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WASHINGTON UNIVERSITY IN ST. LOUIS

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The Effects of Cigarette Smoking During Acute Alcohol Intoxication

by

Kevin Donald Packerham

A dissertation presented to the
Graduate School of Arts and Sciences
of Washington University in
partial fulfillment of the
requirements for the degree
of Doctor of Philosophy

May 2014

Saint Louis, Missouri

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ABSTRACT OF THE DISSERTATION

The Effects of Cigarette Smoking During Acute Alcohol Intoxication

by

Kevin Donald Packingham

Doctor of Philosophy in Psychology

Washington University in St. Louis, 2014

Professor Deanna Barch, Chair

Professor John W. Rohrbaugh, Co-Chair

The consumption, and often abuse, of alcohol is frequently accompanied by cigarette smoking. Between eighty and ninety-five percent of alcoholics also smoke cigarettes, a rate more than four times higher than in the general population. The mechanisms underlying this association remain poorly understood. A general class of explanation is that smoking might affect the acutely intoxicating effects of alcohol. The relationships could take several forms, none of which is necessarily exclusive of another. These could include 1) synergism of effects, especially reward-related feelings of stimulation and positive affect, 2) additive effects, whereby the stimulating effects of nicotine could offset the depressant effects of alcohol, and 3) smoking-related desensitization to the effects of alcohol, by a mechanism of cross-tolerance.

The latter proposal, that smoking (i.e., nicotine) leads to cross-tolerance to alcohol, provides a guiding hypothesis for the research described here. Such a proposal is supported by an extensive body of evidence from animal studies that is consistent with an interpretation in terms of cross-tolerance between nicotine and

alcohol, such that nicotine consumption diminishes sensitivity to the acute intoxicating effects of alcohol (on multiple measures). It has been hypothesized that the reduced sensitivity to the effects of alcohol could lead, in turn, to increased consumption and risk of addiction.

This research examines systematically the acute effects of moderate doses of alcohol and cigarette smoking alone and in combination, on several measures in a controlled laboratory environment. Principal focus is on measures of postural control, which are emphasized because of their known sensitivity to alcohol at moderate doses, and the role they have played in prior studies of individual differences in sensitivity to acute alcohol. Additionally, measures were obtained of subjective effects, oculomotor control, and cognitive functioning.

Eight participants (four female) were tested in four counterbalanced sessions involving alcohol only, cigarette only, alcohol with cigarette, and alcohol placebo only. During all sessions measures were obtained at baseline and at repeated intervals after dosing. Consistent with indications of cross-tolerance between alcohol and nicotine, smoking during the experimental sessions diminished selected effects of alcohol on key measures of postural and, to lesser extent, oculomotor control and subjective effects. The specific cognitive tasks chosen for study proved to be ineffective at detecting effects of alcohol or cigarette smoking. Results are discussed in terms of the physiological and psychological changes associated with the development of acute cross-tolerance, and other forms of interaction between alcohol and nicotine.

The Effects of Cigarette Smoking During Acute Alcohol Intoxication

INTRODUCTION

Alcohol and cigarettes are often consumed together. This joint pattern of drinking alcohol and smoking cigarettes can have a significant negative effect on well-being, which include a variety of psychiatric, medical, legal, and social consequences (Volkow & Ting-Kai, 2005). In addition, a pattern of co-use can lead to excessive consumption since each substance tends to cause increased use of the other (Bobo & Husten, 2000) and ultimately to alcohol dependency (DiFranza & Guerrera, 1990).

The strong association between alcohol and cigarette consumption is apparent from several lines of evidence. For example, smokers who are nicotine-dependent show a four-fold risk of being alcohol-dependent (John, Meyer, Rumpf, & Hapke, 2003). In addition, the amount of tobacco smoked is positively correlated with the amount of alcohol consumed and the severity of alcohol dependence (Dani & Harris, 2005).

Numerous factors may be responsible for the development of abusive alcohol and cigarette consumption patterns including neural mechanisms, interoceptive and exteroceptive cues, pre-disposing genetic traits, personality, demographics, and developmental factors (Fertig & Allen, 1995). This complex set of interactions could include antagonism or enhancement of drug action, enhancement by one drug of the reinforcing actions of the other, or a decrease in sensitization following chronic treatment (Collins & Marks, 1995).

As reviewed below, alcohol and tobacco tend to be used in combination, in ways that may mutually promote excessive consumption. A possible mechanism underlying

this co-occurrence is *cross-tolerance*, by which nicotine and alcohol moderate the physiological and psychological effects of each other. This moderation includes a diminution of the subjective and behavioral response to alcohol, which could subsequently increase drinking (Hurley, Taylor, & Tizabi, 2012). The present research is guided largely by the general hypothesis that cross-tolerance occurs between cigarette smoking and alcohol, as assessed by multiple laboratory measures of postural control (both sensory and motor aspects), eye movements, and subjective response. These measures were chosen because of their known sensitivity to the acute effects of alcohol. Doses of alcohol and nicotine (given in the form of cigarette smoking) were administered, in separate sessions, alone and in combination. The goal was to understand the interactive effects of these common substances, in the hope of contributing to our understanding of the factors that lead to excessive consumption of alcohol.

REVIEW OF LITERATURE

Societal Implications of Alcohol and Tobacco

Understanding the development of patterns that lead to abusive alcohol consumption is particularly important because of the substantial number of individuals who are considered problem drinkers. The National Institute on Alcohol Abuse and Alcoholism (NIAAA) estimates that nearly 18 million Americans abuse alcohol or are alcoholics. Independent of personal consequences, the financial cost to society is estimated at approximately \$185 billion per year, which includes medical costs (cancer, liver cirrhosis, immune system problems, brain damage, and fetal alcohol syndrome), accidents (automobile, recreational, and on-the job), and increased risk of homicide and

suicide (Research Society on Alcoholism, 2011). In addition, alcohol abuse is associated with an increased incidence of depressive episodes, severe anxiety, insomnia, suicide, and abuse of other drugs (Schuckit, 2009).

The consequences associated with smoking cigarettes are equally alarming. The Center for Disease Control (CDC) estimates 43.8 million Americans smoke cigarettes with an annual mortality rate associated with smoking estimated at 440,000 in the United States. Cigarette smoking has been linked to cancer, cardiovascular disease, respiratory disease, and a substantial number of severe burns. Each year an estimated \$96 billion is spent for cigarette-related ailments and the loss of productivity is estimated at \$97 billion (Centers for Disease Control and Prevention, 2014).

Mutual Consumption Patterns of Alcohol and Tobacco

There is extensive evidence that cigarettes and alcohol increase the consumption rate of the other when consumed simultaneously (Johnson & Jennison, 1992). These drugs are governed by the same factors such that the frequency of use of one can be used to predict the consumption of the other (Kozlowski et al., 1993). Falk, Yi, and Hiller-Sturmhofel (2006) found a dose-response relation between alcohol and tobacco with rates of tobacco use, daily tobacco use, and nicotine dependence increasing monotonically with increasing level of alcohol consumption. McKee, Hinson, Rounsaville, and Petrelli (2004) obtained similar findings of a significant increase in smoking after the consumption of alcohol. Conversely, nicotine has been linked to an increase in the consumption of alcohol (Barrett, Tichauer, Leyton, & Pihl, 2006; Le, Wang, Harding, Juzysch, & Shaham, 2003; Lopez-Moreno, et al., 2004)

Links between alcohol consumption and cigarette smoking have been

investigated in several studies of community samples and treatment populations (e.g., Carmody, Brischetto, Matarazzo, O'Donnell, & Connor, 1985; John, Meyer, Rumpf, Schumann, Thyrian, & Hapke, 2003; Madden, Bucholz, Martin, & Heath, 2000; Rose, Brauer, Behm, Cramblett, Calkins, & Lawhon, 2004). The occurrence of nicotine dependence is significantly higher in alcohol-dependent patient groups (Hertling et al., 2005). Among alcoholics, of which almost 90% smoke cigarettes (Burling & Ziff, 1988), the amount of tobacco smoked is correlated with the amount of alcohol consumed and the severity of their alcohol dependence (Batel, Pessione, Maître, & Rueff, 1995; John, Meyer, Rumpf, Schumann, Thyrian, & Hapke, 2003). Alcoholics who smoke often report drinking more frequently and more alcohol per occasion than alcoholics who do not smoke (York & Hirsch, 1995).

Multiple behavioral, genetic, personality, pharmacological, developmental, and environmental factors may underlie these mutual consumption patterns. Istvan and Matarazzo (1984) reviewed the literature dealing with the relation among alcohol, cigarettes, and caffeine consumption. They suggested that of all these factors, the behavioral and pharmacological variables have the greatest effect on joint consumption. Behavioral explanations indicate that the use of one substance may act as a cue to initiate the use of the other or stimulate increased use of other psychoactive drugs. Pharmacological explanations suggest that alcohol and cigarettes are consumed in such a way so that the stimulating effects are augmented and the aversive effects are antagonized. Oliver, Blank, Van Rensburg, MacQueen, Thomas, and Drobles (2013) suggest that this pharmacological interaction creates cravings for nicotine when alcohol is consumed.

A pharmacological interaction was further demonstrated by Rose et al. (2004) who found that alcohol and nicotine potentiate the rewarding and antagonistic effects of each other based on subjective ratings. The amount of alcohol used in this study was relatively low (roughly half that of the current study, without a maintenance dose) and the results were not segmented by ascending or descending Blood Alcohol Concentration (BAC). Their findings suggested that nicotine tended to reverse the sedative effects of ethanol and that the nicotine rewarding effects such as satisfaction, liking, and calming were reduced by the ethanol. Kouri, McCarthy, Faust, and Lukas (2004) found that nicotine enhanced the positive subjective effects of alcohol such as euphoria shortly after alcohol administration, but they did not observe the same reversal in the sedative effects of alcohol during the descending portion of the BAC.

There is some evidence that the joint consumption patterns of alcohol and nicotine vary by gender. Epidemiologic data indicate that the prevalence of co-use and comorbidity is higher in men than women, with the highest rates in the youngest age groups and a steady decline observed in older age groups. Acheson, Mahler, Chi, and de Wit (2006) found that nicotine increased alcohol consumption in men whereas it decreased consumption in women. A possible pharmacological basis was not developed in the study, but it was shown that the subjective effects differed between men and women.

Although the emphasis in the present research is on the effects of smoking on alcohol intoxication, it is important to recognize that the effect may be bi-directional: that is, alcohol may affect the response to nicotine. Having a history of alcohol abuse has been associated with intensified smoking patterns (Keenan, Hatsukami, Pickens, Gust,

& Strelow, 1990). Laboratory studies have demonstrated that smoking intensity increases when alcohol is consumed (Nil, Buzzi, & Battig, 1984; Mello, Mendelson, Sellers, & Kuehnle, 1980). Griffiths, Bigelow, and Liebson (1976), for example, found that smoking rates increased by 35% following the consumption of alcohol. These changes in smoking patterns were dose related: the effect could be identified at BAC levels of 0.05% but not at 0.025% (Nil, Buzzi, & Battig, 1984). Animal studies also have identified diminished response to the effects of nicotine following chronic alcohol treatments (Lopez, White, & Randall, 2001). In general, alcohol decreases the stimulating effects of nicotine when administered together, depending on task and dose (Schaefer & Michael, 1992).

There is also evidence from animal studies that nicotine deprivation may affect the amount of alcohol consumed based on the level of dependence. Alcohol may be consumed to self-treat the impairment associated with nicotine withdrawal, which could result in increased alcohol consumption. Conversely, as alcohol impairment increases, there is a corresponding increase in cigarette consumption (Gulick & Gould, 2008).

Even though there is evidence that a direct causal link exists between smoking and alcohol consumption (Mintz, Boyd, Rose, Charuvastra, & Jarvik, 1985), it should be noted that much of the research in this area has used chronic alcoholics or animals that were chronically exposed to drugs. These effects could therefore be limited to a group that drinks heavily and are genetically at risk for alcoholism (Shiffman & Balabanis, 1995). Whereas alcohol increases cigarette consumption in populations with histories of alcoholism (Griffiths, Bigelow, & Liebson, 1976), the effects on smoking in non-alcoholic populations are more variable (Henningfield, Chait, & Griffiths, 1984).

Genetic Influences on Alcohol and Tobacco Consumption

As noted above, multiple factors may underlie the co-occurrence of cigarette and alcohol addiction. It is likely, given the strong relationship between alcohol and cigarette consumption, that different mechanisms of addiction may be active simultaneously since none of the factors are mutually exclusive (Shiffman & Balabanis, 1995). One interpretation is that the co-occurrence may represent a genetic propensity of some individuals toward addictive behaviors in general, or to engage in behavior that is socially unacceptable (DiFranza & Guerrera, 1990). Similarly, there have been indications that genetic influences contribute to the risk for dual dependence (True, Xian, Scherrer, Madden, Bucholz, Heath, Eisen, Lyons, Goldberg, & Tsuang, 1999).

While the environmental and pharmacological influences are well documented, studies of human twins and studies conducted with laboratory animals support the view that the predisposition to use alcohol and smoke cigarettes has a strong genetic component (Funk, Marinelli, & Le, 2006). Evidence for a common genetic pathway is particularly strong in recent reports from Vrieze, McGue, Miller, Hicks, and Iacono (2013) and Grucza and Bierut (2006). Flatscher-Bader and Wilce (2006) found that chronic alcohol consumption influenced gene expression in the pre-frontal cortex, and that heavy smoking had additive effects on selected genes, which could produce long-term adaptive changes. Some progress identifying the specific genes that regulate sensitivity to alcohol has been reported in both humans (Hinckers, Laucht, Schmidt, Mann, Schumann, Schuckit, & Heinz, 2006; Hu, Oroszi, Chun, Smith, Goldman, & Schuckit, 2005) and animal models (Boehm, Peden, Chang, Harris & Blednov, 2003).

Rodent breeding studies provide another line of evidence regarding the genetic

influence upon alcohol and nicotine response sensitivity. Gordon, Meehan, and Schechter (1993) found that rats bred for alcohol preference (P) were more sensitive to “ethanol-like” effects of nicotine than rats bred as non-preferring (NP). In a similar study Katner, McBride, Lumeng, Li, and Murphy (1996) observed that NP rats were more sensitive to the locomotor depressant effects of nicotine than P rats. These studies provide some indication that innate differences exist in the nicotinic receptors of P and NP rats.

The impact of genetic versus environmental influences in humans may vary by age group. In a study of alcohol and tobacco use in twins, Koopmans, van Doornen, and Boomsma (1997) found that adolescents aged 12-16 years were substantially influenced by shared environmental factors rather than genetics. In contrast, young adults were more influenced by genetic factors and to a less extent by shared environmental effects. In adult twins there was a significant genetic contribution to abstinence from alcohol use and smoking initiation.

Common genetic factors also may underlie observations that smoking cigarettes is associated with the initial use, and escalating consumption, of other addicting substances, including other common substances of abuse in addition to alcohol. The role that cigarettes play in developing future addictive behavior is not clear. Tobacco may escalate dependent patterns of drug use or it may be an early indication of genetic or physiological tendencies toward addiction (Henningfield, Clayton, & Pollin, 1990; Fleming, Leventhal, Glynn, & Ershler, 1989).

There is also evidence, reviewed in greater detail below, that genetic factors underlie individual differences in sensitivity to the acute response to alcohol. McCaul,

Turkkan, Svikis, and Bigelow (1990), for example, found that participants with no family history of alcoholism exhibited a significant increase in body sway during acute intoxication whereas participants with positive family histories were less affected. This suggests that a genetic predisposition for alcoholism diminishes sensitivity to alcohol, which can be measured using techniques such as posturography (discussed in detail below). This general finding has been obtained by other investigators, including the Australian Alcohol Challenge Twin Study (Heath, Madden, Bucholz, Dinwiddie, Slutske, Bierut, Rohrbaugh, Statham, Dunne, Whitfield, & Martin, 1999; Madden, Bucholz, Martin, & Heath, 2000), which observed significant evidence for genetic effects on body-sway and subjective intoxication rating after drinking alcohol.

Sensitivity to Acute Alcohol as a Marker of Risk for Alcoholism

A common thread in many attempts to understand individual differences in vulnerability to alcoholism is that people differ in their acute response to alcohol. Considerable attention has been paid specifically to the hypothesis that a low level of response to an acute dose of alcohol (with level of response regulated in turn by genetic and other factors) poses a risk factor. Even though the present study does not attempt to isolate any changes in sensitivity based on family history of alcoholism, this specific line of research is particularly relevant because it serves as a model for considering diminished sensitivity to alcohol as a risk factor—in the present case caused by smoking rather than associated with a positive family history of alcoholism. This is especially the case for measures of posturography, which often have been used as the cardinal measures of sensitivity for much of the research on family history.

Longitudinal studies, at follow-up intervals ranging from 10 to 25 years, have shown that low sensitivity to alcohol is a risk factor for alcohol-use disorders, independent of typical consumption levels and age at which drinking was initiated (Trim, Schuckit, & Smith, 2009). It has been hypothesized that “alcohol-insensitive” offspring of alcoholics would tend to drink more to achieve comparable levels of intoxication and thereby increase their risk of addiction (Collins & Marks, 1995; Schuckit, 1985; 1988; 1994). This “sensitivity” hypothesis is relevant to the present investigation, insofar as there is evidence (reviewed below) that smoking can regulate the sensitivity to acute alcohol in much the same way as does a positive family history of alcoholism.

Level of response itself appears to be highly heritable (Viken, Rose, Morzorati, Christian, & Li, 2003). In a meta-analysis of the literature in this area Pollock (1992) found support for the general hypothesis that the sons of alcoholics, who are presumed to be at heightened risk for becoming alcoholic, show diminished sensitivity to the acutely intoxicating effects of alcohol throughout the blood-alcohol concentration (BAC) curve—both ascending and descending limbs.

A substantial body of evidence supporting this sensitivity hypothesis has been developed by Schuckit (and other investigators), following early reports that the sons of alcoholics reported less intense subjective intoxication levels (Schuckit, 1994) and less effect on body sway (Schuckit, 1985) than did the sons of non-alcoholics after laboratory challenge doses of alcohol. This finding also was confirmed for daughters of alcoholics (Eng, Schuckit, & Smith, 2005; Schuckit, Smith, Kalmijn, Tsuang, Hesselbrock, & Bucholz, 2000). A combination of family history and laboratory measures of alcohol sensitivity were found to predict several key alcohol-related

outcomes including maximum quantity and frequency consumed along with DSM-IV diagnosis (Schuckit, Smith, Pierson, Danko, & Beltran, 2006)

Newlin and Thomson (1990; see also Newlin & Renton, 2010) concurred that the offspring of alcoholics demonstrate diminished sensitivity on some measures but, as an important extension, proposed that sensitivity is inherently different for the ascending and descending limbs of the BAC curve. It was suggested that the offspring of alcoholics exhibit enhanced feelings of pleasure and stimulation during the ascending limb of the BAC curve while also demonstrating lowered depressant effects during the descending limb. A recent narrative review (Morean & Corbin, 2010) and meta-analysis (Quinn & Fromme, 2011) of the now-substantial literature have generally concurred with this suggestion — sensitivity to alcohol is reduced in the offspring of alcoholics during the descending limb of the BAC, but (somewhat less consistently) increased during the ascending limb of the BAC, particularly on subjective measures related to stimulation.

Although principal emphasis in prior work on alcohol sensitivity has been on subjective measures of intoxication, multiple additional responses have been investigated within this context. These include measures of body sway, autonomic and electroencephalographic activities, neuroendocrine responses, and behavioral performance measures. An important consideration is that there is substantial inter-individual variability in the level of sensitivity across various response domains (Mundt, Perrine, & Searles, 1997), which highlights the importance of assessing sensitivity using multiple measures.

It is also important to note the consistent utility of measures of postural control (as reviewed below), which have the advantage of providing objective measures that

are highly sensitive to moderate doses of alcohol (Goebel, Dunham, Rohrbaugh, Fischel, & Stewart, 1995), and that have consistently proved to be useful as phenotypic markers of alcohol sensitivity in the studies of Schuckit and others. Moreover, there is substantial evidence (reviewed below) for interactions between alcohol and nicotine in the central neural systems that are involved in the control of posture. The utility of postural control measures in prior sensitivity research provides a key motivation for their use in the present context.

Physiological Interaction of Alcohol and Tobacco

Physiologically, the use of cigarettes and alcohol, alone or in combination, produce broad changes in the brain including alteration in the level of transmitters and the distribution of the affected receptors (Al-Rejaie & Dar, 2006; Lajtha & Sershen, 2010). These changes and the subsequent impact on consumption patterns are unique based on the dissimilar physiological effects. Nicotine acts on the brain directly through the activation of nicotinic acetylcholine receptors whereas alcohol does not bind with any single type of receptor. Nicotine has primarily stimulating effects and increases alertness whereas alcohol is a depressant and generally decreases alertness. The withdrawal and deprivation symptoms induced by each vary dramatically (Funk, Marinelli, & Le, 2006).

There is some evidence that the interaction of alcohol and nicotine is hormonal in nature. Pomerleau (1995) suggests that nicotine stimulates central peptides such as arginine vasopressin (AVP) and that smoking may therefore dampen the level of intoxication caused by alcohol. This reduction in intoxication would result in reduced

fatigue and increased arousal compared to alcohol consumed alone (Perkins, Sexton, DiMarco, Grove, Scierka, & Stiller, 1995).

Another contributor to the link between alcohol and smoking is an interaction at the level of neurotransmitter receptors. Ethanol has been linked to a decrease in the release of acetylcholine and a corresponding reduction in sensitivity to nicotine (Majchrzak & Dilsaver, 1992). It may be that the increase in smoking is necessary to counteract the antagonistic effects of alcohol. The chronic nature of this relationship was identified by Keenan et al. (1990) who suggested that individuals who abuse alcohol are more likely to have a tobacco-related pathology. Chronic cigarette smoking creates tolerance to the effects of both nicotine and alcohol, which increases the consumption of both drugs to achieve the same effects that were initially achieved at lower levels of consumption (Gulick & Gould, 2008)

On a chronic basis, alcohol and nicotine administration both lead to changes in the numbers of nicotinic acetylcholine receptors (nAChR) (Davis & deFiebre, 2006), and acute alcohol intoxication may alter or modulate the function of the nAChR receptors (Cardoso, Brozowski, Chavez-Noriega, Harpold, Valenzuela, & Harris, 1988). These receptors are particularly important because they have been shown to activate the release of dopamine (Schlaepfer, Hoft, & Ehringer, 2008). Doyon, Dong, Ostroumov, Thomas, Zhang, and Dani (2013) found that when rodents were pre-exposed to nicotine they increased the self-administration of alcohol and there was also a decrease in the dopamine response.

Tizabi, Bai, Copeland, and Taylor (2007) observed a higher release of dopamine from the nucleus accumbens shell when nicotine and alcohol were administered in

combination, compared to each drug in isolation. Conversely, when nicotinic antagonists were administered, the reinforcing effects of alcohol were partially moderated, indicating that the rewarding effects of alcohol can be mediated by central nicotinic receptors. They suggest that the combined effects of alcohol and nicotine on the reward pathway are a contributing factor to the high rates of cigarette smoking among alcoholics.

Yet another general category of explanation is that some of these effects may derive from an influence of nicotine on the metabolism of alcohol. There is a significant increase in the serum levels of the liver enzyme gamma-glutamyl transferase when alcohol and cigarettes are consumed simultaneously rather than when alcohol is consumed in isolation (Breitling, Raum, Muller, Rothenbacher, & Brenner, 2009). Parnell, West, and Chen (2006) suggest that the primary mechanism for the moderating effects of nicotine is related to gastric function. In a study of female rats, two different experiments were performed that included high nicotine doses (0, 2.0, 4.0, or 6.0 mg/kg) and low nicotine doses (0, 0.25, 0.5, or 1.0 mg/kg) plus alcohol administration through intubation followed by blood-based BAC measurements. In the high nicotine experimental sessions, the control condition had a significantly higher BAC level than the three nicotine conditions. This difference also was observed in the low nicotine condition for the 0.5 and 1.0 mg/kg doses, but not for the 0.25 mg/kg dose. A third experiment was performed using both intra-peritoneal injection and intra-gastric intubation to support the hypothesis that gastric function was primarily responsible for this moderating effect. The lack of interaction from the injection suggests that the nicotine is delaying the gastric emptying of the alcohol into the small intestines and thus

lowering the BAC.

