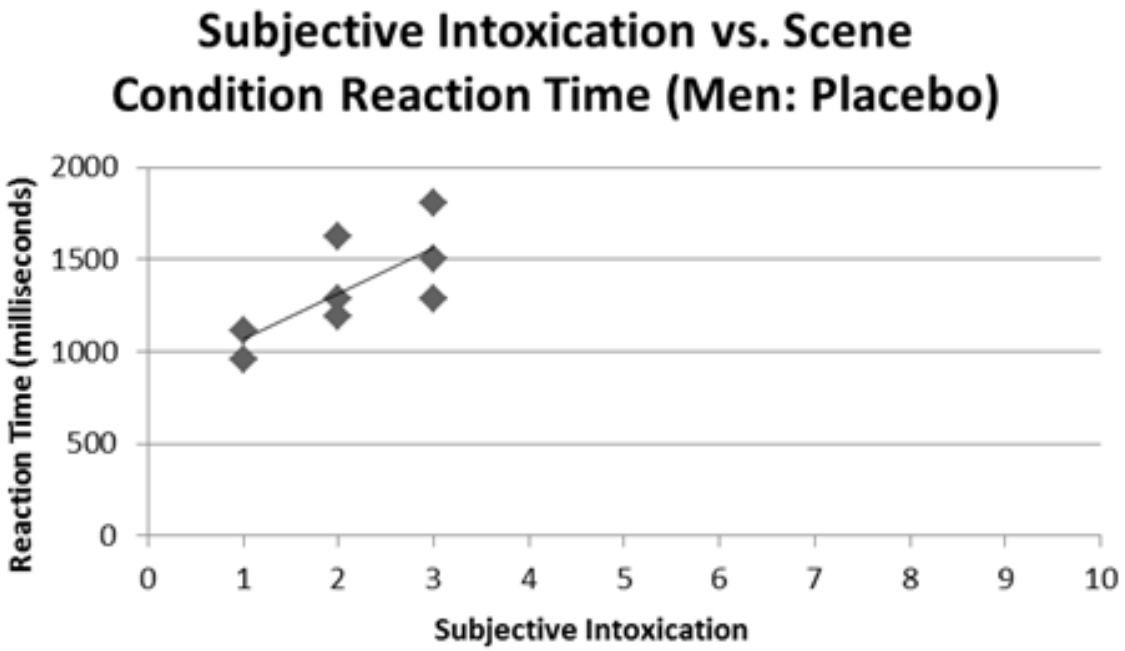

Figure 4-8. Subjective Intoxication vs. Scene Condition Reaction Time (Men: Placebo Dose Group). Correlational analyses revealed that for men who received placebo, but not women, higher subjective intoxication was significantly associated with longer reaction times ($r=0.72$, $p=0.04$).

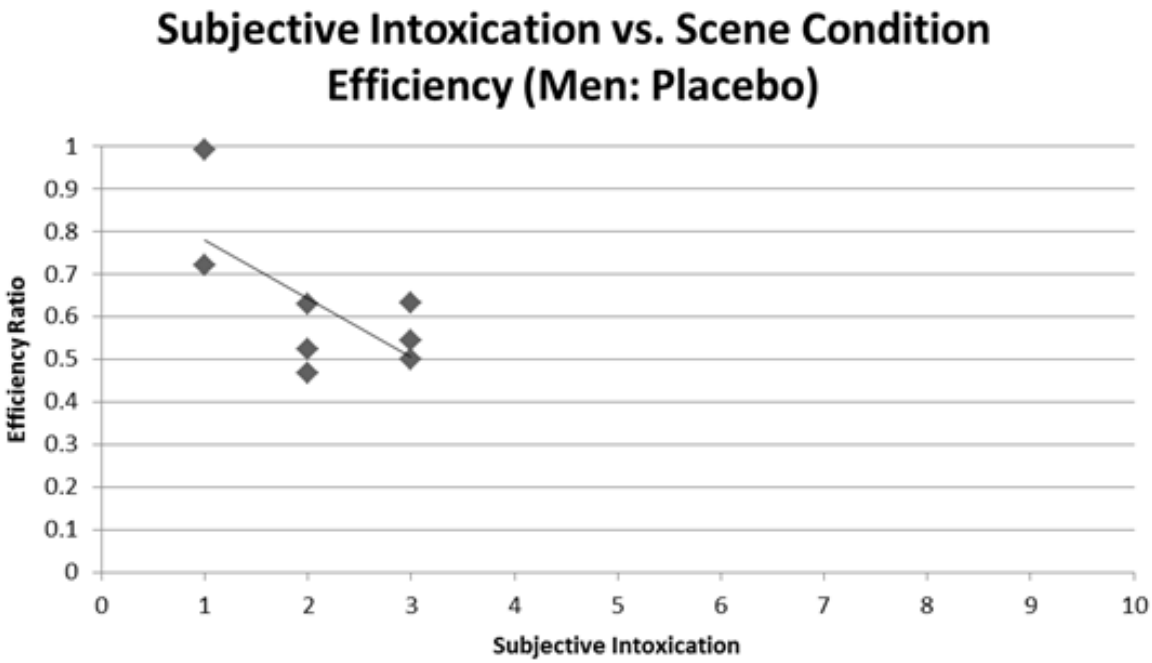

Figure 4-9. Subjective Intoxication vs. Scene Condition Efficiency (Men: Placebo Dose Group). Correlational analyses revealed that for men who received placebo, but not women, higher subjective intoxication was associated with worse efficiency ratios (% accuracy / mean reaction time) in the scene condition (r=-0.67, p=0.07).

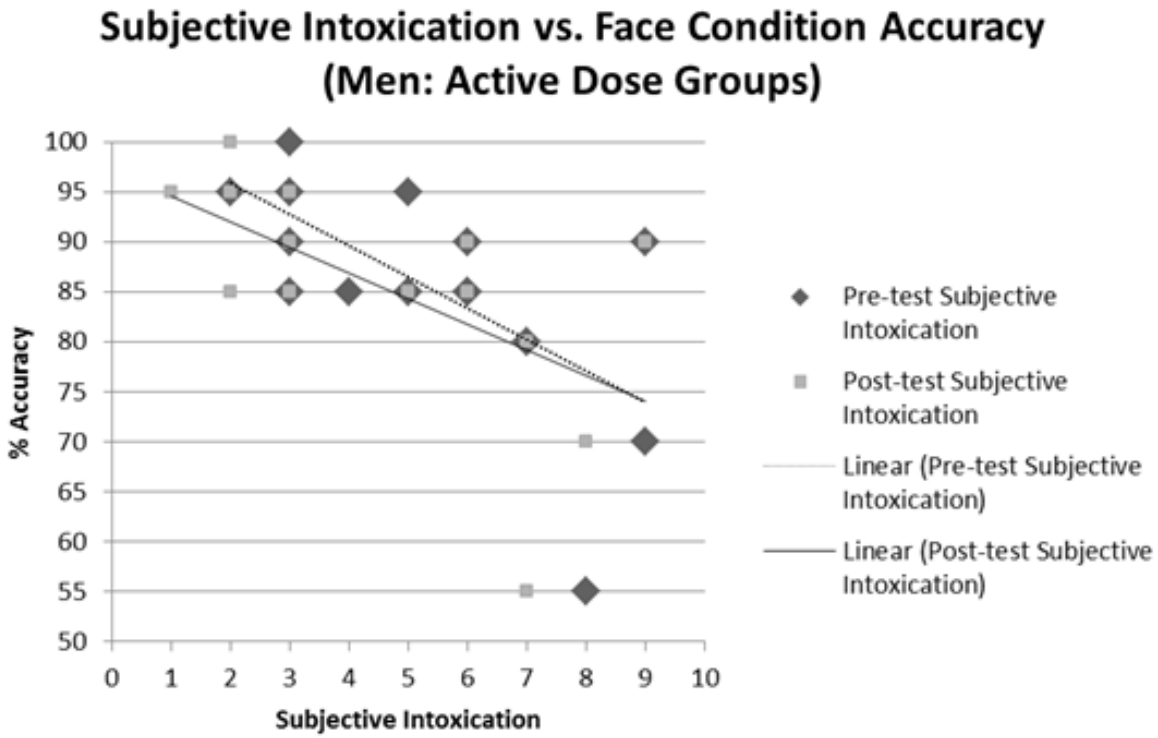

Figure 4-10. Subjective Intoxication vs. Face Condition Accuracy (Men: Active Dose Groups). Correlational analyses revealed that for men who received an active dose, but not women, higher pre and post-test subjective intoxication was associated with worse accuracy under the face condition (r=-0.64, p=0.01; r=-0.58, p=0.02, respectively).