There is evidence for a variety of possible physiological interactions that might underlie the patterns of shared use between alcohol and cigarettes, as described above. Evidence for various types of interactions (which remains quite modest, particularly in humans), is reviewed briefly in the following material with an emphasis on the effects on sensitivity to alcohol.

Evidence for Cross-Tolerance Between Alcohol and Nicotine

It is clear that a positive relationship exists between alcohol and cigarette use, but the exact nature of their mutual reinforcement is not understood (Bien & Burge, 1990). As noted above, there is significant evidence that the separate effects of alcohol and nicotine might combine in such a way that the signs of intoxication will be modified—perhaps even fully or partially offset by nicotine on some measures. Collins and Marks (1995) suggest that the interaction of alcohol and nicotine could include antagonism or enhancement of drug action, enhancement by one drug of the reinforcing actions of the other, and cross-tolerance or sensitization following chronic treatment. Each of these mechanisms could act in isolation or concurrently to increase consumption. Istvan and Matarazzo (1984) hypothesized (and obtained supporting evidence) that people smoke when they drink in order to reverse performance deficits caused by alcohol intoxication. This would suggest that nicotine and alcohol interact on a pharmacological level in such a way that nicotine blunts, by a mechanism of cross-tolerance, the intoxicating effects of alcohol and thereby increases alcohol consumption.

In a study of human twins, Madden, Heath, Starmer, Whitfield, and Martin (1995) examined the relationship between smoking history and performance during an alcohol

challenge. It was found that the history of smoking was strongly associated with a reduction in self-reported intoxication levels for both males and females. However, male smokers demonstrated increased body sway at baseline and following a challenge dose of alcohol. In addition, the recovery from the alcohol challenge, as measured by blood-alcohol concentration, was also accelerated in male smokers. It should be noted that there was no control for the consumption of cigarettes leading up to, or during the laboratory sessions — a limitation that was explicitly acknowledged by the investigators.

In a later study of Madden, Bucholz, Martin, and Heath (2000) it was found that men and women who were current smokers at the time of the alcohol challenge study rated themselves as significantly less intoxicated than did nonsmokers despite receiving the same amount of alcohol. This indicates cross-tolerance between smoking and alcohol (acute versus chronic effects could not be distinguished in their design, because smoking during the testing was not controlled), or some similar interaction that leads to diminished response to alcohol when combined with smoking.

Animal studies have indicated that nicotine increases alcohol consumption and that partial cross-tolerance is developed (Burch, deFiebre, Marks, & Collins, 1988; Collins, Wilkins, Slobe, Cao, & Bullock, 1996). When mice were given nicotine, alcohol, or both for six months, all of the chronic drug-treated mice developed a tolerance to alcohol, which supports the existence of a shared tolerance mechanism between alcohol and nicotine and suggests that chronic nicotine exposure may dramatically decrease sensitivity to alcohol. This link is offered as a possible explanation for the combined abuse of alcohol and tobacco in humans (Collins, 1990; Collins et al., 1996; Collins, Burch, deFiebre, & Marks, 1988).

A parallel factor contributing to co-use may be the additive or synergistic activation of the reward system (Hurley, Taylor, & Tizabi, 2012). This effect may be bidirectional, since there is evidence that ethanol potentiates the pleasurable effects associated with cigarette smoking (Narahashi, Soderpalm, Olausson, Engel, Zhang, Nordberg, Marszalec, Aistrup, Schmidt, Kalouti, Smolka, & Hedlund, 2001). Similarly, Tizabi, Bai, Copeland, and Taylor (2007) found evidence in a murine model for synergism of reward when alcohol and nicotine were consumed concurrently.

In the present study there is limited opportunity to operationalize the assessment of tolerance and cross-tolerance in conventional pharmacological terms and it is therefore used primarily as a framework for interpreting the results and describing potential implications. This framework has been useful in carefully controlled animal studies (e.g., Collins et al., 1988; Collins et al., 1996), and it has been identified as an explanatory concept in related human studies (e.g., Madden et al., 1995). Here, the concept of cross-tolerance is invoked to describe a situation in which the exposure to one drug (smoking/nicotine) regulates the sensitivity to a second drug (alcohol). As is shown in the results of the present study, this often occurs in the absence of any appreciable effect produced by smoking alone, ruling out interpretation in terms of synergistic or additive effects. The results from the present study, along with the existing literature regarding pharmacological, physiological, and behavioral cross-tolerance, provides a basis for additional investigation aimed at explicating in greater detail the interactions between alcohol and cigarettes.

Postural and Oculomotor Control as Measures of Sensitivity to Alcohol

The sensitivity of postural control mechanisms to alcohol has been demonstrated in many acute alcohol challenge studies. These studies have focused in large part on assessing family history as a risk for developing alcohol-related pathologies (see above). The clear effects of alcohol on both postural and oculomotor control make them excellent measures of physiological changes in acute alcohol intoxication and possible effects associated with concurrent cigarette smoking. These measures are also less likely to be contaminated by the expectancy effects, which plague subjective and cognitive measures (Schuckit, 1985).

Postural and oculomotor control engages a large number of central and peripheral reflexive mechanisms. Consequently, the effect of alcohol can be assessed at a variety of levels. These include, but are not limited to, deficits produced by alcohol on cerebellar function, changes in reflexive and adaptive motor control, strategies adopted on a voluntary basis for maintaining balance during acute intoxication, and alterations in visual, somatosensory, and vestibular sensation. The battery of tests utilized for this research leverages the sensitivity of these measures to isolate the impact of cigarettes when consumed jointly with alcohol.

Postural Control

Since the cardinal measures in the study reported here were based on measures of postural control (for reasons cited above), the associated literature is reviewed in some detail in the following sections. Posture consists of positioning the body and limbs relative to one another within a given orientation in space. Kandel, Schwartz, and Jessell (1991) identified three behavioral functions served by postural adjustments.

These include supporting the head and body against gravitational or external forces, maintaining the alignment of the body's mass over a base of support, and stabilizing portions of the body during movements. The sensory mechanisms that contribute to the maintenance of posture include proprioception, vestibular sensation, and vision.

The measurement of postural control or stability typically consists of testing participants while standing on a flat surface that includes force transducers in the base of the platform. Most studies of postural control in the area of alcohol and nicotine have used devices capable of measuring only static ataxia (body sway). These static measures most often include an eyes-open condition and an eyes-closed condition with no additional postural challenges. Computerized dynamic posturography (CDP) is a more sensitive and specific technique for assessing posture because it allows both visual and somatosensory inputs to be manipulated. Dynamic measures allow the support surface and/or the visual surround to move in phase with any sway exhibited by the participant. Thus, the static eyes-open and eyes-closed measures are expanded to include four additional tests in which the support surface and the visual surround are "sway referenced". In this set of tests, vision is either present (eyes-open), absent (eyes-closed), or distorted (sway-referenced), and the support surface (somatosensory input) can be either fixed or sway-referenced

The output of the posturography platform provides a view of sway that can be dissected using various techniques to understand better the nature of postural changes. Figure 1 provides an illustration of a sample sway output during a CDP test. The assessment measures of this sway output often include a peak-to-peak score, a measure of total sway area (sum of successive points), sway velocity, and a spectral

analysis of the sway. As seen in this illustration, the normal pattern of sway is in primarily the anterior-posterior (AP) direction because of the wide stance of the participant during testing, which limits lateral movements. The use of spectral analysis techniques are important for understanding small changes in postural stability and to avoid misinterpreting treatment effects with data that that have been skewed by large amplitude movements.

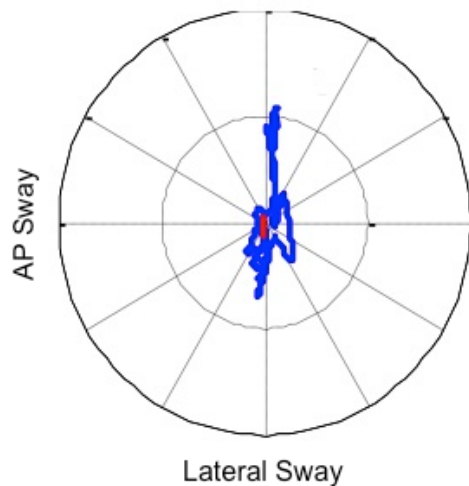


Figure 1. Sample posturography sway output.

Effects of Alcohol on Postural Control

The effects of alcohol intoxication on postural control are commonly observable, and form an important component of field sobriety tests. The associated laboratory research using measures of sway pattern has broadly confirmed the sensitivity of the postural control system to alcohol, although there is some variability in specific effects depending on such factors as dose, assessment methods and instrumentation, and population tested (reviewed below). These changes in sway are dose dependent (Mills

& Bisgrove, 1983) and have demonstrated sensitivity to secondary treatments such as nicotine (Uchida, Hashimoto, Suzuki, Takegami, & Iwase, 1980).

The BAC levels required to demonstrate these changes in postural control have varied greatly from as low as 0.043% (Mangold, Laubli, & Krueger, 1996) to levels as high as 0.22% (which would likely induce stupor) (Kitabayashi, Demura, Noda, & Yamada, 2004). Modig, Fransson, Magnusson, and Patel (2012) found that a moderate BAC as low as 0.06% can cause a complex and multi-faceted deterioration of postural control. Kubo et al. (1989) found that the postural sway pattern increased to 3.8 times the baseline measures during a high dose of alcohol (>0.10%). This range of 0.06% to 0.10% is where most posturography research has reliably demonstrated robust effects attributed to alcohol (see also Goebel et al., 1995). The CDP technique, in particular, has demonstrated sensitivity to very low doses of alcohol. The ability of CDP to detect the effects of alcohol, at various doses, provided evidence that ecologically relevant doses could be used in the current research (Goebel et al., 1995; Tianwu, Watanabe, Asai, Shimizu, Takada, & Mizukoshi, 1995).

There also is evidence that postural measurements are sensitive to the limb of the BAC curve, which as discussed above may have fundamentally different effects during the ascending versus descending limbs (Newlin and Thomson, 1990). Lukas, Lex, Slater, Greenwald, and Mendelson (1989) found that sway was enhanced most during the peak and descending portions of the BAC curve using moderate doses of alcohol. This is consistent with the findings of Modig, Patel, Magnusson, and Fransson (2012) who found that the rate of postural control degradation increased more rapidly as

BAC neared the peak in the range of 0.06% to 0.10% than under the initial portion of the BAC curve from 0.0% to 0.06%.

The sensitivity differences of the specific sway measures have been assessed in prior research. Kubo et al. (1989) found that sway area was the measure most affected by BAC, followed by AP and lateral sway, and sway velocity. Uimonen, Laitakari, Bloigu, Reinila, and Sorri (1994) also observed that alcohol increased body sway area but the sway velocity was the most sensitive measure of alcohol infusion. The most sensitive sway factors identified by Kitabayashi, Demura, Noda, and Yamada (2004) included unit time sway, AP sway, lateral sway (eyes-closed standing on one leg), and sway frequency.

In addition, CDP and static posturography have demonstrated the ability to isolate the physiological impacts of alcohol. For example, this technique can reliably detect the effects of alcohol when the eyes are closed (Ledin & Odkvist, 1991; Goebel et al., 1995), which is critical to distinguishing the visual, vestibular, and somatosensory effects of alcohol. The increase in sway with eyes-closed has been observed primarily in the AP direction, which resembles the pattern of sway seen in clinical patients with cerebellar lesions in the anterior lobe (Diener, Dichgans, Bacher, Hulser, & Liebich, 1983). The augmentation of sway associated with alcohol consumption in the eyes-closed condition suggests that the vestibular system is particularly sensitive. This conclusion is supported by oculomotor data associated with positional alcohol nystagmus, which is reviewed in detail below (Aschan, 1958; Ledin & Odkvist, 1991; Odkvist, 1975). This pattern of prior findings is particularly important in the context of

the current experiment where eyes-closed conditions effectively demonstrated the effects of alcohol (but exhibited only limited moderation from smoking).

As reviewed above, body sway measures also have been shown to be useful as measures of individual differences in sensitivity to alcohol. Several longitudinal follow-up studies have shown the usefulness of body sway-based measures as predictors of the subsequent development of alcohol-use disorders. One series of studies, with average elapsed times of 8.19 and 9.3 years, showed that original measures of body sway and subjective response levels were predictive of subsequent alcohol abuse, independent of drinking patterns at the time of initial testing (Schuckit, 1994; Schuckit & Smith, 1996). Specifically, 25% of the original sample was alcohol-dependent or abused alcohol at follow-up. Of that 25%, all were alcohol-insensitive as demonstrated by body sway measures – with 43% rated in the lowest two deciles of sensitivity and only 11% rated in the top two deciles of sensitivity (Schuckit, 1994).

Lex, Lukas, Greenwald, and Mendelson (1988) confirmed the sensitivity of posturographic measures in a sample of females. A test of alcohol-induced body sway found that women with family histories of alcoholism exhibited less AP sway during acute intoxication. Even though females demonstrated consistent sensitivity to posturographic measures, there were no gender differences in pattern of sway when assessing alcohol effects (Kitabayashi, Demura, Noda, & Yamada, 2004; Mills & Bisgrove, 1983).

Although the relevant studies agree with respect to the overall sensitivity of sway measures to acute alcohol, they often differ with respect to such factors as required dose, time following dose, test conditions, and directionality and nature of sway effects, as well as laboratory instrumentation. The present study aimed to control for some of

the sources of variability. It benefited from the adoption of advanced CDP methods, using equipment and procedures that have been widely studied, validated, and applied in multiple laboratory and clinical settings. Measures were taken at multiple times over the course of the BAC following a standardized dose of alcohol under controlled laboratory conditions, and the participants were selected with attention to the variables of typical consumption patterns, family history of alcoholism, and general health.

Effects of Nicotine on Postural Control

The postural consequences of cigarette smoking have received scant attention in the literature, and many of the available studies suffer from methodological problems. These include unusual or excessive forced inhalation schedules, instruments that lack sensitivity, and inadequate counterbalancing of testing schedules.

Pereira, Strupp, Holzleitner, and Brandt (2001) identified an increase in sway path in both AP and lateral directions beginning approximately one minute after smoking a cigarette. This increase in sway path could be partially suppressed by visual fixation. However, the rate of smoking was not controlled, and participants were wearing masks to measure eye movements, which could have explained some loss in orientation.

Uchida, Hashimoto, Suzuki, Takegami, and Iwase (1980) found that body sway became more regular after smoking and the sway power was concentrated in the 0.5 - 0.6 Hz range. It was also found that instructed saccadic eye movements decreased sway in comparison to eyes closed or fixation conditions. The authors suggested that nicotine exerts its primary influence on the descending brain stem reticulospinal system, which controls the leg muscles. This would result in a co-activation of spinal alpha- and gamma-motor neurons. The stabilizing effect of saccades was attributed to activation,

caused by nicotine, of the pontine and mesencephalic reticular formations. It should be noted, however, that participants consumed a non-filtered cigarette by inhaling 12 times every 15 seconds — an atypically fast puffing pattern that would appear to differ substantially from normal smoking conditions.

Masayuki, Hisayoshi, Aalto, Starck, and Pyykko (1994) measured postural stability in forest workers receiving an annual physical. It was found that smoking habits had a significant effect on balance even after adjusting for age and exposure to noise (e.g., chain saws). This suggests that smoking has long-term effects on postural control. These effects are similar to the short-term effects identified by Uchida et al. (1980). A feasible interpretation is that smoking may reduce blood flow in the inner ear and deterioration in accuracy of the peripheral vestibular system when detecting angular or linear acceleration.

It should be noted that nicotine could cause acute tremor (Edwards, 1946). The sensitivity of the instrumentation used in the current study, and the use of spectral analysis as a primary measure make this finding particularly relevant. Much of the research in this area has focused primarily on finger tremor, which is in the same motor-control domain as posture. Studies have reported consistently that nicotine induces tremor (Shiffman, Gritz, Maltese, Lee, Schneider, & Jarvik, 1983) and that postural tremor occurs immediately after smoking a cigarette and lasts for 30 minutes (Maykoski, Rubin, & Day, 1976).

Motor Control of Posture

When bipeds stand with their center of mass directly above the ankle joints, minimal muscle activity is necessary to maintain control. When perturbations occur,

however, adjustments must be made. These adjustments normally occur with respect to the ankle joint, the hip, or more globally with a combination of ankle, knee, and hip flexion/extension. Adjustments along these axes require activation of muscles with a corresponding antagonist so that continuous adjustments can be made. These include the anterior tibialis and the gastrocnemius for the ankle, the hamstring, gastrocnemius, and quadriceps for the knee, and the quadriceps, abdominals, hamstring, and paraspinal muscles for the hip (Nashner & McCollum, 1985).

The activation of each muscle group occurs in a sequence that proceeds from distal (ankle) and then proceeds proximally. Nashner (1977) identified two general patterns of contraction. The first was gastrocnemius, hamstring, and sacrospinal, and the second pattern was tibialis and quadriceps. This activation pattern was found for induced sway and direct rotations.

The CDP platform is capable of producing abrupt translational (rigid horizontal movement) or rotational movements of the support surface. The attendant corrective movements following these surface perturbations can be evaluated for evidence of motor control factors that are involved in the maintenance of posture.

Effects of Alcohol on Motor Control

Kinematic measurements of rotational and shear forces after postural disturbances have not shown a high level of sensitivity to alcohol (Ledin & Odkvist, 1991). EMG measurements, however, have suggested that the latency, amplitude, and sequencing of muscle contractions are affected by alcohol (Diener et al., 1983; Woollacott, 1983). Sutton and Kimm (1970) found that the reaction time of the corrective EMG response was slower after the ingestion of a low dose of alcohol.

There have been indications that reflexive motor responses are affected by alcohol. Wang, Nicholson, Mahoney, Li, Fitzhugh, and Shea (1993) found that both amplitude and latency of the Hoffman (H) reflex, which is elicited through electrical stimulation of sensory nerves and verifies the presence or absence of problems in the corticospinal tract, was depressed during the ascending limb of the BAC curve. It is unclear, however, if the depression of the H-reflex is a reflection of impairments in motor or sensory activation. This change may involve impairment of nerve conduction, spindle sensitivity, or the excitability of the motor neuron. Chronic alcohol consumption has been associated with significant reductions of motor and sensory nerve conduction velocities produced by thiamine and vitamin deficiencies (D'Amour, Bruneau, & Butterworth, 1991) and in some cases a focal myopathy of the striated muscles (Walsh & Conomy, 1977).

Effects of Nicotine on Motor Control

Cigarettes with high nicotine yields may reduce overall muscular tension (Gilbert & Hagen, 1980). In fact, early findings on the pharmacology of tobacco smoke suggested that nicotine had a direct suppressant effect on spinal reflexes (Clark & Rand, 1964). Nicotine has been associated with a significant reduction of the H-reflex recovery cycle and short-term depression of the patellar reflex, suggesting that nicotine serves as a skeletal-motor muscle relaxant (Domino & von Baumgarten, 1968; Kadoya, Matsuoka, & Domino, 1993).

Oculomotor Control

The robust effect of alcohol on eye movements makes the oculomotor system especially attractive as a modality for assessing the impact of acute intoxication. The

changes in oculomotor performance yield measurable deficits in a variety of cognitive processes and central control mechanisms. It is possible to use changes or abnormalities in eye movements to assess the effects of alcohol in the central nervous system since the cerebellum, which among other structures seems to be strongly affected by alcohol on both an acute and chronic basis, plays such an important role in controlling eye movements (Wilson & Mitchell, 1983).

Effects of Alcohol on Oculomotor Control

Guedry, Gilson, Schroeder, and Collins (1975) suggest that alcohol exerts its greatest influence on cerebellar function. Subsequently, Umeda and Sakata (1978) found that alcohol preferentially affects the cerebellum more at lower levels than other brain regions. This direct impact on the cerebellum makes the assessment of eye movements particularly useful when attempting to isolate the effects of alcohol. Some of the targeted oculomotor effects where the impact can be observed include pursuit, saccadic accuracy, and post-saccadic drift (Kandel, Schwartz, & Jessell, 1991).

Cerebellar degeneration is prevalent among alcoholics, especially evident in the Purkinje cells which appear to be particularly sensitive to the chronic effects of alcohol (Karhunen, Erkinjuntti, & Laippala, 1994). The Purkinje cells in the flocculus and the vermis appear to be especially vulnerable. These areas are involved in the response to optokinetic stimulation and to passive eye movement including saccades and smooth pursuit. Consequently, the greatest impairment can be expected under conditions in which there are discrepancies between brainstem predictions of target motion in space and actual motion (Carpenter, 1988). Variability in the chronic effects of alcohol were demonstrated by Estrin (1987) who compared alcoholics with similar drinking patterns

and found that the cerebellar degeneration was not dose dependent but rather represented apparently idiosyncratic differences in sensitivity to the neuronal effects of alcohol.

Effects of Alcohol on Saccades

Saccades are rapid refoveation movements that change the fixation point of the eyes so that objects of interest are located in the center of the visual field where acuity is the highest (Kandel, Schwartz, & Jessell, 1991; Stapleton, Guthrie, & Linnoila, 1986). In general, the premotor commands for reflexive horizontal saccades originate in the pontine reticular formation whereas vertical saccades originate in the mesencephalic reticular formation. It has been hypothesized that the parallel pathways from the frontal eye fields and superior colliculus control voluntary saccades after converging in the brain stem (Leigh & Zee, 1983). Control of saccade amplitude and adaptation in both pulse duration and step height are a function of the cerebellum. A burst of neural activity in the ocular motor nuclei generates the pulse that produces rapid movements. The eye is then held in the eccentric position with an increased tonic level of neural activity (step). The pulse-step function is responsible for the initiation of the saccade and the maintenance of gaze at the new location. Cerebellar lesions can prevent changes in pulse size and the matching of saccadic step size to the pulse size (Kandel, Schwartz, & Jessell, 1991).

It is doubtful that the effects of alcohol on saccades can be ascribed to any single or focal brain region or process. Lehtinen, Lang, Jantti, and Keskinen (1979) made a comparison to the effects of fatigue and suggested that alcohol, sedatives, and fatigue all operate at the brain stem level since the velocity of saccades is not under voluntary

control. Reductions in saccadic velocity may indicate that alcohol affects the reticular formation of the pons (Guedry, Gilson, Schroeder, & Collins, 1975). However, Wilkinson, Kime, and Purnell (1974) concluded that alcohol affects the cerebral cortex earlier (i.e., at lower levels) and to a greater extent than the mid-brain or the brain-stem.

Saccade latency

Alcohol significantly increases the latency of saccades in a dose-dependent manner with the greatest impact occurring on the ascending portion of the BAC in both high and low alcohol doses (Roche & King, 2010). This increase in latency also is observed in double-step saccadic tasks, which indicate that the alcohol affects both reflexive and adaptive cognition of visual information (Vorstius, Radach, & Lang, 2012)

Saccade latency is less sensitive to the effects of alcohol with significant changes occurring at BAC levels of 0.10%, which is well above legal intoxication levels (Fransson, Modig, Patel, Gomez, & Magnusson, 2010). Levett and Hoeft (1977) found a 21% increase in saccade latency at BAC levels of 0.10% and a 28% increase in latency just prior to the peak BAC with an average of BAC level of 0.095%. Although this effect was ascribed by the investigators to changes in oculomotor control, it is quite possible that it derives from some more generalized slowing which might be equally evident in other measures of motor control, e.g. key press reaction time. The authors concluded that alcohol may introduce a computing delay before saccade execution but did not identify the brain region responsible for the delay. This confirms that the pathways of the central nervous system that control oculomotor reaction time are affected by high doses of alcohol. Increases in latency have also been detected by Baloh, Sharma, Moskowitz, and Griffith (1979) and by Katoh (1988), who observed that

the magnitude of the latency increase was dependent on task complexity. Lehtinen, Lang, Jantti, and Keskinen (1979) found that alcohol did not have a significant effect on the latency of saccadic eye movements but their findings are limited because of very small deviation angles (20°).