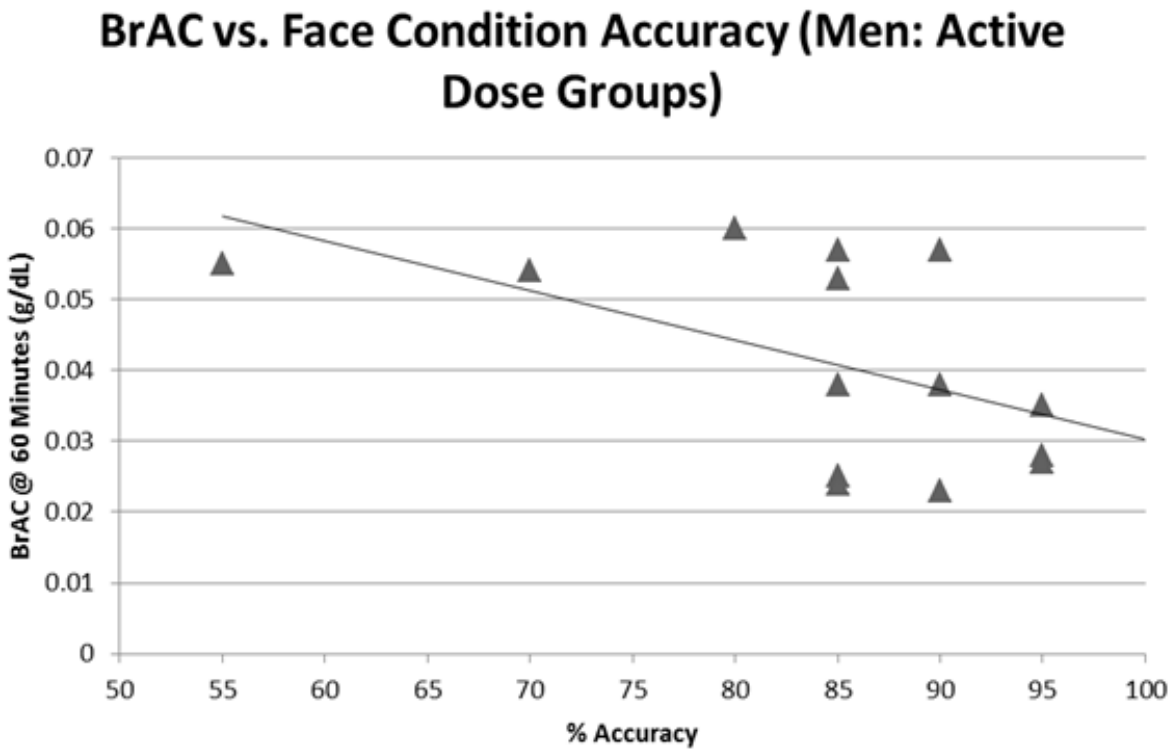

Figure 4-11. BrAC vs. Face Condition Accuracy (Men: Active Dose Groups). Correlational analyses revealed that for men who received an active dose, but not women, BrAC measures at 60 minutes post beverage consumption were significantly associated with poorer accuracy scores under the face condition (r=-0.53, p=0.05).