Saccade velocity

Effects of alcohol on saccade velocity also have been observed. Alcohol slows peak velocity (Roche & King, 2010; Vorstius, Radach, & Lang, 2012) beginning at BAC levels as low as 0.06% (Fransson et al., 2010). Lehtinen et al. (1979) found a significant increase in the duration of movement and a corresponding decrease in eye velocity, as did Baloh et al. (1979). This decrease in saccadic velocity also was identified by Wilkinson, Kime, and Purnell (1974) and by Katoh (1988) who found that moderate doses of alcohol could reduce the velocity of eye movements by 20% and 18.6% respectively. Katoh (1988) suggested that this effect of alcohol persists for at least 3 hours beyond the time of ingestion, but it should be noted that the possible role of fatigue was not discussed in that analysis. Furthermore, Guedry et al. (1975) suggested that lowered visual attention might contribute to velocity reductions for several hours after drinking.

Saccade accuracy

Research on the effects of alcohol on saccade accuracy has not identified any consistent patterns. Roche and King (2010) identified a decrease in accuracy in high dose conditions whereas Lehtinen et al. (1979) found that alcohol did not have a significant effect on saccade accuracy. Guedry et al. (1975) suggest that the centers responsible for reducing retinal slippage of images under selective attention could be

affected most profoundly by alcohol, which would decrease saccade accuracy. If alcohol interferes with the processing of retinal error signals, or image velocity error signals, the feedback from the retina would be distorted and result in decreased accuracy.

Effects of Alcohol on Ocular Smooth Pursuit

Smooth pursuit eye movements involve tracking a target that moves slowly and continuously across the visual field. Images are stabilized on the fovea by matching eye velocity with perceived target velocity up to 60 deg/sec (Levy, Lipton, & Holzman, 1981; Stapleton, Guthrie, & Linnoila, 1986). Pursuit movements are normally associated with a smoothly moving stimulus that can be tracked (i.e., discrete, low velocity) (Leigh & Zee, 1983) from which both velocity and position are extracted from retinal receptors (Carpenter, 1988).

It is thought that the parietal lobe is responsible for directing attention toward a moving target (Leigh & Zee, 1983). The cortical components of the pursuit pathway consist of the striate cortex, the superior temporal sulcus, and the middle temporal and medial superior temporal areas. The output of these areas is then directed to the pons and cerebellar flocculus (Kandel et al., 1991). Purkinje cells in the flocculus and paraflocculus of the cerebellum discharge proportional to gaze velocity during pursuit. The neurons in the vermis encode target velocity in space, which include the eye velocity plus retinal slip velocity. The cerebellum projects to the brainstem structures, including the medial vestibular nucleus and the nucleus prepositus hypoglossi, which discharge according to gaze velocity. These brainstem structures convert the eye

velocity signals to eye position signals and then project to the oculomotor neurons to move the eye smoothly (Ciuffreda & Tannen, 1995).

Alcohol appears to increase the central processing time necessary to generate the appropriate eye movements. More specifically, it seems to impair the functions of the paramedian pontine reticular formation and the flocculus of the cerebellum (Flom, Brown, Adams, & Jones, 1976), both of which are critical for smooth pursuit movements. Oculomotor functions controlling the smooth pursuit movements tend to be more affected than the control of saccades (Fransson et al., 2010).

After the ingestion of alcohol the smooth pursuit activity deteriorates and saccadic eye movements are necessary to keep the eyes fixed on the moving target (Baloh et al., 1979; Fransson et al., 2010; Roche & King, 2010; Wilkinson, Kime, & Purnell, 1974). As the blood alcohol concentration increases there is generally a corresponding increase in the number of corrective saccades and/or increase in the amplitude of individual 'catch-up' saccades (Barnes, 1984; Barnes, Crombie, Edge, 1985; Lehtinen, Nyrke, Lang, Pakkanen, & Keskinen, 1982). This effect has been attributed to impairment in eye movements and an increase in latency, which causes the eye velocity to lag behind the target velocity (Levy, Lipton, & Holzman, 1981). The deterioration of smooth pursuit appears at blood-alcohol levels as low as 0.03% (Takahashi, Akiyama, Tsujita, & Yoshida, 1989).

Effects of Alcohol on Optokinetic Nystagmus

Passing alternating light and dark bands in front of the eyes (full-field stimulation) can induce optokinetic nystagmus (OKN). The slow component of the eye movement will follow the direction of the motion, and a fast component is necessary to return the

eyes toward the forward position (Leigh & Zee, 1983). Optokinetic input is relayed to the cerebellum primarily through the inferior olive via climbing fibers (Carpenter, 1988). The sequence of information flow through the optokinetic pathway consists of the retina, visual cortex, dorsal terminal nucleus of the optic tract, nucleus of the optic tract, inferior olive, cerebellum, vestibular nuclei, and oculomotor nuclei (Ciuffreda & Tannen, 1995).

There is evidence that alcohol has an effect on the slow component movements of the OKN response. Baloh et al. (1979) found that a BAC of 0.10% reduced the slow component velocity of the eye movement by more than 50%. Alcohol also decreases the optokinetic fusion limit, which is the threshold where the eyes can no longer follow individual bands passing in front of the visual field, which is a slow component movement (Blomberg & Wassen, 1962).

Effects of Alcohol on Gaze Nystagmus

Gaze nystagmus occurs while fixating on a target when the eyes approach the edge of their rotational capacity. When individuals without cerebellar or cerebral injuries shift their gaze laterally toward the end-point of fixation, which is normally between 50° and 60° from center, a transient nystagmus appears that beats in the direction of the gaze (Good & Augsburger, 1986).

Previous research has suggested that the ingestion of alcohol decreases the gaze angle at which nystagmus first appears. A review of the literature by Good and Augsburger (1986) concluded that the angle of the gaze nystagmus onset is approximately equal to 51° minus 105 times the blood alcohol concentration. Lehti (1976) observed such a relationship but several problems with this experiment should be noted, the most prominent of which was that the nystagmus was rated subjectively.

Some evidence suggests that gaze nystagmus may not be the most sensitive oculomotor sign of alcohol intoxication. Takahashi et al. (1989) found that spatial gaze fixation could be maintained accurately after small doses of alcohol. The BAC in their tests was as high as 0.06%. There also have been some indications that alcohol-induced gaze nystagmus appears well after other eye movement manifestations such as positional alcohol nystagmus (Umeda & Sakata, 1978).

Positional Alcohol Nystagmus

One consequence of alcohol intoxication is a nystagmus that appears soon after the consumption of alcohol, which is induced by input from the vestibular system when the head is placed in a lateral position (Ledin & Odkvist, 1991; Leigh & Zee, 1983; Ryback & Dowd, 1970; Umeda & Sakata, 1978). Positional nystagmus occurs when a transient signal originates from a displacement of the cupula of the semicircular canals. The resulting stimulus causes a sense of motion that causes eye movements (Leigh & Zee, 1983). Positional nystagmus is different than visually induced nystagmus in that it occurs around the mid-position of the eye (Buttner & Buttner-Ennever, 1988).

There are two phases in the positional alcohol nystagmus (PAN). The first (PAN I) normally begins 30 minutes after drinking alcohol and can persist for 3 to 4 hours. In PAN I the eyes beat with a fast component directed toward the ground (geotropic). The second phase (PAN II) begins 5 to 6 hours after the ingestion of alcohol with the eyes beating in the opposite direction (ageotropic). PAN II can continue for many hours after alcohol has left the blood and may persist 5 to 10 hours or longer (Aschan, 1958; Goldberg, 1966).

Positional alcohol nystagmus results from a differential infusion of alcohol into the cupula and endolymph of the semi-circular canals. During PAN I the alcohol enters the cupula resulting in a lower specific gravity relative to the endolymph. During PAN II the alcohol diffuses out of the cupula more rapidly than from the endolymph which causes the cupula to have a greater relative specific gravity. Since the alcohol is less dense than the fluid of the inner ear, the cupula can be displaced by gravity during positional testing. The resulting displacement of the cupula (either buoyant during PAN I or by gravity in PAN II) triggers eye movements using essentially the same mechanisms as those involved in the vestibular-ocular reflex (VOR). This is an acute condition, however, that persists less than 24 hours after ingesting alcohol (Odkvist, 1975). The second phase of PAN may be involved in the symptoms associated with hangover (Murphree, Price, & Greenberg, 1966).

Effects of Nicotine on Oculomotor Control

Only limited work has been done to assess the effect of cigarette smoking on eye movements. There appear to be no prior studies of the optokinetic reflex and gaze stabilization after smoking. In general, cigarette consumption appears to have only limited acute effects on oculomotor control over a period no longer than about 20 minutes after smoking, which encompasses the peak blood nicotine levels. Nicotine may improve performance on visuospatial tasks and attention tasks by suspending unrelated cognitive processing that could otherwise create distractions. Evidence for this nicotine-induced performance change was provided by Hahn, Ross, Yang, Kim, Huestis, and Stein (2007) who found consistent evidence that specific brain regions

displayed lower activity during visual processing following the application of a nicotine patch.

Effects of Nicotine on Saccades

To the author's knowledge, no study has systematically examined the effects of smoking on saccadic eye movements in adults who do not have psychiatric disorders. Using an eye movement task that indirectly measured saccade latency, Mancuso, Lejeune, and Anseau (2001) found that nicotine, administered through cigarette smoking, produced a faster response time. In a study of body sway Uchida et al. (1980) found that both horizontal and vertical saccadic eye movements to target stimuli significantly reduced postural instability following the consumption of cigarettes. They suggested that nicotine has an excitatory effect on the pontine and mesencephalic reticular formations where saccade signals originate.

Effects of Nicotine on Ocular Smooth Pursuit

Sibony, Evinger, and Manning (1988) found that cigarettes did not affect the mean gain for horizontal smooth pursuit. There was, however, an intrusion of square-wave saccades into the pursuit movement. When compared to recordings done in the dark (i.e., with no pursuit target), the amplitude of the upbeat nystagmus was reduced during pursuit while the amplitude of the square-waves was unchanged. In vertical smooth pursuit, cigarettes did not affect the downward gain but upward tracking velocity was reduced. This lag in upward smooth pursuit necessitated "catch-up" saccades. In some cases the eye moved ahead of the target during downward pursuit and subsequently required "jump-back" saccades. The nystagmus and saccadic square waves were suppressed by fixation on a stationary target.

The work by Sibony, Evinger, and Manning (1988) was replicated in part by Thaker, Ellsberry, Moran, Lahti, and Tamminga (1991). In a study of smokers and non-smokers, saccadic intrusions during pursuit increased by 38% and square-wave saccades appeared after smoking. Overall the pursuit scores were not affected by smoking though.

Nicotine Induced Nystagmus

Using a non-smoking test group, Pereira, Strupp, Holzleitner, and Brandt (2001) identified a nicotine-induced nystagmus that was suppressed with a visual fixation task. This nystagmus was likely a contributor to increased body sway and dizziness (Smith, 2001).

While examining a patient with traumatic cortical blindness, Sibony, Evinger, and Manning (1987) observed a primary-position upbeat nystagmus that developed 1 minute after the patient smoked a cigarette. Further research indicated that this upbeat nystagmus appeared in normal participants while sitting in a dark room after smoking a cigarette. This nystagmus persisted for 10 to 20 minutes after smoking but was completely suppressed by visual fixation. In a later study Sibony, Evinger, Manning, and Pellegrini (1990) found the same effect using nicotine gum, which suggests that nicotine is the agent in cigarettes which is responsible for the nystagmus.

Effects of Nicotine in Populations with Psychiatric Disorders

There is a complementary body of research specific to the effects of nicotine on eye-tracking measurement in schizophrenic patients who tend to generate a greater number of leading saccades during smooth pursuit eye movement tasks. Patients diagnosed with schizophrenia and their biological relatives tend to generate a greater

number of leading saccades during smooth pursuit eye movements. In this population, it has been demonstrated that nicotine reduces the number of leading saccadic eye movements and improves eye-tracking performance (Avila, Sherr, Hong, Myers, & Thaker, 2003; Olincy, Johnson, & Ross, 2003; Sherr, Myers, Avila, Elliott, Blaxton, & Thaker, 2002). This interaction suggests that abnormalities in the nAChR receptor system could be responsible for the neurophysiological deficits in schizophrenics (Avila, Sherr, Hong, Meyers, & Thaker, 2003).

The incidence of smoking is significantly higher in several groups with psychiatric disorders (Farrell et al., 2012). Schizophrenic patients have smoking rates of 70% to 90% compared to approximately 25% for the general population (Dani & Harris, 2005). It is possible that the elevated rate of smoking in patients diagnosed with schizophrenia reflects an attempt to self-medicate and control pathological saccadic eye movement (Kumari & Postma, 2005; Dani & Harris, 2005). This mechanism of sensory gating could represent a similar behavior in alcoholics who use cigarettes to suppress the disorienting effects associated with alcohol-produced nystagmus.

Anti-Saccades

Recent research has identified anti-saccades as a useful phenomenon for measuring the impact of alcohol and nicotine. In the anti-saccade test the participant is instructed to fixate for a short time at a stimulus and then make an eye movement in the opposite direction once the stimulus moves. This requires the participant to inhibit a reflexive eye movement to follow the stimulus. Roche and King (2010) found that both high and low doses of alcohol significantly impaired anti-saccade latency, velocity, and accuracy. Vorstius, Radach, Lang, and Riccardi (2008) identified a similar effect on

latency and peak velocity along with impairment of saccade amplitude that was observed exclusively in the anti-saccade task.

In a study of nicotine using an anti-saccade task, Vorstius, Radach, Lang, and Riccardi (2008) did not detect a main effect on performance. However, nicotine did enhance anti-saccade performance in low-performing participants with a significant reduction in response time variability. Similarly, Petrovsky et al. (2012) found that while nicotine did not reduce error rates overall, it did improve performance in participants who showed poor performance in baseline testing, and it produced some reduction in response time variability.

The clinical instrument used to acquire oculomotor data in this experiment did not support the anti-saccade measurement technique, and it was for this reason that the task was not included. However, it would appear to be a desirable target for inclusion in subsequent research examining the effects of alcohol and nicotine, individually and in combination.

Cognition

The associated literatures describing the effects of alcohol and nicotine on cognitive processes are voluminous, and are cited here only briefly as a way of justifying the inclusion (as secondary measures) of a cognitive task and subjective assessment in the present experiment. Chronic alcohol use has been linked to neurocognitive function deficits. It is possible that chronic smoking could compound a portion of the cognitive deficits traditionally associated with alcohol. The impact of chronic smoking is especially pronounced on measures that emphasize rapid, flexible information processing (Glass et al., 2006).

Effects of Alcohol on Cognition

There have been suggestions that measures of cognitive impairment are more sensitive and less variable than sway measures (Mills & Bisgrove, 1983). For example, tasks such as concept identification are significantly impaired by alcohol consumption (Pishkin, Lawrence, & Bourne, 1983).

In a review of the experimental literature, Moskowitz and Robinson (1988) found that alcohol had an effect on a variety of behaviors associated with cognitive processing. The impairments that were identified included longer reaction times, difficulty processing information, oculomotor impairments, decreased motor coordination, and difficulty concentrating. Of particular importance for this proposal is that short-term memory, problem solving, tracking, and perception were all affected by alcohol along with performance on tasks of divided attention (see also Koelega, 1995, and Finnigan & Hammersley, 1992).

Each person tends to have a profile of reaction to alcohol that incorporates variations in response (Lehtinen, Nyrke, Lang, Pakkanen, & Keskinen, 1985). Tapert, Pulido, Paulus, Schuckit, and Burke (2004) found evidence that the variations in response to alcohol that were associated with cognitive processing could be linked to overall sensitivity. When challenged with a complex task in a placebo condition, the individuals with a low level of response to alcohol used more neural system resources than did individuals with high levels of alcohol response, based on MRI scan. However, the baseline differences in neural system activation were attenuated by moderate doses of alcohol.

Unlike measures of postural control, there may be gender-specific effects related to cognition. Women appear to be significantly more impaired than men after consuming high doses of alcohol (Mills & Bisgrove, 1983). Some reasons why women are affected differently by alcohol include differences in metabolism, size of water compartment, and sensitivity. A difference in the sensitivity of women to alcohol was demonstrated by Lukas et al. (1989) who found that performance on a digit-symbol substitution test was affected most in women during the ascending portion of the BAC. Savoie, Emory, and Moody-Thomas (1988) concluded that women with positive family histories react differently to acute alcohol administration on simple tasks and subjective responses than men. Therefore, caution should be used when attempting to generalize results from studies of men.

Effects of Nicotine on Cognition

To the extent that nicotine has observable direct effects on cognition, they generally are varied and defy any simple categorization (Newhouse, Potter, & Singh, 2004). The cognitive effects in non-smoking volunteers appear to be minimal, whereas in regular smokers they are more appreciable—especially if the exposure to nicotine relieves a state of deprivation. (This characterization does not apply to selected patient groups, including Alzheimer’s dementia, schizophrenia, and attention deficit/hyperactivity disorder, for whom the effects of nicotine appear to be more pronounced.)

There are, nevertheless, several recent studies that have found evidence for improvement in cognition following acute exposure to nicotine. Vossel, Thiel, and Fink (2008) found that nicotine improved response time when participants were asked to

correctly identify cues, but only when cue validity was high. MRI data indicated that the brain areas contributing to this effect were the right fronto-parietal and left anterior cingulate regions. Similar results were found by Hahn, Ross, Wolkenberg, Shakley, Huestis, and Stein (2009) with nicotine exhibiting a greater impact on selective attention tasks than it did on stimulus detection tasks. The authors found that nicotine reduced activation in frontal, temporal, thalamic, and visual regions, and it also enhanced existing deactivation in the areas of the default network of resting brain function. Heishman and Henningfield (2000) found that nicotine increased the rate of responding and decreased response time on a digital recall test, although accuracy was impaired. Therefore, overall performance did not improve.

An earlier review by Sommesse and Patterson (1995) concluded that smoking influences a variety of cognitive variables. Some of the components identified were arousal, vigilance, concentration, and energy. Enhanced performance on cognitive tests often was attributed to increases in arousal. Nicotine also has been linked to an increased speed of processing visual information. When event-related potential (ERP) components were examined before and after smoking a cigarette, the latency of the P3 component was found to decrease. This suggested to the investigators that nicotine has a direct influence on attention or stimulus processing (LeHouzec, Halliday, Benowitz, Callaway, Naylor, & Herzig, 1994).

Most of these earlier studies that attributed enhanced cognitive performance to smoking were unable to distinguish between facilitation caused directly by nicotine versus the relief of impairment associated with withdrawal. Withdrawal leads to performance decrements on digit recall and serial addition/subtraction tasks.

Performance decrements may begin with abstinence periods as short as one hour. This is an important consideration for the present research and is addressed in detail in subsequent sections.

When alcohol and nicotine are administered concurrently there is evidence that ethanol blocks memory improvements associated with low to moderate doses of nicotine and precipitates impairment with high doses of nicotine (Rezvani & Levin, 2002). Rezvani and Levin (2003) found that alcohol not only impaired sustained attention during a visual signal detection task, but also offset the nicotine-induced improvement. In the alcohol-only condition the level of impairment was diminished over the 1-hour test session. When nicotine was administered in isolation there was an improvement in performance. However, when alcohol and nicotine were administered concurrently, the deterioration in performance was sustained through later parts of the test session even though alcohol by itself did not have a significant effect on attention. The same task performance effect was observed by Bizarro, Patel, and Stolerman (2003) in an animal study where nicotine-induced performance improvements were eliminated by alcohol.

EXPERIMENTAL DESIGN AND SCOPE

The existing literature suggests that there are interactions between alcohol and nicotine such that (at least on some measures) nicotine moderates the effects of alcohol. Although previous studies have shown that alcohol intoxication affects eye movements, posture, and cognition, whereas nicotine overall has only modest if any effects, relatively little attention has been given to the nature of cross-tolerance or other interactions between these substances. As reviewed above, there is evidence that a

low level of sensitivity to alcohol's intoxicating effects conveys a substantial risk factor for excessive alcohol consumption. The possible moderation of sensitivity by concurrent exposure to nicotine could thus pose an important and common path to the development of alcohol use disorders.

The study reported here attempts to examine these interactions between alcohol and cigarette smoking in humans, with attention to several design features introduced to enhance the sensitivity of the methods, and to preserve ecological relevance. These features include:

- 1) Inclusion of both male and female participants.
- 2) Rigorous ascertainment criteria, designed to assure that participants were regular drinkers and thus familiar with the laboratory doses of alcohol, and were regular smokers and thus accustomed to the requirement to smoke cigarettes. Individuals with a strong history of alcoholism (who might be expected to show an innately low sensitivity to alcohol) were excluded.
- 3) Administration of alcohol at a time of day (afternoon) when alcohol is often consumed.
- 4) Ecologically relevant and individually adjusted doses of alcohol (which aimed to raise the BAC to a level just under the threshold for legal intoxication) and exposure to smoking.
- 5) Nicotine administration by cigarette smoking, which captures the ecologically relevant administration mode in naturalistic settings, at an intensity and schedule that is typical of normal smoking patterns.

- 6) Attention to the effects at baseline (pre-dosing) and throughout the course of BAC, on both rising and falling limbs.
- 7) Inclusion of alcohol placebo and non-smoking test conditions.
- 8) Assessment of alcohol and smoking effects using a broad battery of measures, selected on the basis of their demonstrated sensitivity in prior research, and to capture multiple response domains. These emphasized objective measures, but also included subjective measures.
- 9) Development and implementation of advanced methods for analyzing the laboratory data.

It was hypothesized that when alcohol is combined with cigarettes the impairment induced by the alcohol will be reduced. The primary focus of this experimental design is a select number of postural measures that previous research identified as being particularly sensitive to alcohol consumption. In addition to increased sensitivity in comparison to static posturography measures that are normally used, these dynamic postural assessment methods offer the potential to identify the specific sensory and motor systems affected. This set of postural measures was expanded to include oculomotor measures, in particular smooth pursuit and nystagmus, because they share some of the neural control mechanisms involved in postural control and could increase the overall sensitivity of the assessment battery as well as provide information on the extent of effects in multiple response systems. An additional advantage of these physiological measures lies in their reflexive response patterns, making them less prone to the influence of practice effects and to subjective influences. Additional measures relating to subjective and cognitive effects also were included on a

more exploratory basis. These measures were introduced so as not to distract from the principal emphases above even though extensive data were collected using a variety of techniques that have demonstrated sensitivity to alcohol and/or nicotine.

A repeated measures design was chosen, to support examination of effects on an intra-individual basis. Four conditions were presented in a counter-balanced order, representing the combinations of alcohol (or alcohol placebo) and smoking (or non-smoking).

METHODS

Participants

The participants were eight “light” to “moderate” social drinkers and regular smokers (four female) ranging in age from 21 to 30 years. They reported consuming fewer than four standard alcoholic drinks each day, on average, and did not drink in binges (defined as 7 or more drinks per occasion). Candidate participants were excluded if they endorsed items relating to abusive patterns of drinking (expression of concern, guilt, desire to reduce drinking, or development of high tolerance) or had a family history of alcohol dependency. Average self-reported daily consumption of cigarettes ranged from 12 to 20 cigarettes. The screening assessment was designed carefully to identify participants with normal alcohol and cigarette consumption levels to minimize the likelihood of chronic acquired tolerance confounds while also increasing the likelihood that participants could tolerate experimental doses. Participants were recruited by advertisements placed at several locations throughout the Washington University School of Medicine and Washington University Danforth campuses. The eligibility of each participant was initially assessed using a screening telephone

interview designed to exclude individuals with a family history of alcoholism or medical illnesses such as balance disorders, otological trauma, or neuromuscular disease (see Appendix A). All participants were compensated at a rate of \$15.00 per hour. The time required to complete the testing in each of the four separate sessions ranged from four hours to approximately five and a half hours depending on the dose of alcohol given and time taken for it to clear before participants could be released. All participants remained in the laboratory until their BAC (estimated by breath analysis) was below .015%.