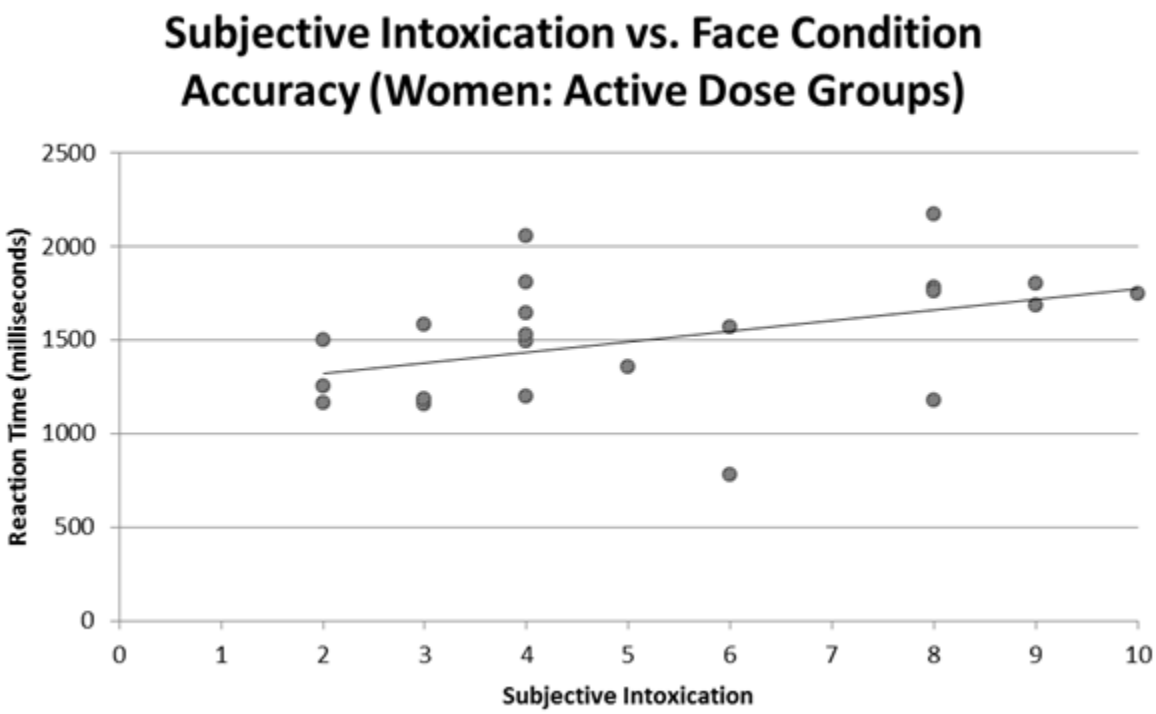

Figure 4-12. Subjective Intoxication vs. Face Condition Accuracy (Women: Active Dose Groups). Correlational analyses revealed that for women who received an active dose, but not men, subjective intoxication was significantly associated with slower reaction times under the face condition (r=0.43, p=0.04).

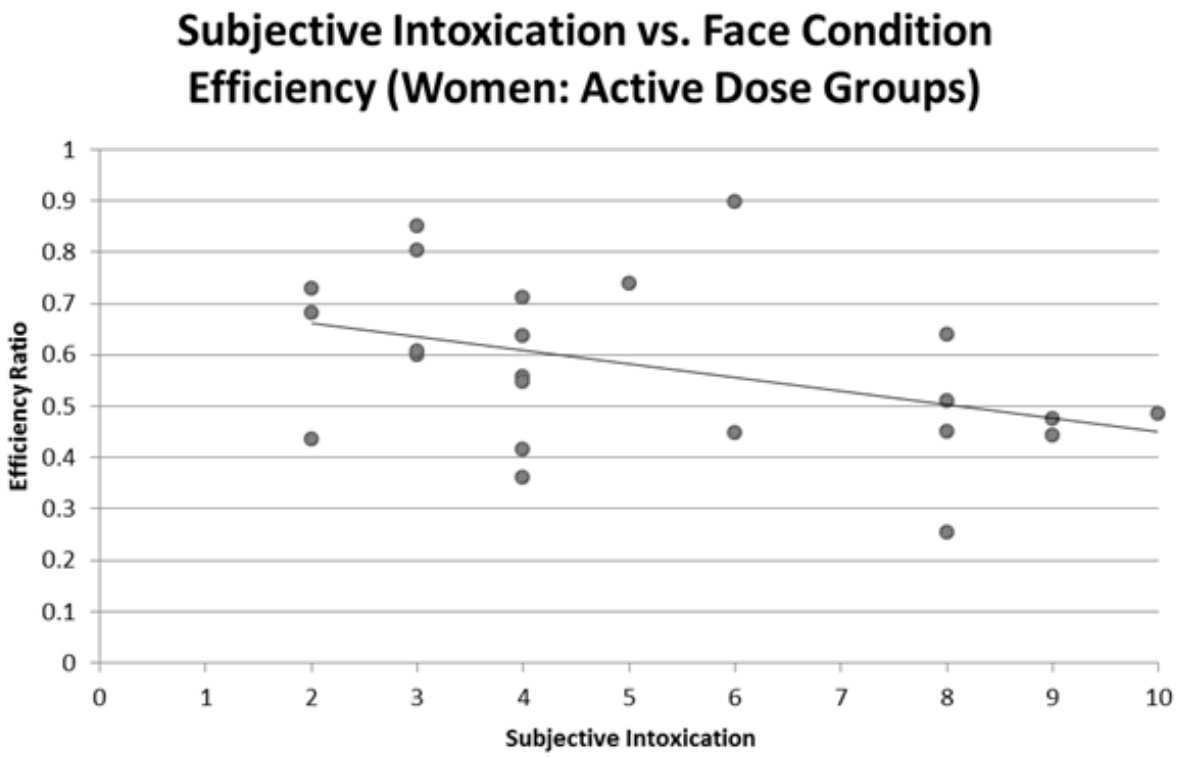

Figure 4-13. Subjective Intoxication vs. Face Condition Efficiency (Women: Active Dose Groups). Correlational analyses revealed that for women who received an active dose, but not men, subjective intoxication was significantly associated with worse efficiency ratios (% accuracy / mean reaction time) under the face condition (r=-0.41, p=0.05).

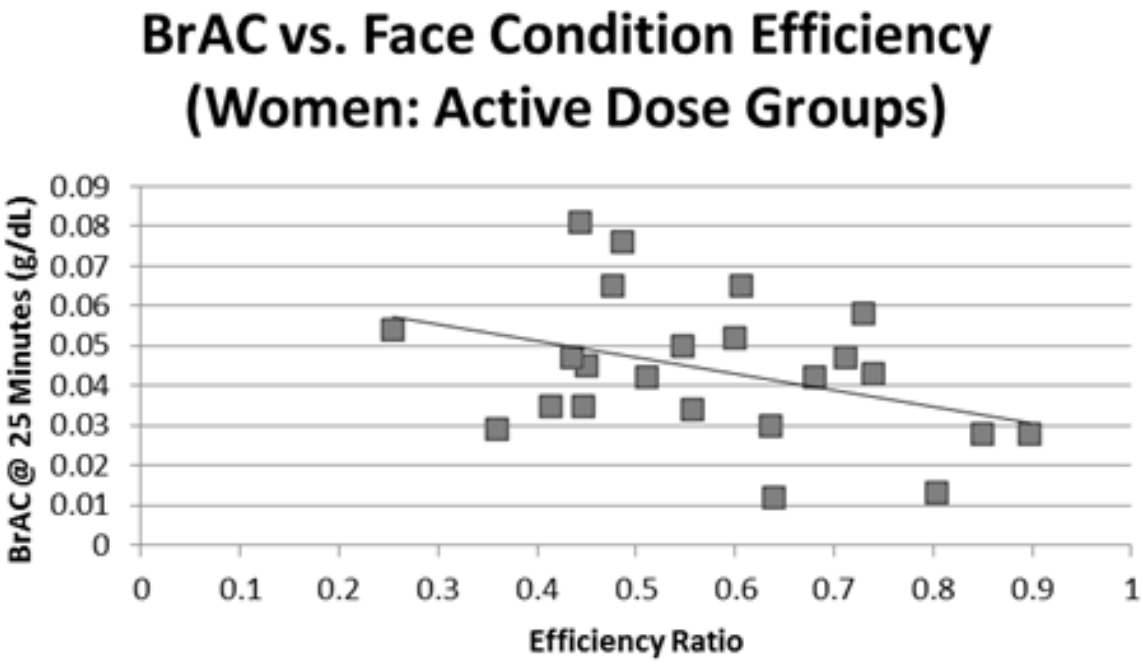

Figure 4-14. BrAC vs. Face Condition Efficiency (Women: Active Dose Groups). Correlational analyses revealed that for women who received an active dose, but not men, BrAC measures at 25 minutes post beverage consumption were associated with poorer efficiency ratios (% accuracy / mean reaction time) under the face condition (r=-0.38, p=0.08).