Procedure

Interview

The Biphasic Alcohol Effects Scale (BAES) was used on a repeated basis during the experimental sessions to assess the subjective response to alcohol. The BAES contains 14 items that yield two scales relating to the stimulant and sedative effects of intoxication (see Appendix B). The stimulation scores were found by Earleywine and Martin (1993) to be highest during a time corresponding to ascending BAC, whereas depressant scores peaked at a time of descending BAC phase. A version of the BAES was also used during the initial interview. In this modified form, the questions were rephrased slightly to refer to “expected” rather than current effects of alcohol (Martin et al., 1993). Participants were asked to rate the effects expected at two times after drinking alcohol (1 hour and 1.5 hours), for two different amounts (1 standard drink and 4 standard drinks). The assessment of expectancy effects during the initial interview was included on a pilot basis and no attempt was made to identify individual differences.

A combined quantity-frequency and time-line follow back alcohol consumption questionnaire (see Appendix D) was completed before each session (Sobell & Sobell, 1992). During the first session, participants were asked to complete the time-line follow back calendar detailing their consumption of alcohol for the month prior to testing. During subsequent sessions only the immediately preceding two weeks of consumption history was obtained. Participants were given a list of standard drinks and asked to identify the total number alcoholic beverages consumed each day. A composite measure of daily drinking was derived by expressing these reports in terms of standard drinks, where a 12 oz. bottle of beer, or glass of wine (4 oz.), or a shot of whiskey (1 1/2 oz. of 80 proof alcohol) are each equivalent to one standard drink. This information was obtained to permit assessment of possible chronic tolerance associated with typical drinking level. Analyses of these data confirmed that all of the participants were within the ascertainment criteria, i.e., “social” drinkers with a typical consumption pattern not exceeding three occasions per week, and not drinking at abusive levels. Beyond this general observation, the variability in the associated reports (as well as the BAES expectancy questionnaire reports described above) was not considered sufficient to support analysis of possible associated effects, or as a covariate in other analyses—particularly in view of the small participant sample size.

Participants were given a detailed face-to-face semi-structured interview during the second of the four sessions. The principal assessment instrument during the interview was the Semi-Structured Assessment for the Genetics of Alcoholism (SSAGA), which probes current and past alcohol and cigarette intake, and provides a diagnosis of alcohol dependence according to DSM-III-R and Feighner criteria (Bucholz,

Cadoret, Cloninger, Dinwiddie, Hesselbrock, Numberger, & Reich, 1994). The SSAGA results confirmed that none of the participants were alcohol dependent or exhibited signs of depression or other psychiatric disorders. The interview included additional items to elicit information about medical history, somatization, drug use, comorbid psychiatric illnesses, antisocial personality, and anxiety disorders. These items, along with the Profile of Mood States (POMS) and the Temperament and Character Inventory (TCI), were administered for pilot purposes as part of a larger project and the data obtained are not presented here.

Participants were also screened medically by Dr. Joel Goebel, a practicing physician specializing in balance disorders, at Barnes Hospital and the Washington University School of Medicine (see Appendix E). Medical screening included a detailed neurologic and balance examination to identify clinical signs of gait disorder, nystagmus, difficulties with the Romberg test, or any medical counter-indication to laboratory administration of alcohol or cigarettes.

Two candidate female participants were excluded from the testing at an early stage. One female exhibited a chronic nystagmus during the physical exam, indicating a possible oculomotor or balance disorder. The second participant started the experiment but vomited during consumption of the alcohol dose and declined to continue testing (Participant 6). The data from this participant were not used in the analysis and a replacement participant was recruited (Participant 9). Upon reviewing the data from the 8 participants who completed testing, it became clear that data from 2 female participants were unusable, and their data were excluded. One participant (Participant 8) showed a substantial level of postural instability including falls on one of

the test days, even during baseline testing (i.e., before dosing). The impairment pointed to a significant anomaly of unknown origin, but of a magnitude that would be consistent with a possible balance disorder that was not present or was not detected in the initial medical screening. The second participant (Participant 9) was excluded on the basis of self-reports of extreme nausea (although without vomiting) during the session involving combined alcohol and cigarette smoking. In addition, this participant was severely obese (body mass index = 42.8), and was likely inappropriate on a kinematic basis for testing on the posturography instrument (even though there were no explicitly stated weight-based restrictions in the test manual or associated literature). The data presented here are therefore based on a total sample of 6 participants (2 female), all of whom completed the multi-session protocol and produced the full complement of measures.

Testing Sessions

Prior to the first session, participants were invited to the laboratory to complete the screening procedures, which included a test of visual acuity and measurements of height, weight, and body fat using a skinfold caliper. This initial visit to the laboratory also included a brief tour of the facilities and familiarization with the equipment. Female participants were scheduled to begin testing two days after the beginning of their menstrual cycle, with a goal of completing testing by day 8-10. Due to scheduling challenges both of the female participants that were included in the data analysis were unable to complete all sessions prior to day 12 and testing was suspended until the beginning of another menstrual cycle. In addition to completing a menstrual cycle questionnaire, female participants were asked to take a pregnancy test and given

literature concerning the potential consequences of consuming alcohol during pregnancy.

Each participant completed four testing sessions under a within-subject design, involving the various combinations of alcohol (or placebo alcohol) and cigarette smoking (or non-smoking) (see Table 1). Conditions were given in counter-balanced order, with a minimum of 48 hours between each session (see Table 2). (In addition, participants completed a fifth session, given always as the last session, which involved the combination of alcohol and nicotine delivered in the form of nasal spray (NNS). This session was conducted on a pilot basis, to examine the feasibility of using this mode of nicotine delivery, and is not reported further here.)

Table 1. Dosing conditions.

Alcohol	Cigarette Smoking	Label
Alcohol Placebo	No Smoking	A-S-
Alcohol Placebo	Cigarette Smoking	A-S+
Alcohol	No Smoking	A+S-
Alcohol	Cigarette Smoking	A+S+

Table 2. Counterbalancing.

Males

	Session 1	Session 2	Session 3	Session 4
Participant 1	A-S-	A+S-	A+S+	A-S+
Participant 2	A-S+	A+S+	A+S-	A-S-
Participant 3	A+S+	A-S-	A-S+	A+S-
Participant 4	A+S-	A-S+	A-S-	A+S+

Females

	Session 1	Session 2	Session 3	Session 4
Participant 5	A+S-	A-S+	A-S-	A+S+
Participant 7	A-S+	A+S+	A+S-	A-S-
Participant 8*	A-S-	A+S-	A+S+	A-S+
Participant 9*	A+S+	A-S-	A-S+	A+S-

*Data excluded from analyses, for reasons cited above.

Alcohol and Cigarette Dosing.

A counterbalanced within-subject design was used during the four sessions (as described above). The alcohol-loading dose (0.80 g/kg lean body weight in males, 0.75 g/kg in females) was based on the known pharmacological properties of alcohol, as well as a series of dose-response trials from another study (Goebel, Dunham, Rohrbaugh, Fischel, & Stewart, 1995) and pilot testing with laboratory personnel. This dose was designed to produce moderate levels of impairment while maintaining a borderline-intoxicating BAC (in the range of 0.08%--the legal limit in the US for driving while intoxicated), which for a 170 lb male of normal body fat composition is roughly equivalent to consuming three 12 oz. cans of beer or three 5 oz. glasses of wine in 8 minutes. Dosing studies indicated that this level of alcohol, while modest and

ecologically relevant, still produced measurable results. The slightly lower dose per unit of lean body weight used for females was intended to compensate for gender-related metabolic differences (Frezza, DiPadova, Pozzato, Terpin, Baraona, & Lieber, 1990)

The loading dose of alcohol was administered as 95% ethanol and juice (fruit punch) in a constant volume of 400 ml. This dose was divided into four small cups of approximately 100 ml each and consumed at two-minute intervals, with total consumption over a period of eight minutes. The companion alcohol placebo was the juice alone. A small amount of alcohol was floated on the surface of each cup to provide olfactory and taste cues of alcohol. A maintenance dose was administered one hour following the loading dose. The maintenance dose consisted of 0.075 g/kg lean body weight (0.072 g/kg in females) in a constant volume of 200 ml and was intended to stabilize the BAC and mimic natural conditions where alcohol is consumed over extended periods of time. Participants were instructed to rinse their mouths vigorously with tap water after consuming the dose to prevent contamination of the breath analysis of BAC.

It was decided on the basis of pilot testing that cigarette smoking was the most effective and ecologically relevant mechanism for nicotine delivery, with the fewest confounding effects (skin irritation, dizziness, nausea, headaches) and producing a pharmacological response that captures the naturalistic conditions. In the two smoking sessions a single Benson & Hedges 100 cigarette (listed by the FDA as containing an approximate nicotine content = 1.2 mg) was consumed while the participant drank the loading dose (alcohol or placebo). A second cigarette was smoked simultaneously with the maintenance dose and a third cigarette one hour later. These times corresponded

with the ascending, peak, and descending limbs of the blood-alcohol concentration curve. It should be noted that peak blood-nicotine concentrations occur at approximately 10 minutes after the initial inhalation of the cigarette, which is followed by a sharp decline through 20 minutes (Armitage, Dollery, George, Houseman, Lewis, & Turner, 1975).

Participants were asked to smoke over the 8-minute dosing periods but otherwise *ad lib*. Female participants were asked to stop smoking at a line that was approximately 15mm from the filter after reports of nausea during pilot testing. Male participants were instructed to smoke the cigarette over the course of the entire dosing period, and the cigarette was normally smoked to a point just short of the filter. Armitage et al. (1975) found that smokers tended to dose themselves to a comfortable nicotine level. All smoking was recorded on videotape for examination of smoking topography as part of a pilot study for another project.

Laboratory Procedures.

Participants were instructed to eat a low-fat lunch between 12:00 and 1:00 p.m. and arrive at the laboratory at 2:00 p.m. Before each session they were given a brief interview to assess any alcohol or drug use between sessions and to assess compliance with eating restrictions (see Appendix F). The minimum requested (and reported) period of alcohol abstinence before each session was 24 hours.

One female participant was asked to repeat the A+S+ condition due to nausea during the testing. The testing was stopped during the second set of postural control tests at the onset of the nausea. Arrangements were made to repeat the session approximately two weeks later, following the onset of the next menstrual cycle.

Testing for all participants began at approximately 3:00 p.m. following one hour of enforced cigarette abstinence. (Time of day was an important consideration, insofar as this begins a period of the day in which it is not uncommon to consume alcohol, in contrast to many prior studies of alcohol sensitivity which have involved morning dosing; see Newlin & Thomson, 1990). The period at the start of each session was used to complete experimental questionnaires, apply electrodes, and to enforce a minimum standardized period of abstinence from smoking. In some cases the period of enforced abstinence was slightly longer depending on the participant's ability to complete the pre-test activities. The first session normally required an additional 30 minutes to complete intake procedures before beginning the baseline measurements. A precise timeline and testing sequence was followed for all sessions (see Appendix G).

Questionnaire Measures of Subjective Effects.

Principal emphasis to assess subjective effects was placed on the 14-item BAES test (described above), which, again, includes two scales, relating to stimulation and sedation. The BAES questionnaire as administered during testing referred to subjective feelings "at the present time". Subjective responses during intoxication are biphasic, with items relating to stimulation endorsed during the ascending BAC and depressant responses dominating on the descending limb (Martin, Earleywine, Musty, Perrine, & Swift, 1993; Wood, Erickson, & Sher, 1996). The BAES was administered on multiple occasions during baseline, and during ascending and descending limbs of the BAC curve as described below.

Participants also completed the Nicotine Effects Scale (NES) (LeHouzec, Halliday, Benowitz, Callaway, Naylor, & Herzig, 1994) which includes 10 items that are

rated on a 10-point scale (Appendix C). Although smoking is not explicitly cited, some of the items refer to common sequelae of cigarette smoking including light-headedness, nausea, and sensations of tachycardia. The NES was included with the intention of supporting detection of bidirectional effects, of alcohol on smoking effects, as well as the converse. The NES was administered at the same times as the BAES, as described below.

Computerized Dynamic Posturography.

The sensory aspects of balance were tested with a commercially available Equitest Computerized Dynamic Posturography (CDP) platform (Neurocom, Clackamas, OR) designed as a clinical instrument to measure dynamic postural performance. The design of CDP is based on a compositional analysis of individual postural control strategies and a series of theoretical predictions of the conditions under which each strategy is used (Nashner & McCollum, 1985). The validity and reliability of CDP was demonstrated by Hu, Hung, Huang, Peng, and Shen (1996) who used equilibrium score and sway area to discriminate among the sensory conditions. The methods are applicable to both male and female participants. Since the mechanisms underlying balance are largely reflexive, it is assumed in clinical testing that the results are stable over repeated testing. In the absence of orthopedic and/or musculoskeletal disorders, prolonged response latencies and strength asymmetries in CDP can be used to support a clinical diagnosis of extra-vestibular CNS lesions or long-loop automatic response abnormalities (Nashner & Peters, 1990). CDP has attracted wide use for clinical assessment of balance disorders.

Sensory Organization Battery.

The CDP procedure uses six general sensory organization (SO) tests. Participants are presented with combination of vision present or absent, sway-referenced or stable visual surround, and sway-referenced or stable support surface conditions (see Table 3, and Figure 2). These tests are designed to isolate the contributions of vision, somatosensory, and vestibular sensory inputs that contribute to the maintenance of postural stability. Five force transducers in the platform, sampled at 50 Hz, provide data on the AP sway, lateral sway, shear, center of gravity, and velocity. All participants wore a safety harness as specified by the manufacturer.

Table 3. Equitest SO battery.

Test	Vision	Support Surface	# Trials
SO1	Eyes Open, Stable	Stable	1
SO2	Eyes Closed	Stable	3
SO3	Sway-Referenced	Stable	2
SO4	Eyes Open, Stable	Sway-Referenced	2
SO5	Eyes Closed	Sway-Referenced	2
SO6	Sway-Referenced	Sway-Referenced	2

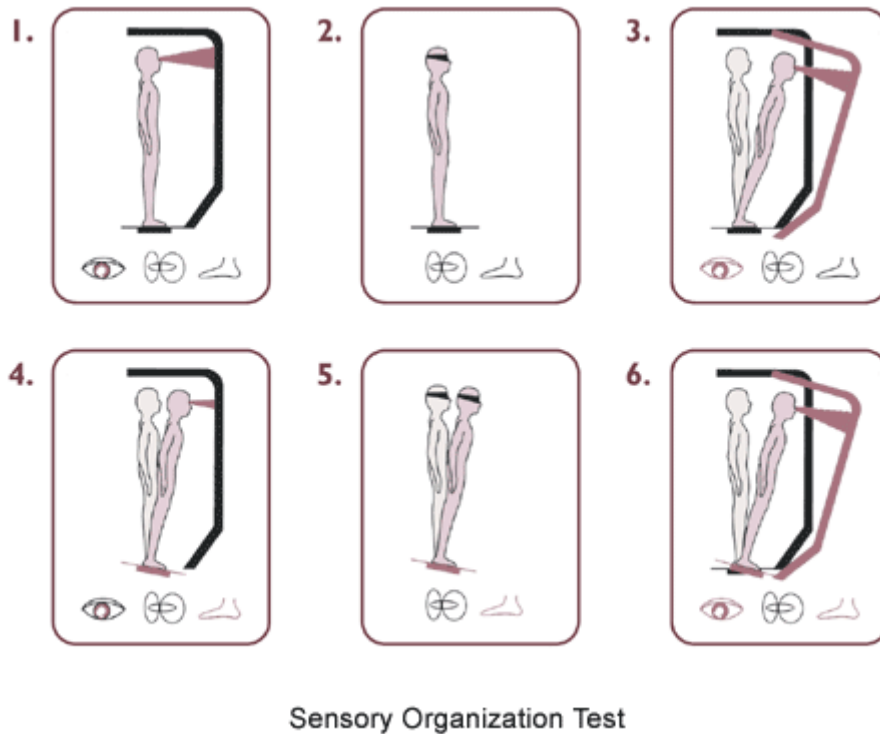


Figure 2. CDP sensory organization test (NeuroCom, Inc., 2012).

The first sensory organization test (SO1), in which the visual surround is visible and stable, and the support platform is stable, provides a measure of static ataxia that is roughly equivalent to the traditional Romberg test (although with a wider stance). In the SO2 test, participants are instructed to close their eyes to remove visual cues so that vestibular and proprioceptive cues must be used to maintain balance. In the SO3 test, the visual surround is sway-referenced so that the entire scene viewed by the participant moves exactly in proportion to the AP sway. This creates a situation where the visual cues are invalid and participants must rely preferentially on vestibular and proprioceptive information. The SO4 test invalidates proprioceptive cues (while maintaining stable vision) by sway-referencing the platform so that visual and vestibular

cues must be favored. The SO5 and SO6 tests force participants to rely almost exclusively on vestibular sensations by sway-referencing the platform and removing or sway-referencing visual cues, respectively.

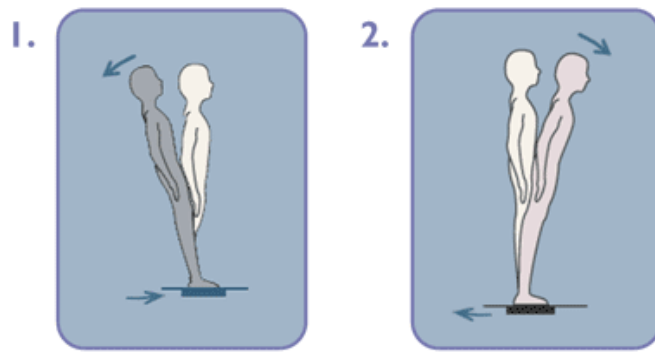
The duration for each SO test was 20 seconds, with the beginning announced before start of data acquisition. In accord with common practice in the balance clinic, SO1 was given 1 time (at each assessment), SO2 was given 3 times in succession, and SO3-SO6 were each given 2 times, always in ascending order. If the participant's loss of stability during any test exceeded the system's definition of a "fall," the test was repeated one extra time. The raw output from the SO tests were 20-second time series data, from each of the 4 sensors (at the corners of the support surface) and the central shear signal. The Equitest instrument produces a clinical report of stability based on analyses of the peak-to-peak excursions in these signals, with reference to a theoretical cone of stability defined on the basis of patient somatotype. In the results reported below, these measures were replaced by measures produced by custom methods, which were developed to address some of the weaknesses identified in the standard clinical methods (see below).

Motor Control Battery.

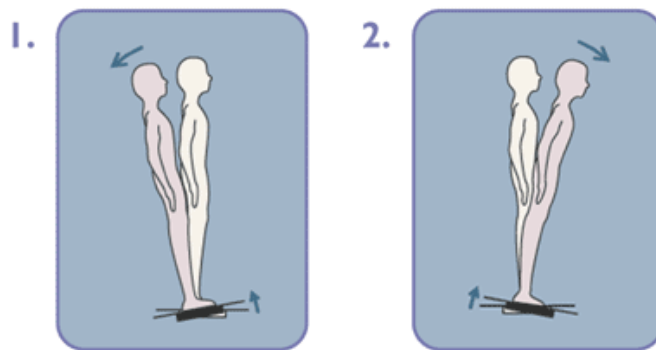
A second major contributor to the maintenance of postural stability (in addition to sensory aspects) involves motor control (MC). The CDP methods for assessing MC involve systematic, abrupt perturbations of the support surface, and measurement of the accompanying movements that are used to preserve stability. The standard methods involve evaluation of the kinematic forces detected by the sensors in the support surface. The Equitest instrument also supports simultaneous recording of the

electromyographic (EMG) signals, which enhances the sensitivity of the method and provides more detailed information regarding the sequencing and relative involvement of the principal engaged muscles. This methodology is particularly useful because the results are generally not influenced by motivation or effort of the participant (Nashner, 1997).

MC testing involved four different perturbations of the support surface: 1) forward translations, 2) backward translations, 3) toes-up rotations, and 4) toes-down rotations. The translation and rotation conditions are illustrated in Figure 3, which also illustrates the associated destabilizing effects on posture. The translations were scaled in amplitude to the height of the participant so that the amplitude, in inches, was equal to the height of the participant divided by 72 and multiplied by 2.25, over a duration of 400 msec. As an example, for a 6'0" person, the total movement would be 2.25 in (5.7 cm, velocity = 14.3 cm/sec). The rotations were always 8°, at a velocity of 50°/sec.



Forward/Backward Translations



Toes Up and Toes Down Rotations

Figure 3. Motor control and adaptation test (NeuroCom, Inc., 2012).

Each of these platform movements is designed to assess control over motor activity of specific postural muscles. These movements, particularly the platform rotations, produce a complex distal to proximal sequence involving early mono- and supra-segmental spinal reflexes, followed by corrective movements that involve long loops through the cerebellum and other central structures (Ghez, 1991). Collectively, these responses support a detailed analysis of peripheral and central factors. An

illustration of the muscle activation sequence, involving toes-up rotations, is provided in the Results section (Figure 12).

EMG was recorded from electrode pairs placed bilaterally over the gastrocnemius, tibialis anterior, quadriceps, and paraspinal muscles, with a sampling rate of 1000 Hz. The electrode pairs were imbedded in a package that included early-stage amplification and signal conditioning, and were attached using double-sided, pre-gelled foam adhesive pads over the belly of the muscle, along the longitudinal dimension of the muscle. The skin areas were shaved if necessary, and cleaned with an alcohol scrub patch before electrodes were attached. Five trials of each stimulus were presented in fixed order (forward translation, backward translation, toes-up, toes-down). The MC portion of the testing followed the SO tests described above.

Oculomotor Battery.

All oculomotor measurements were obtained with the Nystar 3.0 (Nicolet Biomedical, Inc. Madison, WI). This is a pre-programmed instrument that was developed for the clinical assessment of oculomotor and balance disorders. A curved light bar containing light emitting diodes (LED), with a visual field of 80° by 10°, was used to display the stimuli. The dimensions of the individual LED's was 0.1" by 0.25" with uniform brightness. The curve in the light bar was designed to maintain a constant viewing distance and minimize errors of target position and target velocity. Participants were seated in a chair with an adjustable headrest to maintain a fixed head position. Horizontal eye position was recorded electrooculographically (EOG) between surface electrodes located on the outer canthus of each eye. Vertical EOG electrodes were

placed above and below the left eye and centered on the pupil. The right mastoid prominence was used as the ground.

Seven general tests were included in the EOG battery, given in fixed order. The tests were:

- 1) Resting nystagmus while seated upright in the dark, in the absence of any fixation or gaze requirement (included principally for purposes of confirming absence of nystagmus under unchallenged conditions, and no nystagmus was identified).
- 2) Vertical smooth pursuit using a 0.4 Hz stimulus at 40 deg/sec peak velocity.
- 3) Gaze nystagmus at deviation angles of 20°, 30°, and 40° on both the left and right side with gaze held for 10 seconds each.
- 4) Horizontal smooth pursuit using 0.1 Hz at 10 deg/sec, 0.2 Hz at 20 deg/sec, and 0.4 Hz at 40 deg/sec for 20 seconds each.
- 5) Tests of saccade timing and accuracy, including a random amplitude saccade test (6-32 deg jumps) with 28 target jumps (repeated twice), and a single fixed amplitude saccade test (30 deg jumps) with 14 target jumps (7 in each direction), lasting 40 seconds each.
- 6) Positional alcohol nystagmus while participants were recumbent with their head tilted to the left and right.
- 7) Optokinetic nystagmus assessed bi-directionally for 20 seconds each at 10 deg/sec and 20 deg/sec with 5.12 degree spacing.

Calibrations were performed periodically throughout the testing. Although the Nystar clinical instrument produced several measures for each test on an automated

basis, the results described below are based on custom methods (also described below) developed by the project investigators.

Assessment of Cognitive Functioning: SYNWORK.