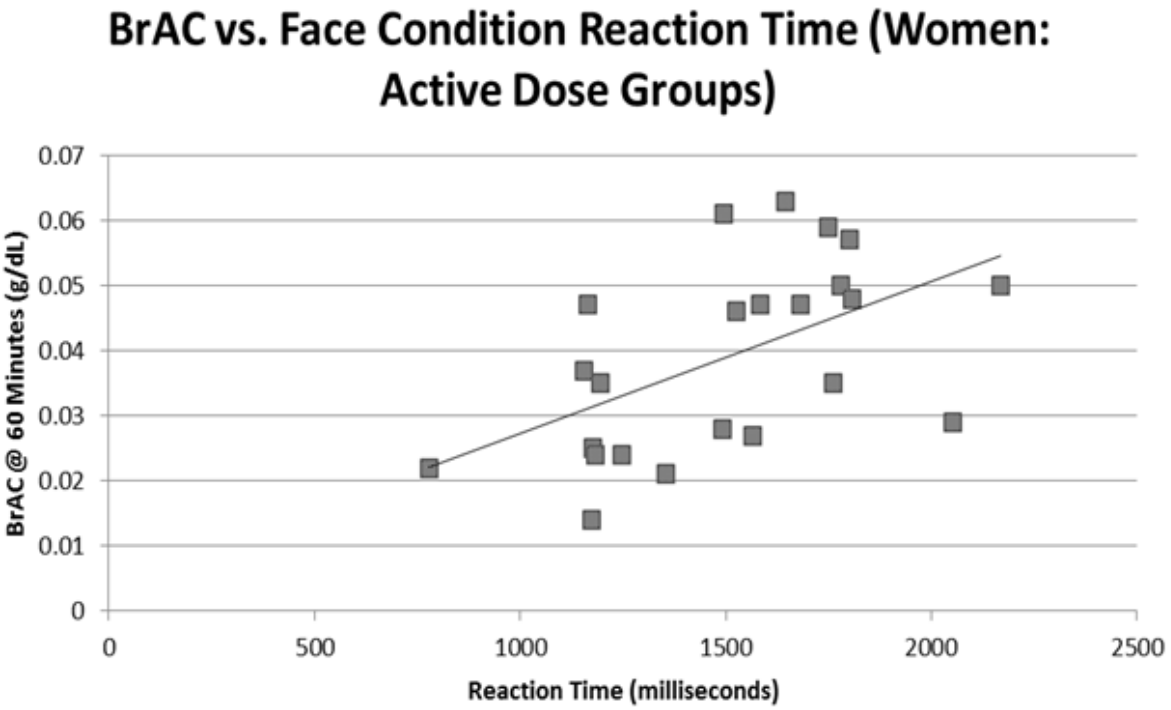

Figure 4-15. BrAC vs. Face Condition Reaction Time (Women: Active Dose Groups). Correlational analyses revealed that for women who received an active dose, but not men, BrAC measures at 60 minutes post beverage consumption were significantly associated with longer reaction times under the face condition ($r=0.54$, $p=0.008$).

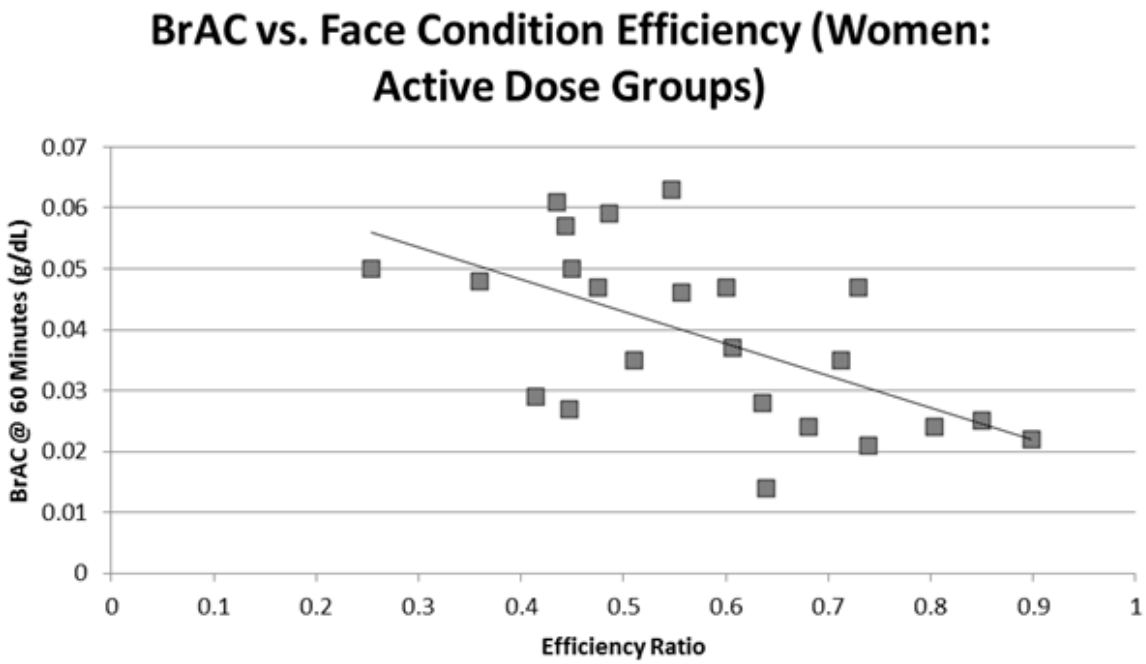

Figure 4-16. BrAC vs. Face Condition Efficiency (Women: Active Dose Groups). Correlational analyses revealed that for women who received an active dose, but not men, BrAC measures at 60 minutes post beverage consumption were significantly associated with worse efficiency ratios (% accuracy / mean reaction time) under the face condition (r=-0.59, p=0.003).