A synthetic work environment (SYNWORK) was used to assess the cognitive effects of alcohol and cigarettes, on an exploratory basis, to evaluate its possible utility in this context. Its inclusion served the additional function of maintaining participant alertness during the periods over the course of the BAC curve separating the cardinal CDP assessments. The SYNWORK task was included for evaluation purposes even though there were prior indications that it was susceptible to training effects (e.g., Branscome, Swoboda & Fetkin, 2007). SYNWORK continues to be used in studies of stress and affect, multi-tasking, fatigue, sleep deprivation, automation, aging, individual differences, operational readiness, personnel selection, workplace design, pharmacological countermeasures, and extreme environments. It is a computer-based test of performance that presents four tasks concurrently (see Appendix I). The screen is divided into four quadrants, which include a Sternberg memory task, an arithmetic task, a visual-monitoring task, and an auditory-monitoring task (Elsmore, 1992). Participants performed the SYNWORK task five times during each session for 5 minutes each.

During the data analysis, clear order effects emerged, which made it impossible to isolate the effects of alcohol or nicotine. Due to the obvious improvements that occurred with increased exposure to the SYNWORK tasks, the scores were not included for analysis as part of these findings. The task most likely helped participants remain alert and engaged during the extended period of time in the laboratory, but

otherwise was not judged to be useful. A description of the instrument and the research results are presented in Appendix I for reference.

Testing Schedule.

Measurements were obtained during each session prior to alcohol and/or cigarette dosing (baseline) and at multiple times afterwards, as indicated in Figure 4. The tests indicated there include the CDP battery (with separate SO and MC components, as described above), oculomotor tests, and the SYNWORK task. Blood Alcohol Concentration (BAC) was estimated using a portable breath analysis instrument (Intoximeter Alco-Sensor III) performed at frequent intervals, as were the BAES and NES subjective effects questionnaires. The timeline was developed on the basis of extensive pilot testing, and it was adhered to during testing with deviations less than 2 minutes. The dosing and timing of each component of the test battery was designed to ensure that data were collected during the ascending, peak, and descending portion of the BAC for each measure.

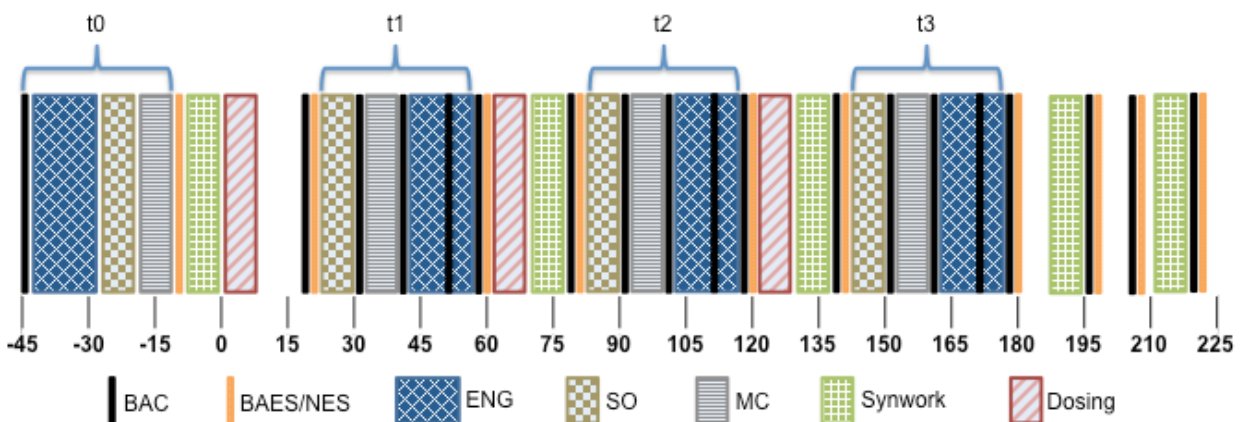


Figure 4. Timeline of test administration (in minutes).

RESULTS

Any examination of alcohol and nicotine interactions in a population of regular smokers is complicated by the difficulty of selecting an appropriate no alcohol condition to serve as the baseline for gauging alcohol effects. The issue with the A-S- dosing condition is that as the session progresses, the regular smokers will begin to experience nicotine deprivation effects. The magnitude of this deprivation effect is likely to vary as a function of individual participants' levels of nicotine addiction. Similarly, comparisons involving the A-S+ as the baseline could be confounded by any direct effects of nicotine on the measure of interest.

Because both A-S- and A-S+ baseline conditions were available based on the design of the present study, an analysis strategy was employed that leveraged this comparison. The A-S+ baseline was selected as the best no alcohol baseline as it most closely conforms to the self-selected state experienced by regular smokers during daily life. Comparisons between this condition and responses on the A+S- and A+S+ sessions were used to estimate the direct effects of alcohol as well as moderation of these effects by smoking. In contrast, both baselines were employed to determine whether direct effects of smoking were present. If smoking was found to affect a given measure, both when alcohol was present (A+S+ vs. A+S-) AND when alcohol was absent (A-S+ vs. A-S-), it was not further pursued as an interpretable measure of alcohol-smoking interactions.

Unless otherwise noted, analyses were restricted to the baseline (t0) and the first three post-dose measurement periods (t1, t2 and t3) (see Figure 4) for all four dosing conditions designated in Table 1 (i.e., A-S-, A-S+, A+S- and A+S+). For each

participant, the resulting twelve observation data vector (3 time points x 4 dosing conditions) was submitted to a z-transformation in order to: 1) control for the considerable between-participant variability present in many of the responses; and 2) permit a direct comparison of effect sizes across the disparate response domains.

In recognition of the power limitations imposed upon the interpretation of the data set obtained in this study, traditional inferential statistical approaches were not employed—especially given that the number of potential analysis cells (4 doses x 2 time points x 2 genders, etc.) exceeded the number of participants. The unacceptably high probabilities of making both Type I and Type II interpretive errors, and the complications of correcting for multiple comparisons, led to the decision to restrict the analysis to the conditions and measures that were expected on an *a priori* basis to exhibit sensitivity to the main effects of alcohol and the moderating influences of cigarette smoking within this sample.

To this end, the following strategy for the interpretation of results was employed. The sample alcohol effect sizes (and smoking moderation percentages) were computed from z-transformed scores – enabling their direct comparison across different metrics and response domains. To evaluate whether an observed effect size was relatively consistent across all individuals (rather than driven by only one or two participants), two additional measures were evaluated. The first represented the input to a simple non-parametric sign test (i.e., the number of individuals for whom the valence of obtained alcohol and smoking moderation effects was in the predicted direction). Secondly, given the expectation that the bulk of the measures were of sufficient quality to support parametric testing, the *p*-value of the associated *t*-test was also examined. Note, this *p*-

value is only an indication of the magnitude of the ratio of within- to between-subject variance in this sample. Therefore, in this context, it is to be interpreted as a descriptive rather than an inferential statistic.

To clarify, this approach allows us to make statements such as “Measure x appears more sensitive to smoking moderation than measure y in the present sample”, but statements such as “There was a statistically significant effect of alcohol in condition y”, or that “Smoking significantly modulated the effect of alcohol in participant 3” cannot be supported. Thus, this study was designed to provide a roadmap for future investigation rather than to definitively demonstrate cross-tolerance between alcohol and cigarette smoking. More specifically, the results obtained from this sample were intended to inform succeeding studies as to the specific conditions most likely to produce alcohol x cigarette smoking interactions, as well as to indicate which measures most sensitively measured this interaction.

Some observations on the sheer volume of the measures presented in the results section are in order. Admittedly, a large number of analyses were conducted, and the Results section includes descriptions of observations that are of only incidental interest, in addition to the core findings. Several measures (noted in the text) were included to maintain ties with the existing literature and good clinical practice rather than due to the anticipation that evidence of moderation by cigarette smoking would be obtained. Also, alternative (and highly correlated) methods of measuring the same basic phenomenon were included (e.g., area vs. spectral analyses of sway) with the intention of determining which techniques (if any) were more sensitive to the experimental manipulations.

It could be argued that in the presence of this kind of intensive analyses, at least some interesting results would undoubtedly be obtained. Three points can be made to address this issue in the current context. First, the cardinal importance of the posturographic measures was identified in advance. Second, without exception, the valence of anticipated alcohol effects for all measures was also specified *a priori*. Finally, there was no attempt to “cherry-pick” the data; measures excluded from the results section were found to be either highly correlated with other measures (and therefore redundant), or unacceptably sensitive to known sources of “noise” in the data.

In view of these considerations, in the subsequent presentation and discussion of results, the magnitude of alcohol effects will be assessed by a direct comparison of data from comparable time points from the A+S- and A-S+ dosing conditions (unless otherwise specified). Moderation after smoking cigarettes will be assessed by determining the percent change in the effect (towards the no-alcohol baseline) represented by the introduction of cigarettes (i.e., the A+S+ vs. A+S- comparison). Responsivity will be assessed in three ways: 1) by comparing the difference between the mean levels of the z-corrected response; 2) by determining the total number of participants showing the effect; and 3) by computing the probability level of the *t*-test conducted upon the difference between the means. The analysis of *p*-values is, again, intended less as an exercise in inferential statistics than as a descriptive technique for assessing the relative levels of between vs. within participant variance for a particular measure. Measures identified as particularly sensitive based on these criteria will then be identified as potential candidate measures for use in future studies of alcohol and smoking interactions.

In summary, the following comparisons were performed to fully assess the effects of smoking cigarettes during acute alcohol intoxication:

- 1) Alcohol Effect = A+S- versus A-S+ (single baseline);
- 2) Smoking Effects = (A-S+ versus A-S-) and (A+S+ versus A+S-) (dual baseline); and
- 3) Smoking Moderation = A+S- versus A+S+

Blood Alcohol Concentrations

All participants were moderate social drinkers as indicated during the initial screening, and they reported that no alcohol was consumed in the 48-hour period prior to each session. All pre-test BAC measurements were negative for signs of alcohol.

BAC levels for all test participants rose quickly following the initial loading dose of alcohol. In all alcohol conditions the average peak BAC occurred 50 minutes after the initial dose of alcohol. The maintenance dose, which was administered at 60 minutes, was effective in producing a relatively stable BAC for one hour (see Figure 5).

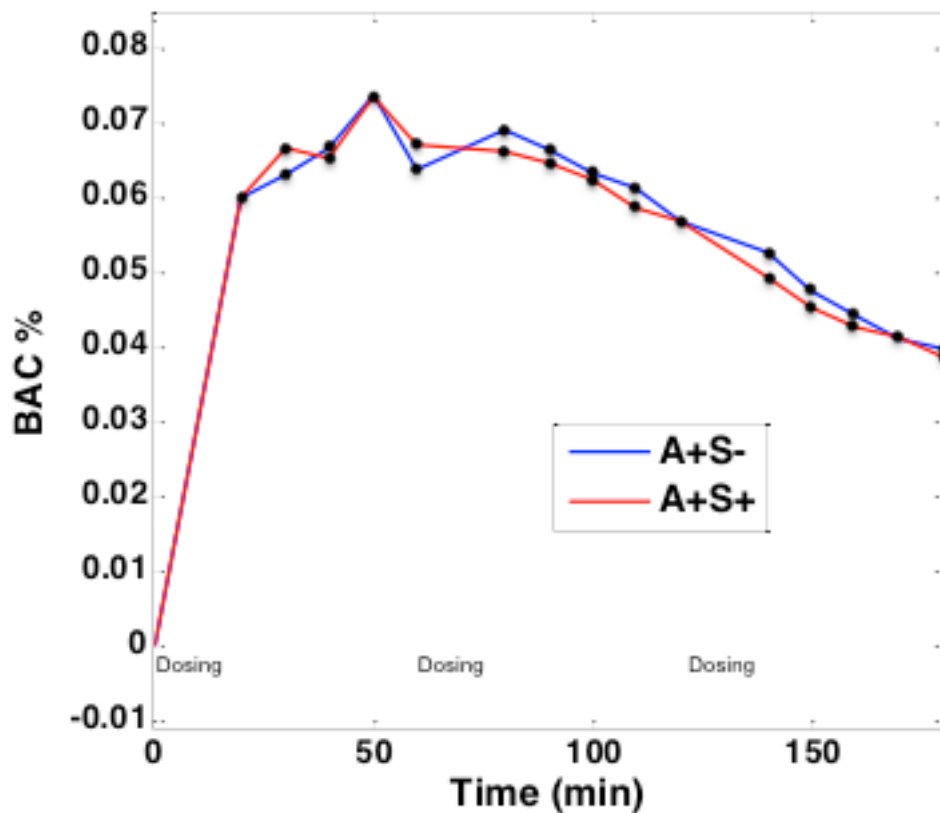


Figure 5. Mean blood alcohol concentration levels for the two sessions involving consumption of alcohol.

Participants generally had consistent BAC levels that followed the expected pattern. Individual peak BAC levels ranged from 0.064% to 0.104%. Importantly, there was no evidence that smoking consistently affected BAC. Any resultant changes in level of response associated with smoking thus could not be attributed to differences in BAC. Even though the mean BACs achieved during the two alcohol drinking sessions (A+S- and A+S+) were nearly identical, inspection of the BACs for individual participants discloses some variability between these two sessions. This type of variability appears to be a general finding, even in studies in which such factors as diet have been carefully

controlled (Fraser, Rosalki, Gamble and Pounder, 1995). There were notable spikes in BAC for two male participants that briefly resulted in levels above the target (see Figure 6). Although participants rinsed vigorously after the dosing, there was most likely some level of residual alcohol contamination that contributed to the BAC spikes.

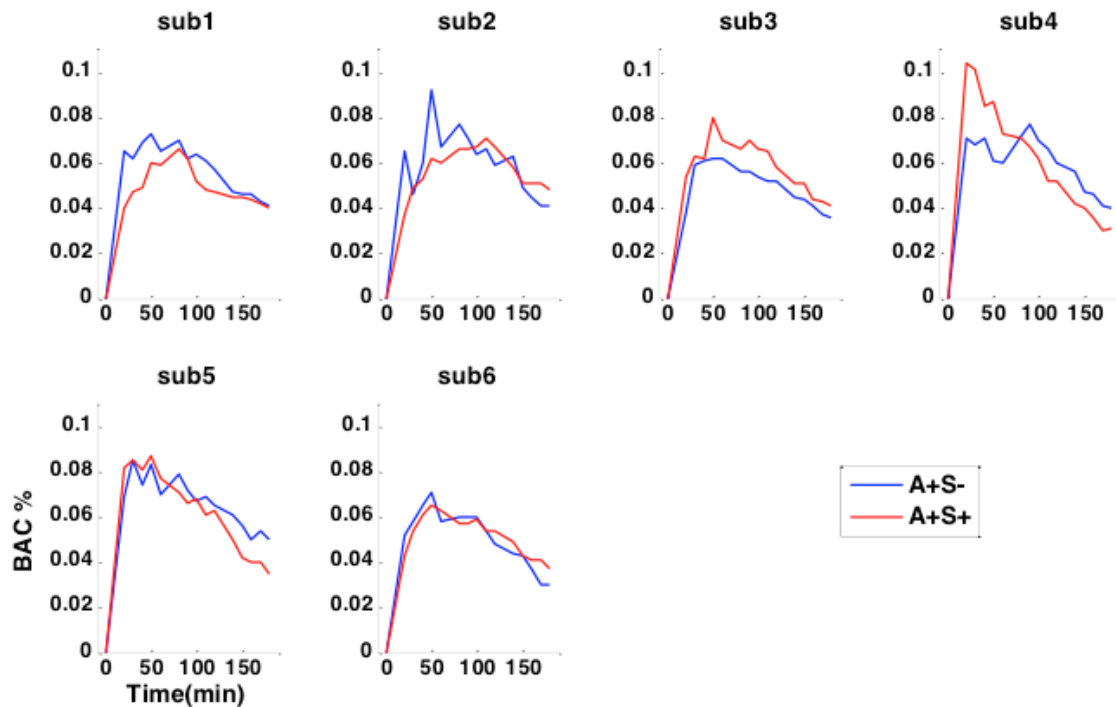


Figure 6. Individual participant BAC curves.

Sensory Organization (SO) Test

Data Computation and Analysis

The raw data from the Equitest platform were analyzed using software developed for this project in Matlab (Mathworks, 2013) by laboratory staff. Measures of performance included computed equilibrium scores (EQ) and spectral analyses of sway patterns.

A spectral analysis was performed on AP sway, lateral sway, shear, center of gravity in the AP direction (COG), and center of gravity in the lateral direction (COGL). For the spectral analysis measures, the total spectral power density function consisted of the combined distribution for all SO test repetitions within each trial (1 SO1, 3 SO2, 2 SO3, 2 SO4, 2 SO5, and 2 SO6). If the participant stepped off the platform at any time during the testing, the trial was identified as a fall and was excluded from the analysis.

The spectral data were computed by comparing the signals of the individual force transducers in the base of the platform. The transducers were located in each corner of the platform (LR = Left Rear, LF = Left Front, RR = Right Rear, RF = Right Front) with a fifth transducer in the center that measured shear forces in the AP direction. AP movements were computed by subtracting the signals of the front and rear transducers. Lateral movements were calculated by subtracting the signals of the left and right transducers.

Procedures enumerated in the Equitest manual (Equitest System Operators Manual, 2000) were employed to generate estimates of instantaneous body sway. First, an estimation of the AP projection of the patient's center of gravity (P_y) was calculated using the formula:

$$P_y = [(LF+RF) - (LR+RR)] / (LF+RF+LR+RR) * 4.2$$

In this formula 4.2 represents the distance in inches between the force transducers and the x-axis at the center of the force plate. Next, instantaneous AP sway angle calculated using the formula:

$$AP \text{ sway angle} = \arcsin(P_y/H_{cog}) - 2.3$$

Hcog represents the horizontal Center of Gravity (equal to 0.5527 * participant's height in inches) and 2.3 is the population value for the "forward lean" of Center of Gravity from vertical when calculating sway from about the ankle joint.

A number of summary measures of body sway were generated using procedures detailed in the Equitest system manual. EQ scores were obtained for each SOT trial in two steps. First, data in the AP sway channel were low-pass filtered using a second order Butterworth filter with a frequency cutoff of 1.5 Hz. The EQ score for a given SOT trial was computed as:

$$\text{EQ} = 100 * [(12.5 - \text{APdiff}) / 12.5]$$

APdiff represents the difference between the maximum and minimum instantaneous AP sway, and 12.5 serves as the normal limit of the AP sway angle range in degrees.

According to this formula, participants demonstrating minimal sway would achieve EQ scores near 100, while individuals approaching the limits of stability would generate scores near 0.

In addition to the EQ measures, sway area scores, which have proven sensitive to postural deficits (Diener, Dichgans, Bacher, & Gompf, 1984), were calculated by summing across successive deviations in the AP and lateral sway directions. The total sway area score was then computed by summing the AP and lateral sway area estimates. A single EQ and sway area score for each SOT was obtained by averaging across the estimates for each repetition of the individual conditions. A composite SOT score also was computed by averaging across SOT conditions. Furthermore, composite eyes-open (SOTs 1, 3, 4 and 6) and eye-closed (SOTs 2 and 5) scores were

obtained by averaging across relevant SOT conditions. An illustration of the sway area output is provided in Appendix H.

Additional sets of measures were obtained using standard spectral methods. Power Spectral Density (PSD) functions were computed from the AP sway and shear channels for each 20 sec SOT trial using routines available within the MATLAB (Mathworks, 2013) signal processing suite. The epochs for each SOT trial were Parzen windowed before being submitted to a 512-point Fast Fourier Transform (FFT) using Welch's method of overlapping epochs. Given the sampling rate of 50 Hz, the resulting frequency resolution equaled 0.0488 Hz per spectral bin (Nyquist frequency/#FFT points = $25/512$).

Mean PSD functions also were obtained by averaging across the PSDs associated with the repetitions of each SOT condition. Low frequency spectral power was estimated by summing across values of the mean PSD functions in the range between 0 and 0.6 Hz. High frequency spectral power was computed in the range between 2.0 and 5.0 Hz. As with the EQ and sway area scores, mean low and high frequency spectral estimates were obtained for each condition in addition to composite, eyes-open and eyes-closed averages.

In this analysis, the conventional EQ score (which is the default measure used for clinical purposes) measures the difference between minimum and maximum points of sway in the AP dimension (peak to peak). The value can be driven principally by a single large sway excursion, even though this might not be representative of the general postural stability over the entire 20-second period. The sway area measure summarizes changes across the entire 20-second trial and is therefore most affected by

large amplitude, low-frequency instances of sway. The spectral measures, in contrast, allow for a more nuanced exploration of body sway. In addition to the possibility that these measures will be more sensitive in general, the spectral estimates enable total sway to be decomposed into low and high frequency components which may or may not show equivalent responses to the administration of alcohol and cigarettes.

Overall Performance

As outlined above, alcohol effect sizes were estimated by examining differences between z-transformed scores at comparable time points during the A+S- and the A-S+ sessions. For the SOT analysis, time 2 (occurring approximately 80 min after administration of the initial alcohol dose) was selected. The first three columns of Table 4 display the alcohol effect size, the number of participants (out of 6) showing an effect in the predicted direction, and the p -value for the effect size. It should be noted that increases in sway produced increased sway area and spectral estimates (yielding positive effect size estimates) whereas increased sway is associated with smaller EQ scores (yielding negative effect size estimates). Robust evidence for alcohol effects were obtained for all measures of low frequency sway at all SOT conditions as well as for the composite, eyes-open and eyes-closed averages (the only exception being SOT1 where strong evidence for an alcohol effect can be seen only in the low frequency Shear spectral measure).

The moderating effects caused by the introduction of cigarettes are presented in the three columns on the right side of Table 4. Smoking moderation percentage was estimated by first determining the z-score difference between the A+S+ and A+S- sessions. The percent reduction from the alcohol effect size to this difference was then

computed. For example, given an alcohol effect size of 2 (A+S- minus A-S+), and an A+S- minus A+S+ difference score of 1.5, the smoking moderation effect size would be reported as 25% (i.e., $100 * [(2-1.5)/2]$). Negative values of smoking moderation indicate instances where smoking actually exacerbated the effect of alcohol. Finally, although always included for the sake of completeness, the smoking moderation scores can only be interpreted in the presence of clear alcohol effects since the smoking effect is based on the size of alcohol effect (if the effect of alcohol is small then minor changes associated with smoking will appear significant).

The best evidence for smoking moderation during the individual SOT conditions was found in SOT 4 where the moderation percent estimates range from 75% to 88% across the measures. Cigarettes clearly reduce alcohol-induced sway in SOTs 3 and 6, as well. In SOT 5, only the spectral measures evidence a moderating effect of smoking, and in SOT2 no discernable moderation is present. Thus, the beneficial effects of cigarette smoking are less evident in the eyes-closed conditions. This result is reinforced by the composite measures. The eyes-open and total composite scores both show smoking moderation (in the range of 45% to 64% across measures). For the eyes-closed composite scores, on the other hand, only the low frequency AP power score shows any evidence of smoking moderation (see Figure 7 for a depiction of the low frequency AP power measures across time points and composite score categories).

Table 4. Summary of sensory organization test (SOT) results.

		Alcohol Effect			Smoking Moderation		
		Effect Size	n-sub	p-value	Mod. %	n-sub	p-value
SOT 1	EQ Score	-0.96	5	0.11	1.1	2	0.48
	Sway Area	0.46	4	0.573	-96	4	0.3
	Low AP Power	0.95	5	0.14	-0.19	2	0.34
	Low Shear Power	1.78	5	0.011	49	6	0.005
SOT 2	EQ Score	-1.84	5	0.007	16.5	3	0.34
	Sway Area	1.47	5	0.02	-19	4	0.35
	Low AP Power	1.86	6	0.0007	5.85	4	0.37
	Low Shear Power	1.14	5	0.08	-47	3	0.16
SOT 3	EQ Score	-1.68	4	0.035	70	5	0.01
	Sway Area	2.02	6	0.0082	56	6	0.02
	Low AP Power	1.87	5	0.006	69	6	0.014
	Low Shear Power	1.4	6	0.013	36	4	0.14
SOT 4	EQ Score	-2.4	6	0.0001	75.5	4	0.016
	Sway Area	2.76	6	0.0002	79.5	5	0.013
	Low AP Power	1.91	6	0.0013	82	5	0.013
	Low Shear Power	1.89	6	0.0014	88	5	0.0045
SOT 5	EQ Score	-1.64	5	0.011	32.52	4	0.23
	Sway Area	1.48	5	0.015	35.12	5	0.12
	Low AP Power	2.18	6	0.005	75.24	5	0.012
	Low Shear Power	2.1	6	0.0065	74	5	0.013
SOT 6	EQ Score	-2.01	6	0.0008	73.31	5	0.012
	Sway Area	1.36	5	0.007	56.13	5	0.11
	Low AP Power	1.32	5	0.042	83	5	0.034
	Low Shear Power	1.35	5	0.043	83	5	0.022
Composite	EQ Score	-2.53	6	0.00001	58.96	6	0.0006
	Sway Area	2.03	5	0.0048	44.66	5	0.011
	Low AP Power	1.68	6	0.0004	55	5	0.0005
	Low Shear Power	1.64	6	0.0005	53	6	0.0012
Eyes Open	EQ Score	-1.76	6	0.0001	63.53	6	0.0006
	Sway Area	1.65	6	0.0006	55.32	5	0.01
	Low AP Power	1.51	6	0.0008	62	6	0.0058
	Low Shear Power	1.64	6	0.0002	64	6	0.0001
Eyes Closed	EQ Score	-1.74	6	0.002	24.09	4	0.27
	Sway Area	1.47	6	0.003	7.97	4	0.25
	Low AP Power	2.02	6	0.0002	43	5	0.04
	Low Shear Power	1.62	6	0.0033	31	5	0.16

Note: bold represents the presence of smoking moderation.

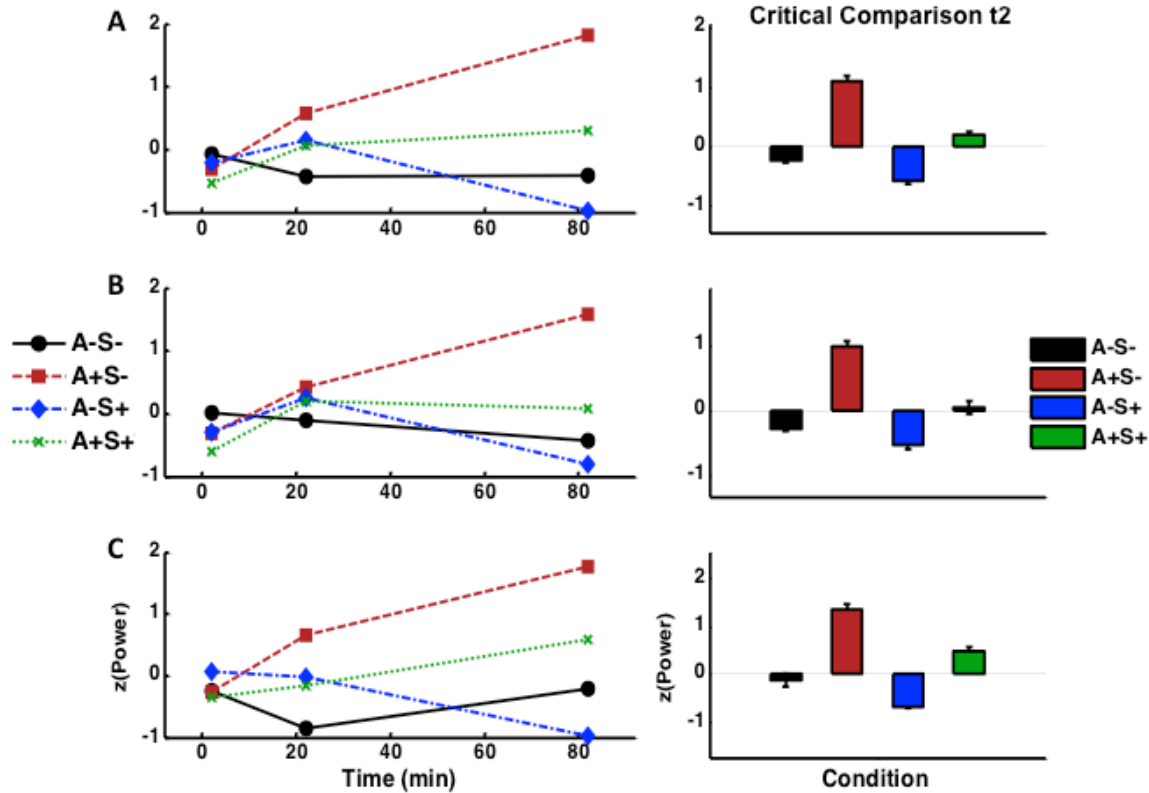


Figure 7. Composite (A), eyes open (B), and eyes closed (C) for low frequency AP spectral power with comparison at t2.

In clinical use the EQ scores are combined variously in ratios, so as to characterize differential effects in the vision, somatosensory, and vestibular systems. A comparison between the SOT1 and SOT2 conditions provides an assessment of the participants' ability to maintain balance using primarily somatosensory input. A somatosensory ratio was derived by dividing average EQ score in SOT2 by the EQ score in SOT1. There was deterioration in somatosensory performance caused by alcohol, but it was only mildly affected by cigarette smoking (see Figure 8). This is consistent with findings described above that the moderating effects of smoking are less prominent in the eyes closed conditions.

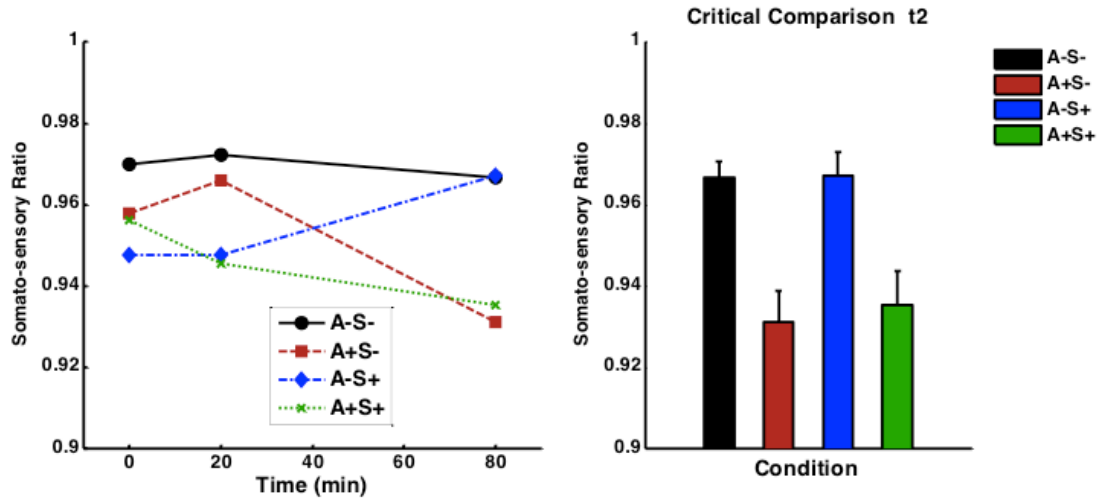


Figure 8. Somatosensory ratio of SOT2/SOT1 (eyes closed / eyes open).

A comparison between the SOT1 and SOT4 conditions provides an assessment of the participants' ability to maintain balance using primarily visual input. A visual ratio was derived by dividing average EQ score in SOT4 by the EQ score in SOT1. As seen in Figure 9 there is deterioration in the participants ability to maintain balance using visual cues when alcohol is consumed. However, when cigarettes are smoked concurrently with alcohol the performance is roughly equal to the smoking only condition.

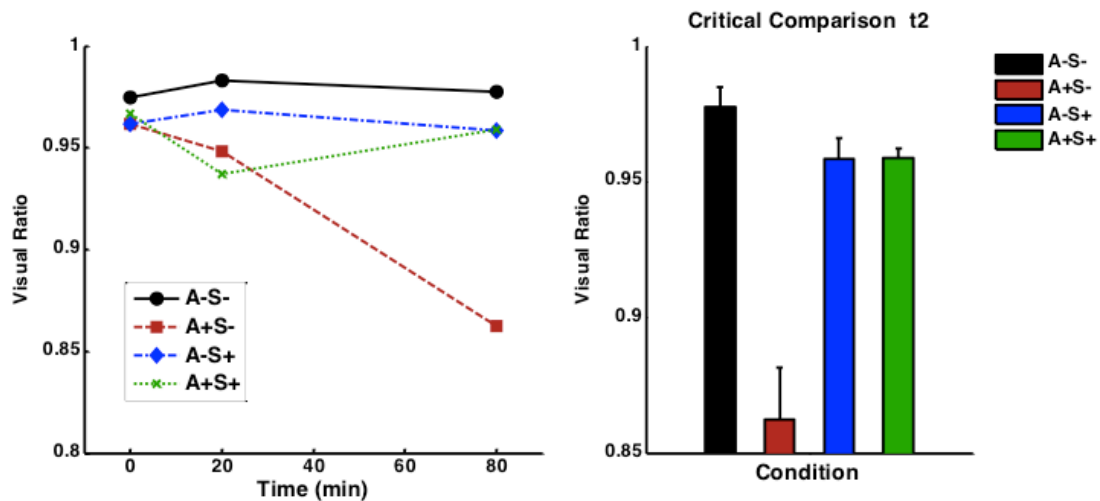


Figure 9. Visual ratio of SOT4/SOT1 (platform sway-referenced / stable).

A comparison between the SOT1 and SOT5 conditions provides an assessment of the participants' ability to maintain balance using primarily vestibular input. A vestibular ratio was derived by dividing average EQ score in SOT5 by the EQ score in SOT1 (ability to suppress inappropriate visual cues). Alcohol causes deterioration in performance on this task (although baseline performance is also lower). There was some improvement when cigarettes are consumed along with alcohol (see Figure 10), suggesting that smoking does moderate some of the vestibular impacts of alcohol. However, this improvement is roughly the same as the baseline variance.

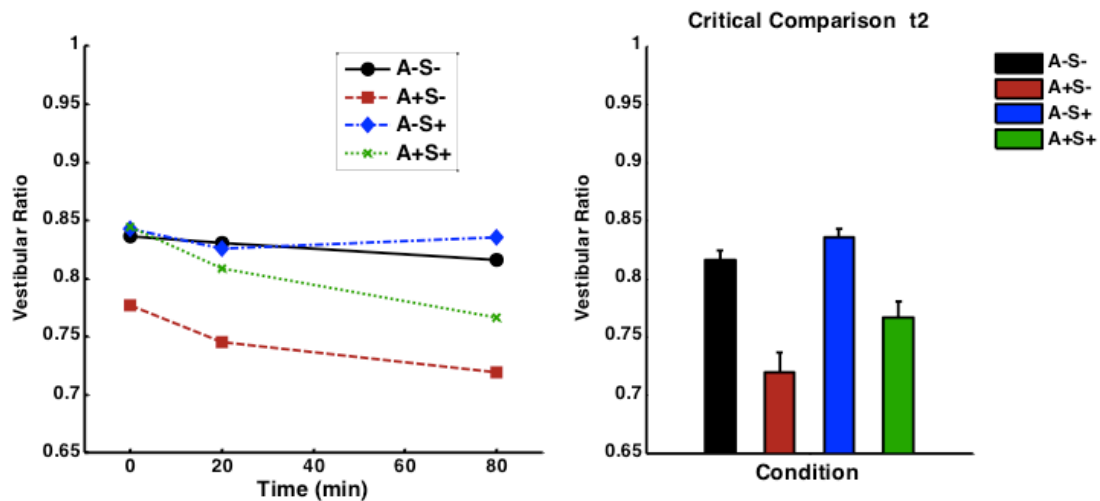


Figure 10. Vestibular ratio of SOT5/SOT1 (eyes closed with sway-referenced platform / eyes open stable).

A comparison between the eyes-closed conditions (SOT2 + SOT5) and sway-referenced visual surround conditions (SOT3 + SOT6) provides an assessment of the participants' reliance on visual information, despite the information being incorrect. A visual preference ratio was derived by dividing average EQ scores in SOT3 plus SOT6 by the average EQ score in SOT2 plus SOT5 ((SOT3+SOT6)/(SOT2+SOT5)). In this comparison the combination of alcohol and cigarettes has the highest scores, even exceeding the baseline (see Figure 11). This reinforces the importance of accurate visual references during intoxication and could suggest that nicotine heightens the participants' awareness of visual cues.

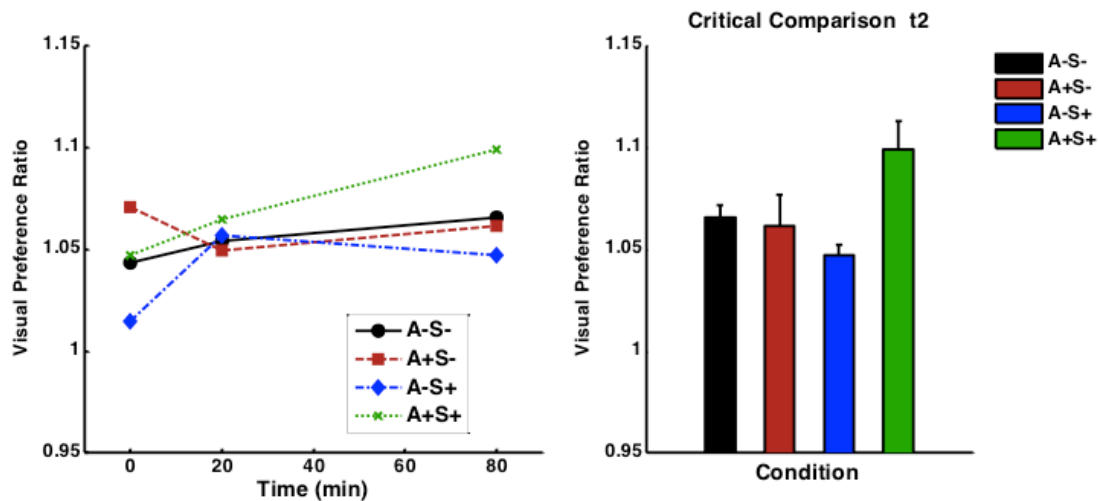


Figure 11. Visual preference ratio of SOT3+SOT6 / SOT2+SOT5 (platform sway-referenced / stable).

Motor Control Tests

MC tests are a reliable indicator of alcohol consumption due to the consistent effects on both latency and amplitude (Karch, 2010). The EMG results of the current research displayed changes in latency and amplitude associated with alcohol ingestion with only isolated indications of moderation by cigarette smoking.

As described above, EMG data were recorded from relevant muscle groups (gastrocnemius, quadriceps, tibialis, paraspinal) in response to platform movements designed to assess control over motor activity (toes-up, toes-down, forward translation, backward translation). Each MC condition consisted of 5 trials, with EMG recording beginning 258 msec prior to the movement and continuing for 1000 msec. The EMG signals for individual trials were visually inspected for excess noise, and the trial was rejected if necessary. The remaining raw data from the EMG recordings were analyzed using software developed for this project in Matlab (Mathworks, 2013) by laboratory staff. The EMG signals were high pass filtered using a fourth order Butterworth IIR filter

(cutoff = 40Hz) so as to exclude gross movement-related artifacts. The signals for each trial were full wave rectified and averaged after the mean of the 258 msec baseline was removed. EMG response amplitude was computed as the area in prescribed windows individually defined for the specific muscle groups analyzed for each challenge condition. The positions of these windows (which were referenced to the beginning of the platform shift) were chosen on the basis of experience obtained during the analyses of the MC data from the pilot study (described above) used to establish the alcohol dosing procedures for male and female participants (Goebel et al., 1995). EMG latency was measured as the last zero-crossing of the EMG response in a specific analysis window.

Three principal factors complicated the interpretation of the MC data. First, EMG response amplitudes will vary significantly across sessions spread over multiple days due to even slight changes in the precise location of the recording electrodes with respect to the muscle groups of interest. Considerable effort was applied to ensure consistency, but it is extremely difficult to guarantee exact replication of electrode placement across repeated applications without permanently marking the skin. For this reason, the values obtained during the initial pre-dose (i.e., before alcohol administration) tests for each session were subtracted from subsequently measured response amplitudes and latencies. Second, it proved extremely difficult to maintain good electrode connections across the course of sessions lasting for several hours as were used in this study. For every participant, the left and right responses for each muscle group and all MC conditions were visually examined and the side exhibiting the most stable responses was selected for subsequent analysis. Finally, examination of

the data quickly revealed that the strategy (elaborated at the beginning of the Results section) of using the data from the A-S+ session as the best comparison against which to evaluate alcohol and smoking modulation effect sizes was not appropriate for the MC data. Many EMG responses evidenced direct effects of smoking (i.e., substantial differences between the A-S- and A-S+ sessions at both early and late post-dose time points). For this reason, the effects of alcohol administration and the modulation of these effects by cigarettes on the EMG measures were evaluated using the A-S- session as the baseline.

To maintain the integrity of the clinical MC testing protocol, the conditions involving translational platform shifts were included in the testing protocol and the EMG responses from these conditions were analyzed (the translation conditions provided evidence for direct smoking effects – see Appendix J). However, as described earlier, it was anticipated that the rotational movements (toes-up, toes-down) would be most sensitive to the effects of alcohol due to the combination of a short latency stretch reflex and long latency adaptive muscle contractions (Diener et al., 1983). The long latency postural restabilizing reflexes caused by quick ankle rotations are especially sensitive to alcohol (Woollacott, 1983) and the analysis was concentrated on those measures.

Toes-up Rotations

It was anticipated that the toes-up rotation stimulus would be especially sensitive to the effects of alcohol and cigarettes due to the combination of both early/mid latency spinal reflexes (mono- and supra-segmental) and long-latency corrective reflexes involving trans-cerebellar loops. In this condition the movement of the platform into a toes-up position elicits a stretch reflex in the gastrocnemius muscle, which then

contracts so that additional pressure is applied to the ball of the foot. This reflexive reaction further destabilizes the participant and must be overcome by a corrective long-latency response that involves contraction of the tibialis and quadriceps to relieve pressure on the ball and restore posture to the upright position (Diener, Dichgans, Bootz, & Bacher, 1984).

Four EMG responses were evaluated. First, the amplitude of the early gastrocnemius response (mono-segmental spinal reflex) was measured as the area in a window from 30-50 msec, and the latency was estimated as the last zero-crossing in a window from 25-35 msec. Second, the amplitude of the mid-latency gastrocnemius response (supra-segmental spinal reflex) was measured as the area in a window from 75-125 msec, and the latency was estimated as the last zero-crossing prior in a window from 70-80 msec. Third, the late tibialis response (supra-spinal reflex) was quantified by first identifying the maximum response in a window from 90-200 msec, and the onset latency was identified as the last zero-crossing preceding this maximum. The amplitude of the tibialis response then was measured as the area in a 150 msec window commencing at the latency onset point. Finally, the late quadriceps response amplitude was measured as the area in a window from 150-250 msec. A super-average across participants for the right leg in Figure 12 illustrates the contraction sequence for each muscle group in the toes-up test condition. Note that the latency values cited in the text refer to the onset of platform rotation, marked in the figure by the vertical dotted line.

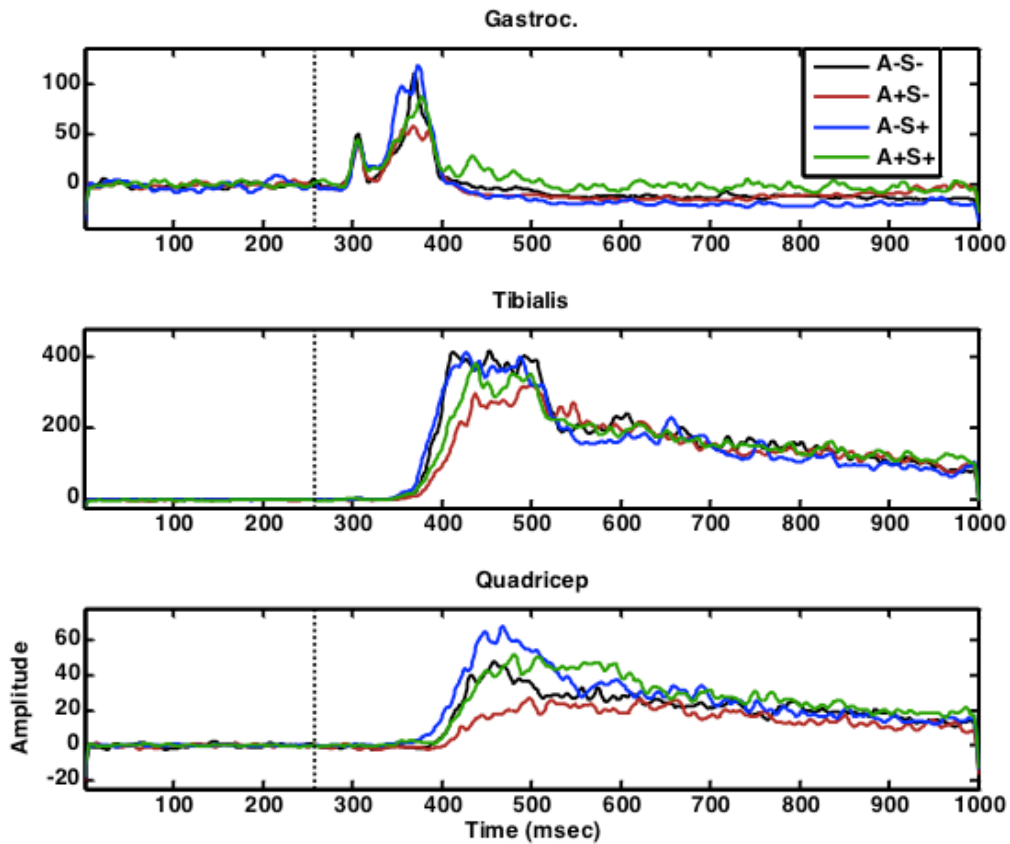


Figure 12. Toes-up super average for right leg (dotted line represents onset of platform rotation).

Table 5 presents the alcohol and smoking moderation effects for EMG activity during the toes-up condition at t1 (approximately 36 min following start of administration of the first dose of alcohol). Alcohol robustly increased the amplitude of the tibialis and quadriceps responses analyzed at this time-point (with some evidence of a reduction in the early gastrocnemius response as well). There was no evidence of an effect of alcohol on response latency for any muscle group. However, alcohol effects were identified for decreases in the amplitude of the tibialis and quadriceps contractions. The

35% change in the reduction of the quadriceps amplitude response due to alcohol represents the best evidence for a smoking moderation effect (see Figure 13).

Table 5. Toes-up rotation at t1.

		Alcohol Effect			Smoking Moderation		
		Effect Size	n-sub	p-value	Mod. %	n-sub	p-value
Early	Latency	0.01	2	0.495	-11095	5	0.052
	Gastroc Amplitude	-1.65	5	0.056	101	4	0.071
Mid	Gastroc Latency	-0.54	4	0.2275	289	5	0.0207
	Amplitude	-0.45	3	0.2377	173	4	0.078
Tibialis	Latency	-0.09	3	0.4555	-581	3	0.2662
	Amplitude	-1.7	6	0.0067	-2.65	4	0.4677
Quadricep	Amplitude	-1.317	6	0.0005	34.7	4	0.0267

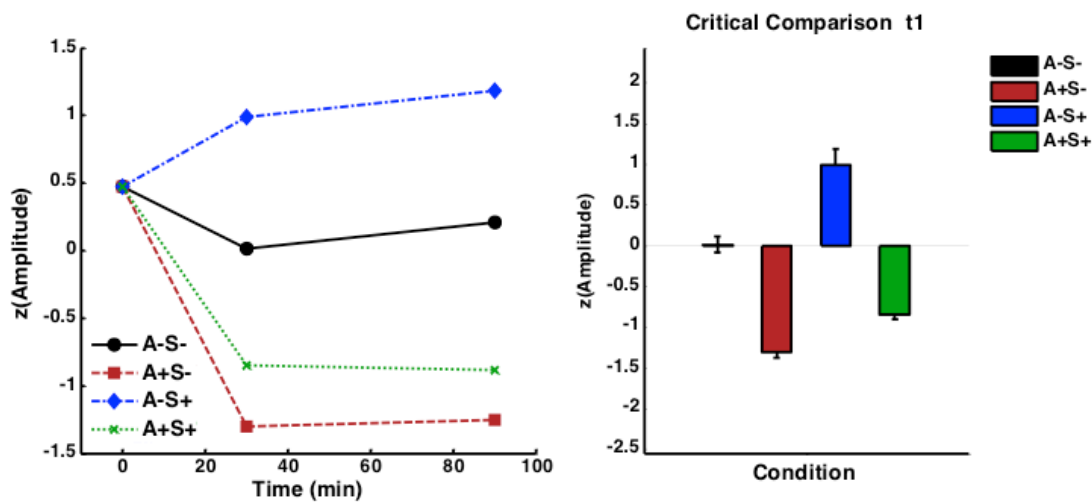


Figure 13. Toes-up quadriceps amplitude with comparison at t1.