CHAPTER 4
DISCUSSION AND CONCLUSIONS

A lifestyle of moderate drinking is shown to promote healthy physical and cognitive aging. However, few studies have examined the more immediate cognitive effects of acute alcohol consumption among older adults. Furthermore, research addressing behavioral sex differences among the older adult population in relation to acute moderate alcohol consumption is almost nonexistent. Therefore, the current study was performed in an effort to determine whether the behavioral consequences of moderate or low dose alcohol administration differed between older men and women. For this study, we established one hypothesis and three empirical questions: Hypothesis 1) Subjects administered the moderate alcohol dose (0.065% g/dL) will perform worse on tasks assessing psychomotor, set-shifting, and working memory performance, than those administered the low dose (0.04% g/dL) or placebo (0.0% g/dL), Empirical Question 1) Will administration of the low dose facilitate performance (compared to the placebo and moderate dose) on psychomotor, set-shifting, or working memory tasks (WMT), Empirical Question 2) Will older men and women perform differently on tasks assessing psychomotor abilities, set-shifting, or attention mediated working memory, Empirical Question 3) Will there be a dose by sex interaction on any of the behavioral tasks?

Discussion: Hypotheses and Implications

The hypothesized effect of dose (Hypothesis 1) was not observed for TMT-A or TMT-B, implying that low and moderate dose alcohol did not influence psychomotor or set-shifting performance among this particular population of older adults. However, relevant to Hypothesis 1 and Empirical Question 1, dose effects were observed for

accuracy and efficiency in the WMT. Ss who received the low dose (40 mg/dL) were significantly more accurate and efficient than those who received the moderate dose (65 mg/dL). However, no difference between the placebo group and the low or moderate dose groups was observed. Results suggest that acute moderate alcohol intake has differential effects at varying doses, regardless of sex. Pertaining specifically to Empirical Question 1, the difference between the low and moderate dose groups was largely driven by the slight facilitative effect of the low dose and the modest detrimental effect of the moderate dose on working memory performance (accuracy & efficiency).

A dose X condition interaction revealed that the low dose group responded more efficiently than the placebo or moderate dose groups under the 'face condition', with no significant difference between the placebo and moderate dose groups. Additionally, all doses performed similarly under the 'scene condition'. This interaction suggests that administration of low dose alcohol facilitated functional performance on the WMT under the 'face condition' (Empirical Question 1). Moreover, it is suggested that among older adults, administration of moderate dose alcohol does not significantly impair the efficiency of working memory performance relative to placebo.

Sex differences (Empirical Question 2) in psychomotor performance were not observed. However, analyses revealed sex differences in set-shifting performance and response efficiency on the WMT. Women exhibited better set-shifting skills than men, whereas men responded more efficiently on the WMT across doses and task conditions. It seems that among this study population, women's ability to set-shift and display cognitive flexibility may be better than men's. However, replication of this finding is required to more thoroughly characterize sex differences in set-shifting abilities

among older adults. The sex effect observed for efficiency may be explained by the slightly faster, albeit statistically insignificant, mean reaction time observed among men. Perhaps women were more cautious when responding to stimuli; however, this is not clear. This result should be explored further with an assessment of the confidence of one's response (etc.), in order to fully understand the reason behind the slightly faster reaction times observed among men.

Results stress the importance of the task administered and the dependent measure of interest when assessing sex differences. Opposing effects were observed dependent upon the task and the cognitive domain of interest. Furthermore, the dependent measure may alter the interpretation of results. For example, although men and women in this study were equivalently accurate and had similar reaction times to accurate trials, the efficiency of the response seemed to be a more sensitive measure of sex differences in working memory performance for this particular study. Additionally, sex differences may be more difficult to detect depending on the cognitive domain of interest (e.g. psychomotor; Houx & Jolles, 1993). Therefore, the task difficulty should be taken into consideration when interpreting results.

Dose by sex interactions (Empirical Question 3) were not observed for any of the analyses, suggesting that placebo, low, and moderate doses do not differentially affect older men and women who maintain a lifestyle of moderate drinking. Although much of the acute alcohol literature implies that women are more susceptible to the effects of alcohol relative to men (e.g. Miller et al., 2009), this finding was not true for the current study. This conclusion derived from other studies may be due to the administration of equal alcohol doses across Ss, resulting in unequal BrACs between men and women.