Toes-down Rotations

In the toes-down condition the platform movement elicits short and mid-latency stretch reflex in tibialis and quadriceps muscles, which further decreases pressure on the ball of the foot and thereby destabilizes the participant. This is followed by a long

latency gastrocnemius contraction that increases pressure on the ball of the foot and stabilizes posture.

Four EMG measures were calculated for this condition. First, the amplitude of the early quadriceps response was measured as the area in a window from 75-150 msec, and the latency was estimated as the last zero-crossing preceding the maximum amplitude in this window. Second, the amplitude of the mid-latency quadriceps response was measured as the area in a window from 150-250 msec, and the latency was estimated as the last zero-crossing preceding the maximum amplitude in this window. Third, the early tibialis responses were quantified by first identifying the maximum response in a window from 75-100 msec, and the onset latency was identified as the last zero-crossing preceding this maximum. The amplitude of the tibialis response then was measured as the area in a 50 msec window commencing at the latency onset point. Finally, the late gastrocnemius responses were estimated by first identifying the maximum response in a window from 140-250 msec, and the onset latency was identified as the last zero-crossing preceding this maximum. The amplitude of the gastrocnemius response then was measured as the area in a 150-msec window commencing at the latency onset point. A super-average across participants for the right leg in Figure 14 illustrates the contraction sequence for each muscle group in the toes-down test condition.

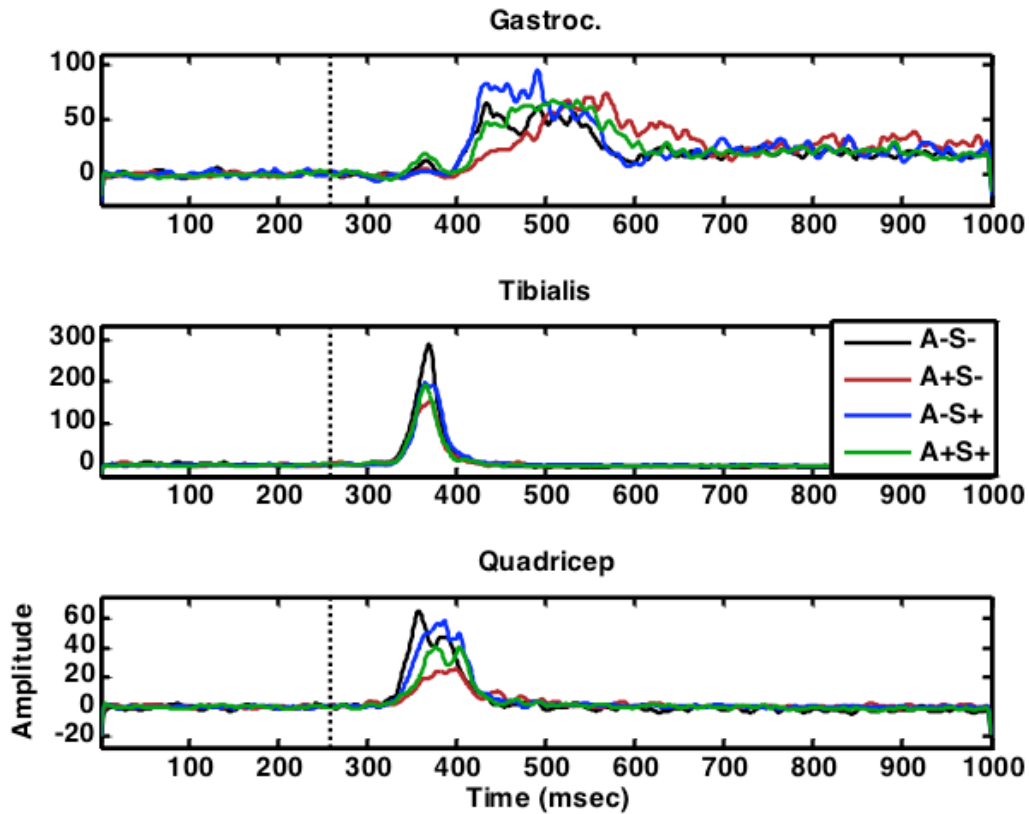


Figure 14. Toes-down super average for right leg (dotted line represents onset of platform rotation).

Table 6 presents the alcohol and smoking moderation effects upon EMG activity during the Toes-down condition collapsed across times t1 and t2 (approximately 38 and 98 min following the start of administration of the first dose of alcohol, respectively). The only measures affected by alcohol were the latency of the gastrocnemius response (which was increased), the amplitude of the early quadriceps response (which was decreased), and the amplitude of the late quadriceps response (which was increased). Only the early quadriceps response showed some indication of smoking moderation

(average modulation = 69% evidenced by 4 of the 6 participants), but not at statistically significant levels.

Table 6. Toes-down rotation at t1 + t2.

		Alcohol Effect			Smoking Moderation		
		Effect Size	n-sub	p-value	Mod. %	n-sub	p-value
Gastroc	Latency	1.79	6	0.0015	13.9	3	0.259
	Amplitude	-0.03	3	0.4748	-1448	5	0.112
Tibialis	Latency	0.559	4	0.1425	17.7	4	0.431
	Amplitude	-0.359	2	0.3137	1.59	3	0.4958
Early Quad	Amplitude	-1.075	4	0.0404	68.6	4	0.0965
Mid Quad	Amplitude	1.3054	5	0.0308	10.9	4	0.3874

Oculomotor Measures

Consistent with prior evidence, it was expected that alcohol would have a clear effect on eye movements. As described above, the oculomotor battery (which was based on a standard clinical assessment protocol) included fixed and random saccade tracking tasks, smooth pursuit tracking tasks, and positional, optokinetic, and gaze nystagmus tests. The fixed and random amplitude saccade tasks did not produce either alcohol or smoking effects, so these data will not be further presented in detail.

Smooth Pursuit

For the pursuit tasks, participants were seated in a chair with a headrest and asked to track the position of a smoothly moving visual stimulus which moved in either the vertical or horizontal dimension (described in detail above). A single vertical pursuit tracking test was performed. This was included principally on the basis of prior findings (reviewed in the Introduction section) that smoking affects vertical smooth pursuit. Data

from this condition did not demonstrate robust alcohol effects and are discussed in Appendix J (which contains a description of smoking effects). Horizontal smooth pursuit performance was tested using three different velocities for the tracking signal (0.1 Hz at 10 deg/sec, 0.2 Hz at 20 deg/sec, 0.4 Hz at 40 deg/sec) for 20 seconds. The 0.1 Hz condition was included to preserve the integrity of the clinical oculomotor test battery even though it was recognized that tracking performance is generally erratic under such slow velocities (i.e., the pursuit mechanism is not robustly engaged), and it was thus considered unlikely that reliable drug effects would be observed. This prediction was confirmed and the following discussion will be limited to data obtained from the 0.2 and 0.4 Hz conditions.

The vertical and horizontal EOG signals were sampled at 250 Hz during each of the 20 second tracking tasks. The EOG data were then low pass filtered using a sixth order Butterworth filter with frequency cutoff of 10 Hz. Standard spectral analysis routines available with the Matlab (Mathworks, 2013) signal-processing suite were used to derive a number of measures of tracking performance. The Power Spectral Density function was computed using Welch's method of overlapping epochs (Welch, 1967). The data were Hanning windowed and then submitted to overlapping (overlap points = 100) 2048 point Fast Fourier Transforms (FFT).

Three principal measures were computed from the pursuit data to assess task performance: signal to noise ratio (SNR), coherence, and root mean square error (RMSe). SNR was computed by: 1) estimating signal strength as the spectral power at the tracking frequency (i.e., either 0.1, 0.2 or 0.4 Hz); 2) obtaining a noise estimate by summing the power in all the other bands from DC to the Nyquist frequency; and 3)

dividing the log corrected signal estimate by the log corrected noise estimate.

Coherence was intended to provide a comparison measure between the participant's data and a pure sine of the appropriate frequency and phase. Standard analysis routines in MATLAB (Mathworks, 2013) were used to estimate the coherence function. A second measure of tracking performance was defined as the value of the coherence function at the appropriate tracking frequency. Finally, the phase and magnitude of the transfer function between the pure sine and the obtained data also were estimated. A "calibrated" response signal was produced by multiplying the obtained data by the magnitude estimate at the appropriate frequency. A RMSe measure of the difference between the pure sine and the calibrated response function then was computed. The RMSe measure was not used in subsequent analyses as it proved less sensitive than the SNR and coherence measures.

An additional measure was computed by examining the velocity transform of the filtered EOG signal. The obtained velocity function was examined for points that deviated from the prescribed pursuit tracking behavior. Points with velocities below 0.05 units were defined as belonging to fixation pauses. Points with velocities above 2.0 units were defined as belonging to the "catch-up" saccades required in order to make up for the lags induced by fixation pauses. The sum of the points contained in these two aberrant tracking categories were then divided by the total number of points in the signal to produce an estimate of "intrusion ratio" – the degree to which poor tracking performance intruded upon the desired smooth pursuit tracking movements. Finally, a composite tracking score was computed as the average of the z transforms of the SNR, coherence, and intrusion ratio measures (the valences of the SNR z-scores

were inverted prior to averaging so that poorer performance on all scales was indicated by increasing values).

Table 7 presents the results for the 0.2 Hz horizontal smooth pursuit condition. These measures provide good evidence for an effect of alcohol with five of the six participants demonstrating a decrease in SNR, and increased intrusion ratio and composite scores. There was no consistent evidence for smoking moderation at this frequency of tracking.

Table 7. Horizontal Smooth Pursuit at .2Hz at t2.

	Alcohol Effect			Smoking Moderation		
	Effect Size	n-sub	p-value	Mod. %	n-sub	p-value
Coherence	-0.77	4	0.15	-40	3	0.38
SNR	-1.43	5	0.022	-6	3	0.46
Intrusion Ratio	1.67	5	0.046	51	4	0.12
Composite	1.29	5	0.043	11	3	0.42

A similar pattern can be seen in the results of the 0.4 Hz condition (see Table 8). For this condition, however, the coherence measures, rather than SNR, were sensitive to alcohol and there is some evidence of smoking moderation of the alcohol-induced decrease in coherence (four of six participants showed moderation which on average equaled a 56% reduction in the alcohol effect) (see Figure 15).

Table 8. Horizontal Smooth Pursuit at .4Hz at t2.

	Alcohol Effect			Smoking Moderation		
	Effect Size	n-sub	p-value	Mod. %	n-sub	p-value
Coherence	-1.62	5	0.014	56	4	0.028
SNR	-0.42	4	0.13	50	3	0.38
Intrusion Ratio	1.12	5	0.046	-17	3	0.36
Composite	1.06	6	0.01	29.32	3	0.18

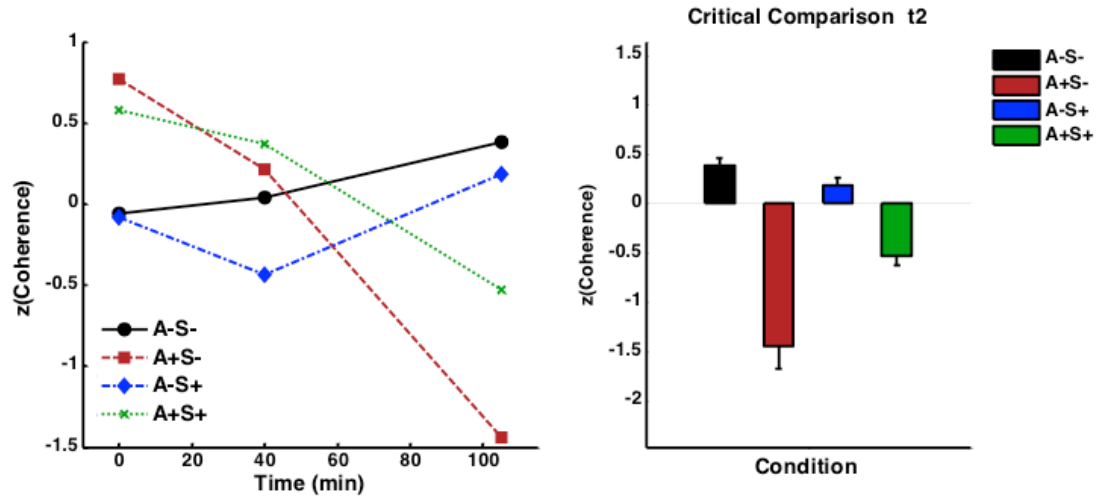


Figure 15. Horizontal smooth pursuit coherence at .4HZ with comparison at t2.

Optokinetic Nystagmus

The data analysis for optokinetic oculomotor tests was performed using software supplied by the equipment manufacturer (Nicolet Biomedical, Inc. Madison, WI). The number of nystagmus eye movements (beats) was evaluated during the optokinetic stimulation as the number of fast component eye movements that shifted gaze back to the central fixation direction. The system criteria for automatic detection of nystagmus included a minimum velocity of 40 deg/sec and a minimum duration of 40 msec. Artifacts, including blinks, were automatically removed from the analysis by the system and manually confirmed as artifacts (see Baloh, Kumley, & Honrubia, 1976).

It was anticipated that the optokinetic task would be especially useful as a measure of the effects of alcohol due to the reflexive nature of the nystagmus. This task did not require volition or active tracking and was therefore not as susceptible to participant fatigue, cooperation, or strategy. Table 9 provides a summary of the effect

size, the number of participants who exhibited a change in the expected direction, and the p -value of the change along with the smoking moderation. As seen in Figure 16, alcohol reduced the number of nystagmus beats for all participants and this reduction was moderated by smoking.

Table 9. Optokinetic nystagmus at 20 deg/sec at t1 + t2.

	Alcohol Effect			Smoking Moderation		
	Effect Size	n-sub	p -value	Mod. %	n-sub	p -value
Number of beats	-1.69	6	0.0008	62	6	0.0035

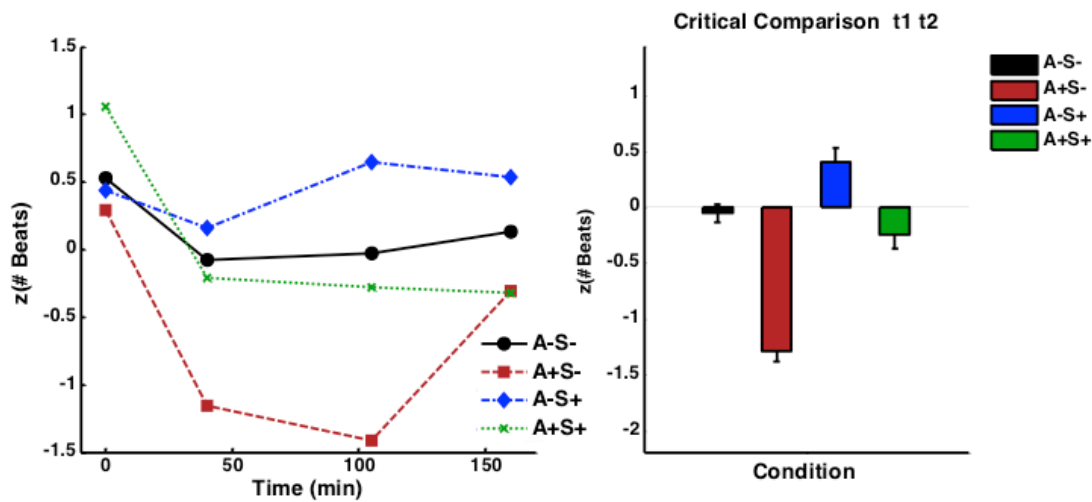


Figure 16. Optokinetic nystagmus at 20 deg/sec stimulation with comparison at t1 + t2.

Positional Nystagmus

Evaluations of positional and gaze nystagmus were performed by Joel Goebel, M.D. All data were coded and presented in a random order for identification of nystagmus. The data were evaluated separately for head right and head left and nystagmus was scored on a scale of 0 (no nystagmus) to 3 (strong nystagmus). Scores then were added for left and right positions and averaged across participants for each

condition. Table 10 provides a summary of the effect size, the number of participants that exhibited a change in the expected direction, and the p -value of the change along with the smoking moderation. As seen in Figure 17, alcohol increased the rate of PAN, and there was no moderation by cigarettes.

Table 10. Positional nystagmus.

	Alcohol Effect			Smoking Moderation		
	Effect Size	n-sub	p -value	Mod. %	n-sub	p -value
Number of beats	1.5079	5	0.0094	0.14	3	0.4985

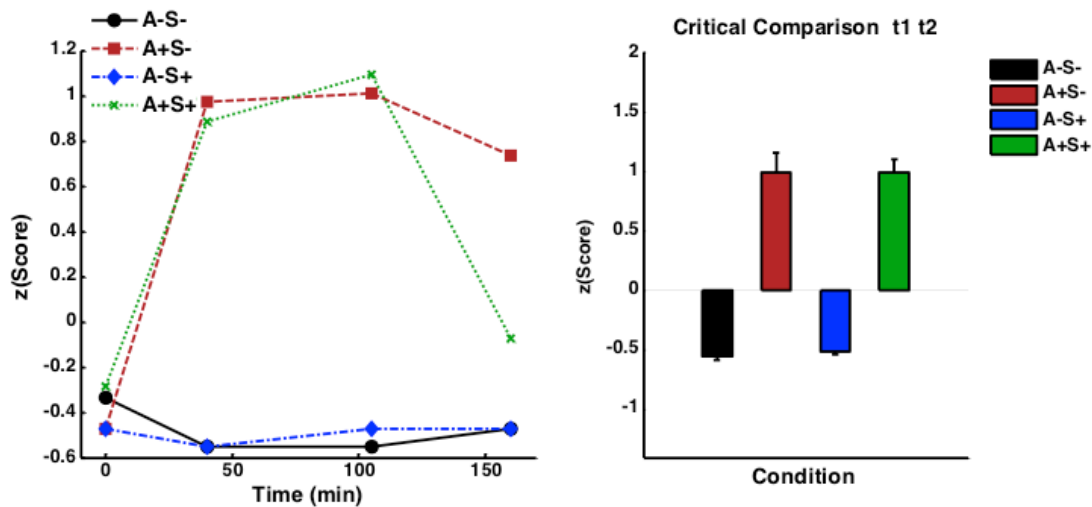


Figure 17. Mean positional alcohol nystagmus scores.

Gaze Nystagmus

The evaluation of gaze nystagmus was performed in the same manner as positional nystagmus. Evaluations of gaze nystagmus did not identify any alcohol-induced nystagmus.

There are two possible explanations for the lack of nystagmus. First, the dose of alcohol for this experiment was generally sub-intoxicating and participants may not have reached BAC levels sufficient to induce a gaze nystagmus. Takahashi et al. (1989) also did not detect evidence of gaze nystagmus at similar BAC levels as the present study. The second explanation is that the angle of gaze deviation (20°, 30°, and 40°) was not sufficient to induce the gaze nystagmus that normally occurs during alcohol intoxication. Good and Augsburger (1986) suggested that the onset angle of gaze evoked nystagmus could be determined by multiplying the BAC by 105 and subtracting that product from 51°. When that formula is applied to the average BAC level in this study [$51 - (.07 * 105) = 43.65^\circ$] there is some question of the adequacy of the 40° deviation angle. However, if the 40° deviation angle had been exceeded there would be an increased risk of eliciting an end-point nystagmus for some participants.

Subjective Response

Throughout each experimental session the participants were periodically asked to provide a subjective assessment through both the BAES and the NES. There were a total of 10 assessments during each session including the baseline. Because these assessments occurred more often than the SOT/EMG/EOG testing, the timing labels do not coincide. Assessments 1, 2, and 3 roughly correspond to the ascending and plateau portion of the BAC and 4, 5, and 6 were on the descending portion. (Refer to Figure 4 for the t0 through t9 timing for BAES/NES).

BAES

The cardinal measure of subjective response to alcohol and cigarettes was the BAES. Of the 14 items on the BAES scale, 7 were combined to create a scale of

stimulation (elated, energized, excited stimulated, talkative, up, vigorous) and the remaining 7 were combined for a scale of sedation (down, difficulty concentrating, heavy head, inactive, sedated, slow thoughts, sluggish). Alcohol robustly increased stimulation on the ascending portion of the BAC while also increasing sedation scores on the descending portion. Table 11 provides a summary of the effect size, the number of participants who exhibited a change, and the *p*-value of the change along with the smoking moderation. The moderating effect of smoking was not consistent across all participants, but there were suggestive indications of prolonged stimulation and reduced sedation in the A+S+ condition (note that this pattern mirrors that associated with a positive history of alcoholism, as reviewed above). The Stimulant portion of the BAES is plotted in Figure 18.

Table 11. BAES.

		Alcohol Effect			Smoking Moderation		
		Effect Size	n-sub	<i>p</i> -value	Mod. %	n-sub	<i>p</i> -value
Stimulation	t2 + t3	1.08	4	0.04	-44	4	0.1985
Sedation	t4 + t5 + t6	1.833	5	0.0497	36.8	5	0.074

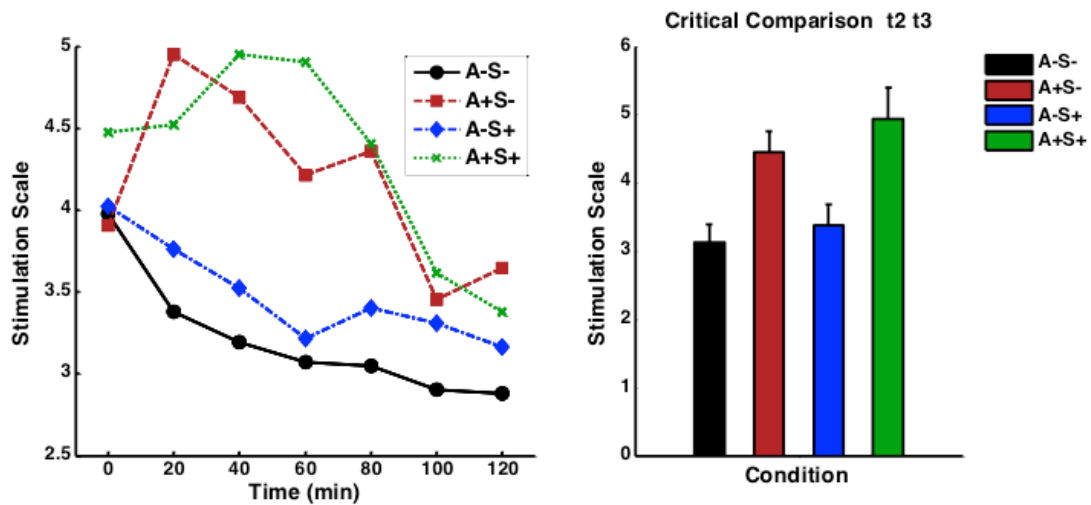


Figure 18. BAES Stimulant score with comparison at t2 + t3.

As seen in Figure 19, there was a sharp increase in the Sedation portion of the subjective ratings during the descending limb of the BAC. This increase was somewhat moderated by smoking, although the effect was not consistent. The subjective ratings overall were clearly bi-phasic in nature.