However, these results could be specific to the tasks administered, doses administered, and/or the population of interest. Further assessment of low and moderate dose alcohol administration is necessary to better characterize the effects of dose and sex on behavior.

Correlational Analyses

Results indicate that measures of intoxication (i.e. subjective intoxication and BrAC) did not share a relationship with psychomotor or set-shifting performance regardless of sex or dose.

Furthermore, outcomes suggest that subjective intoxication under the placebo dose influenced performance on the scene condition more so for men than women. Due to differences in task difficulty (‘face condition’ vs. ‘scene condition’), it seems fitting that subjective intoxication correlated with performance under the more difficult task condition. However, the reason for the differential sex associations is unclear.

Additionally, findings indicate that subjective intoxication and BrAC are associated with poorer working memory performance under the ‘face condition’. However, measures of intoxication seem to affect working memory performance for men and women differently; actual and self-reported measures of intoxication were associated with poorer measures of reaction time and efficiency among women, whereas and actual and self-reported intoxication measures were associated with poorer accuracy among men. It is unclear why measures of intoxication affected men and women in this way. However, one could speculate that observed differences were due to implementation of different strategies (e.g. women slowing their reactions to the stimuli in order to attempt to respond more accurately; Carriere et al., 2010; Salthouse, 1979; Sklar et al., 2012).

Conclusion

Documented sex differences in behavioral performance among older adults and the influence of acute low-dose alcohol consumption on those behaviors are largely lacking in the literature. These data provide new and useful information regarding the behavioral effects (psychomotor, set-shifting, and working memory performance) of acute alcohol consumption on the older adult population. Further investigation of the relationship between sex, acute low-dose alcohol administration, and behavior among older adults is needed to make evidence based conclusions.

Study Limitations

Age Range

We recruited older Ss within a restricted age range (55-70). Therefore, the study did not provide information regarding low-dose alcohol's effects on psychomotor/set-shifting abilities or working memory performance for those younger than 55 or older than 70. Although the current study was not an assessment of the aging process and its effects on cognition, future studies should include age groups outside of this range to make more thorough conclusions from results.

Dose Range

In order to focus the direction of the study, only two active doses (40 mg/dL & 65 mg/dL) were used to assess the effects of acute moderate alcohol consumption. Future work should assess the effects of other doses/BrACs associated with a common social drinking episode (i.e. BrACs <0.03 g/dL and >0.07 g/dL). Specifically, sex differences among older adults may exist at BrACs not assessed in this study.

Sample Size

Because of the thorough screening processes implemented during recruitment, many older adults were unable to participate in the study. Reasons for exclusion included greater than moderate drinking status, high levels of education, common health conditions (e.g. uncontrolled diabetes/high blood pressure), and the use of medication that contraindicated alcohol consumption. A larger sample size may have allowed for more thorough and detailed characterizations of the relationships observed between moderate alcohol, sex, and behavioral performance. Therefore, further work should assess these relationships with a larger sample of healthy older adults.

Task Limitations

For study feasibility, only one task was used to assess each behavioral domain (i.e. psychomotor performance, set-shifting, and working memory). However, further assessment of moderate alcohol's effects on these domains, through the use of various tasks, is required to make detailed conclusions about sex differences among older moderate drinkers. The complexity of the tasks and the time at which the tasks are administered in relation to the time of alcohol administration must be varied to acquire a better understanding of the relationships reported above.

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BIOGRAPHICAL SKETCH

Lauren Hoffman was born in Los Angeles, CA. She graduated from Reseda High School in 2007 and earned a Bachelor of Arts in psychology from San Diego State University in 2011. As a child and adolescent, Lauren became very interested in her father's work as a neurosurgeon and began learning about the structural components of the brain. During her undergraduate education, she became especially fascinated with neuropsychology. Specifically, she developed interest in the behavioral and neurophysiological consequences of drug consumption and addiction. As a graduate student, Lauren's enthusiasm for empirical science and the methods employed to obtain evidence based conclusions cemented her professional career.

Upon completion of her M.S., Lauren plans to continue in Dr. Nixon's lab as a Ph.D. student and pursue training in addictions research and electrophysiology. When Lauren is not working in the laboratory, she enjoys outdoor activities such as hiking, biking, and camping with her beloved dogs and family.