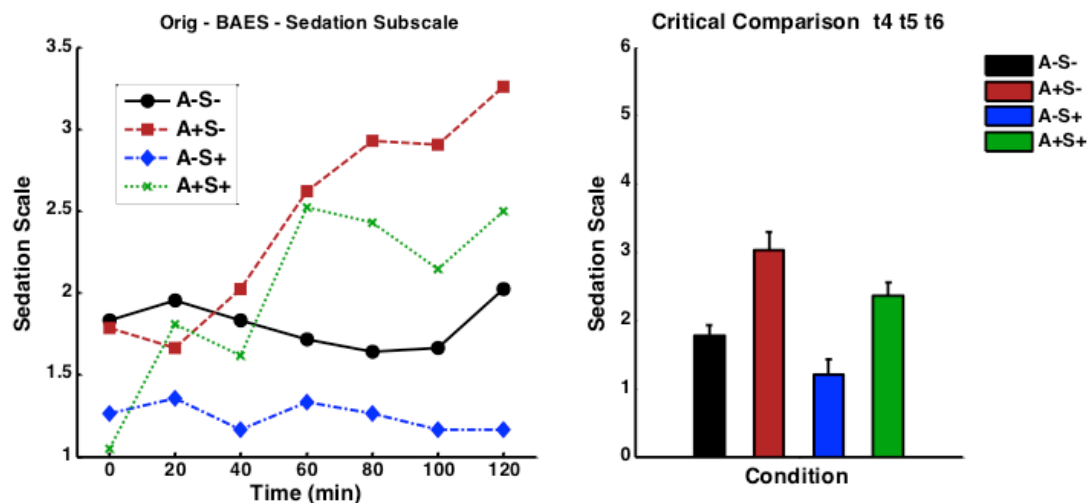


Figure 19. BAES Sedation score with comparison at t4 + t5 + t6.

Nicotine Effect Scale

The NES was administered concurrently with the BAES as a measure emphasizing the subjective effects of cigarette smoking. Of the 10 components on the NES, there were 5 that exhibited appreciable changes following the dose of alcohol and/or cigarettes (I feel lightheaded or dizzy, I feel high, I feel nauseated, I feel anxious or tense, my heart is beating faster). Table 12 provides a summary of the effect size, the number of participants who exhibited the change, and the *p*-value of the change for the combination of t1, t2, and t3. Table 13 provides the same information for the combination of t4, t5, and t6. This is provided for both the alcohol effect and the smoking moderation effect. The only robust alcohol effects were observed on the ascending portion of the BAC for the Lightheaded (see Figure 20) and High (see Figure 21) scales. There was no consistent smoking-associated moderation.

Table 12. NES at t1 + t2 + t3.

	Alcohol Effect			Smoking Moderation		
	Effect Size	n-sub	<i>p</i> -value	Mod. %	n-sub	<i>p</i> -value
LightHeaded	2.222	5	0.0146	-42.5	4	0.1239
High	1.889	3	0.047	-38.24	5	0.2368
Nausea	0	1	0.5	sz= -.67	5	0.137
Anxious	-0.389	2	0.17	214	4	0.0378
Hi HeartRate	0.44	2	0.2	-88	5	0.2946

Table 13. NES at t4 + t5 + t6.

	Alcohol Effect			Smoking Moderation		
	Effect Size	n-sub	<i>p</i> -value	Mod. %	n-sub	<i>p</i> -value
LightHeaded	1.22	4	0.11	-54.5	5	0.033
High	1.1667	4	0.054	-52.4	4	0.2478
Nausea	0.2778	2	0.1917	-60	6	0.1016
Anxious	-0.389	3	0.1	200	4	0.026
Hi HeartRate	0	1	0.5	sz= -.5	5	0.2513

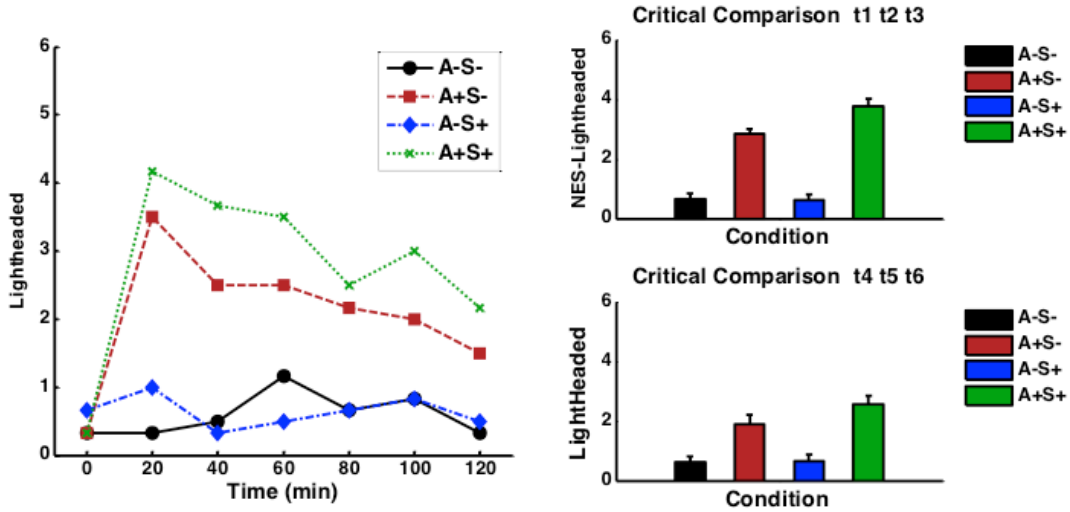


Figure 20. NES Lightheaded score with comparison at t1+t2+t3 and t4+t5+t6.

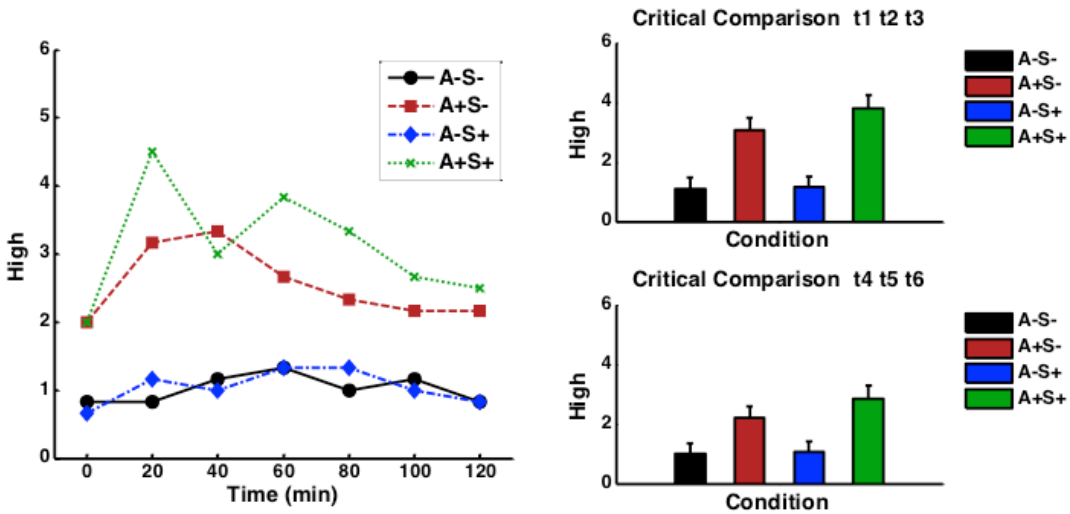


Figure 21. NES High score with comparison at t1+t2+t3 and t4+t5+t6.

As described earlier, there was an increase in self-reported nausea that was highest during the A+S+ condition. This was especially true for the female participants. There was not a robust alcohol effect, but overall an increase in Nausea scores was observed (see Figure 22).

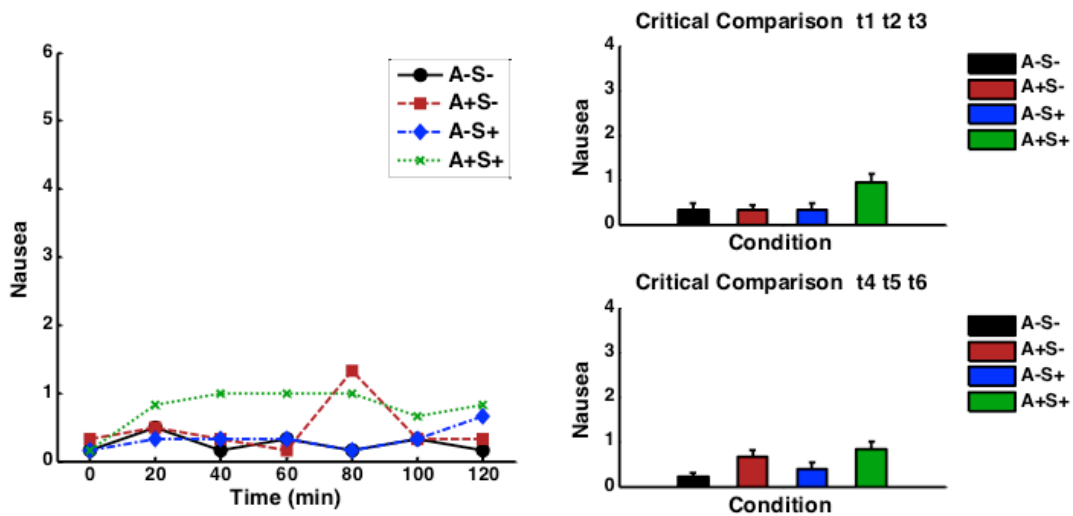


Figure 22. NES Nausea score with comparison at t1+t2+t3 and t4+t5+t6.

In general, alcohol in isolation resulted in a decrease of scores for the Anxious scale. However, in both cigarette conditions, the Anxious scores were higher for both the ascending and descending portions of the BAC (see Figure 23).

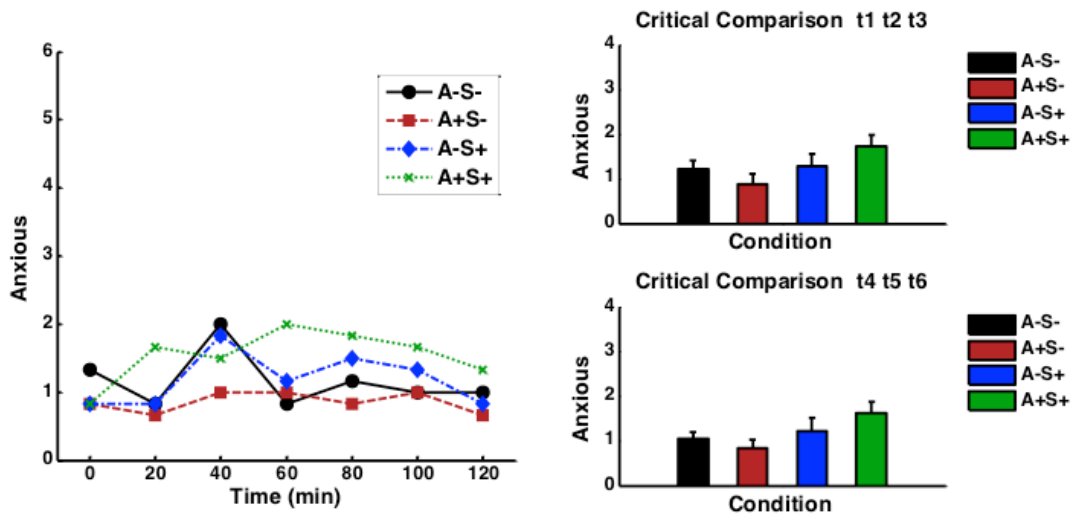


Figure 23. NES Anxious score with comparison at t1+t2+t3 and t4+t5+t6.

Alcohol did produce some increase in reports of High Heart Rate. However, the magnitude of the increase was small and there was no moderation by cigarettes (see Figure 24).

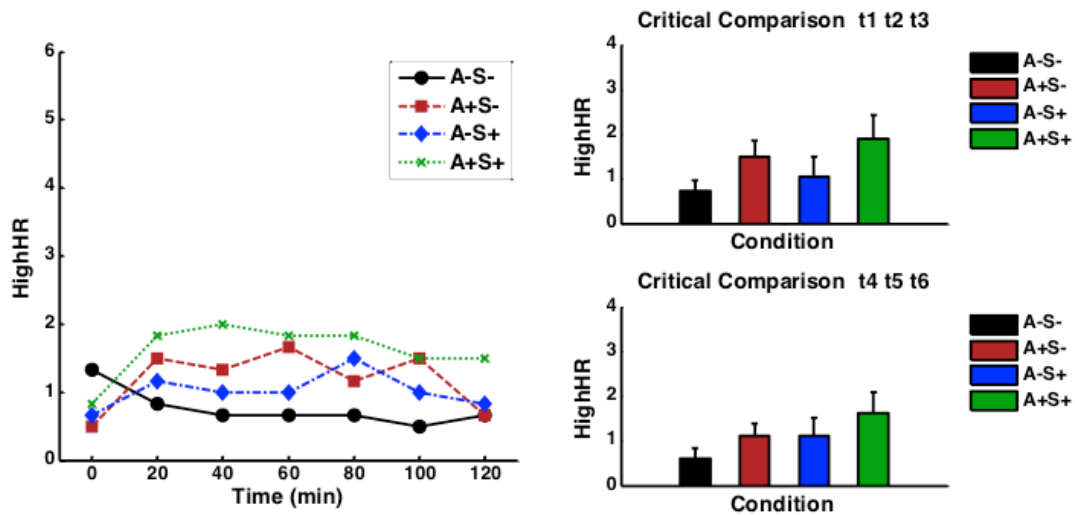


Figure 24. NES High Heart Rate score with comparison at t1+t2+t3 and t4+t5+t6.

Summary of Results

The measures that were used in the present study were chosen based on their sensitivity to alcohol and the subsequent opportunity to assess the effect of smoking cigarettes. Table 14 provides a summary of the measures that reliably produced alcohol effects along with the corresponding smoking moderation. Although not exhaustive, this illustrates the overall sensitivity of the measures to alcohol and the ability of posturography measures specifically to detect the moderating effects of smoking. Note that in the interests of simplifying this table, only the SOT4 posturography condition is presented (eyes open with sway referenced support), even though the general pattern shown there extended to multiple SOT conditions.

Table 14. Summary of measures with alcohol effects and smoking moderation.

		Participants with Alcohol Effect	Participants with Smoking Moderation
Composite SOT	Equilibrium score	6	6*
	Sway area	5	5*
	Low AP power	6	5*
	Low shear power	6	6*
SOT 4	Equilibrium score	6	4*
	Sway area	6	5*
	Low AP power	6	5*
	Low shear power	6	5*
Toes-up MC	Tibialis amplitude	6	4
	Quadricep amplitude	6	4*
Toes-down MC	Gastrocnemius latency	6	3
	Early quad amplitude	4	4
	Mid quad amplitude	5	4
Horizontal smooth pursuit at .2Hz	Signal to noise	5	3
	Intrusion ratio	5	4
	Composite	5	3
Horizontal smooth pursuit at .4HZ	Coherence	5	4
	Intrusion ratio	5	3
	Composite	6	3
Optokinetic nystagmus at 20 deg/sec	Number of beats	6	6*
BAES	Stimulation	4	4
	Sedation	5	5

* Smoking moderation $p < .05$

DISCUSSION

Several convergent lines of evidence in prior research motivated the current study. Extensive evidence suggests that diminished sensitivity to the acute intoxicating effects of alcohol can lead to increased consumption and liability for abuse. It also has been established that there is a strong association between the use of alcohol and cigarettes, to the point where consumption of one can be used to predict the level of consumption of the other. The present research represents a systematic laboratory

investigation of a possible mechanism underlying this association, namely whether changes in alcohol sensitivity are caused by the concurrent consumption of cigarettes, in a manner suggestive of an interpretation in terms of cross-tolerance.

Consistent with this general hypothesis, the study produced evidence that the intoxicating effects of a moderate dose of alcohol were partially reduced by smoking, on several measures that were selected on the basis of their known effectiveness as markers of individual differences in alcohol sensitivity. Evidence of moderation was detected for several key variables, including postural stability, eye movements, and, to a lesser extent, motor control of posture and subjective ratings of intoxication. The nature of the moderation was consistent with a model of cross-tolerance whereby cigarette smoking diminished the intoxicating effects of alcohol. The findings suggest that the effects of smoking mirror in some respects the effects of a genetic risk for alcoholism (i.e., a reduction in sensitivity), and that smoking could thus present a kindred risk for the development of alcoholism.

Sensitivity of Posture and Oculomotor Measures to Alcohol

The dependent measures in this study were selected because of their sensitivity to the acute effects of alcohol in earlier studies (Schuckit, 1985) and their resistance to expectancy or order effects. It was demonstrated that these tests were effective in isolating the effect of alcohol and providing reliable baseline measures against which to assess the effects of concurrent smoking. Measures were retained for further analysis only after a reliable alcohol effect was detected.

Postural Control

The experimental measures chosen for this research were selected based on their known sensitivity to the acute effects of alcohol. The primary measures were postural control tests adopted in prior research to evaluate the relationship between family history of alcoholism and sensitivity to alcohol. The extensive literature describing the sensitivity of postural control measures, extended here to include advanced CDP measures, was a key element in the design of the research test battery. It was anticipated that CDP measures, and associated custom data-analysis procedures developed for this project, would increase measurement sensitivity and would also support inferences regarding the specific mechanisms affected. It was hypothesized that the effects of smoking itself (i.e., A-S+ in comparison to A-S- conditions, as well as A+S+ in comparison to A+S-) would produce minimal if any effects on these cardinal posturography measures, whereas effects associated with alcohol (A+S- in comparison to A-S+) and possible moderation of alcohol effects by smoking (A+S- in comparison to A+S+) would be more appreciable. These expectations were generally borne out, as discussed below.

The SO tests included as part of the CDP assessment of postural control were indeed extremely effective at detecting alcohol effects. The decline in postural stability was similar to the pattern identified previously (Kubo et al., 1989), including studies that have used CDP testing procedures (Ledin & Odkvist, 1991; Goebel et al., 1995). All six tests isolated the effect of alcohol in at least one of the measures (EQ score, sway area, AP power, shear power). The sway referenced support surface was especially effective

in eliciting an alcohol effect, which further reinforced the use of CDP as a tool for assessing alcohol sensitivity.

The spectral analysis of the sway data was particularly effective at detecting small changes in postural stability. There was some evidence that the spectral analysis was superior to the traditional peak-to-peak measurement techniques. The low frequency shear signal provided robust evidence for alcohol effects in all conditions except SOT2, and low frequency sway in the AP direction was sensitive to alcohol in all conditions except SOT1, which is consistent with the findings of Diener et al. (1983) and Mangold, Laubli, and Krueger (1996). Along with increased sensitivity to small postural adjustments, the spectral values provided a method for isolating the nature of the changes associated with alcohol consumption.

The inclusion of motor control tests as a secondary measure during the posture assessment was effective in further isolating the nature of the alcohol inducement impairment. Results generally were consistent to the findings of Diener et al. (1983) and Woollacott (1983) who found that the amplitude decreased and long latency responses were prolonged following alcohol consumption. Overall, there was some suggestion, albeit equivocal, that alcohol produced a direct effect on the peripheral motor system, as observed in the amplitudes and latencies of the early and mid-latency spinal EMG reflexes. In the toes down rotation condition, the amplitude of the early quadriceps reflex was reduced, although this was paradoxically accompanied by an increase in amplitude for the immediately following mid-latency reflex. In the case of the toes-up rotation, there was a statistically borderline indication of a decrease in the amplitude of the early gastrocnemius reflex.

More substantial evidence was found for alcohol effects on the long latency corrective reflexes (involving supraspinal loops through the cerebellum). In the case of the toes down rotations, the latency of the corrective gastrocnemius reflex was increased, and in the case of the toes up rotations the amplitudes of the anterior compartment tibialis and quadriceps reflexes were decreased by alcohol. These results suggest that the effects of alcohol are manifested strongly at the central level.

Oculomotor Control

Previous research suggests that pursuit eye movements are the most sensitive to alcohol, with impairments being manifested in the form of frequent catch-up saccades following fixation pauses (Barnes, 1984; Barnes, Crombie, Edge, 1985; Lehtinen et al., 1982). In the present research the consumption of alcohol increased the incidence of fixations and catch-up saccades. The greatest effect was observed at t2, which corresponds to the early stages of the descending limb of the BAC. This impairment was expressed by a delayed phase of the eye movement relative to the position of the target, in which case the direction of gaze lags the position of the target thus requiring corrective eye movements (Levy, Lipton, & Holzman, 1981). The results of this research are thus consistent with prior findings, and are consistent with the suggestion that alcohol increases the central processing time necessary to generate pursuit eye movements (Flom et al., 1976).

Alcohol had a similar effect on performance during the optokinetic testing where higher stimulation frequencies (.2 Hz and .4 Hz) were the most sensitive to the effects of alcohol. This is consistent with the findings of Baloh et al. (1979) where the velocity of the slow component of the nystagmus during optokinetic stimulation was reduced by

alcohol. As described earlier, the optokinetic test was especially sensitive to the effects of alcohol partially due to the passive and largely reflexive nature of the task.

Nystagmus also was reliably generated during the positional tests, consistent with expectations and pointed to the involvement of peripheral as well as central mechanisms.

There was no indication that alcohol had an effect on any of the saccade tasks. This is inconsistent with previous research such as Levett and Hoefft (1977), but agrees with the findings of Fransson et al. (2010) who found that smooth pursuit measures were more sensitive to alcohol effects than saccade-based tasks. This discrepancy in findings could be a result of differences in BAC levels. It is also possible that the lack of an alcohol effect in the current study is attributable to the simplicity of the experimental task. Katoh (1988) suggested that there was a relationship between the complexity of the task and the magnitude of the latency increase. This task was also susceptible to fatigue, which could create performance deterioration in all conditions. In general it appears that when participants concentrated on the saccade task they were able to overcome the effects of alcohol and when they lost concentration they disengaged from the task to the point where the tracking signal was so inconsistent with the stimulus signal that it was automatically discarded during the analysis as noise.

Subjective Measures

The subjective instruments (BAES and NES) were included as secondary measures to assess the psychological impact of the drug treatments and to a lesser extent to help the participants remain engaged and alert. As expected, the BAES instrument was effective in identifying both the stimulation associated with the

ascending portion of the BAC and the sedation of the descending limb of the BAC. Conversely, the NES instrument only showed limited sensitivity to the experimental treatment, specifically during the ascending portion of the BAC for two attributes (Lightheaded and High). There was also some indication of mean increase in reported nausea following the enforced laboratory smoking, although this effect did not approach statistical significance. The limited results from the NES perhaps can be attributed to the timing and frequency of the test administration since it was repeated every 20 minutes after dosing, whereas peak nicotine levels are typically within 12 to 14 minutes while smoking a cigarette (Mello, Peltier, & Duncanson, 2013).

Patterns of Smoking Moderation

This experiment was motivated by the growing body of literature that supports the notion that cigarettes partially offset the performance deficits caused by alcohol consumption (Istvan & Matarazzo, 1984). Collins et al. (1996, 1990, 1988) linked exposure to nicotine with decreased sensitivity to alcohol in mice. The current research provides evidence to support this link in humans.

It is recognized that these results do not provide a definitive basis for operationalizing a model of cross-tolerance. However, the nature of the observed interaction is not consistent with other possible forms of interaction including potentiation (i.e., additive effects) or synergism (i.e., multiplicative effects – with the possible exception of self reports of stimulation). Cross-tolerance is inferred because the effects of smoking (nicotine) by itself, or nicotine deprivation, had little if any impact

on the cardinal posturographic and oculomotor measures. Rather, its principal or sole effect for these measures was on the sensitivity to alcohol.

As discussed above, the combination of alcohol placebo conditions (A-S- and A-S+) were critical to differentiate the alcohol effects from the smoking effects and to isolate the components of moderation. Smoking moderation was subsequently identified through A+S- and A+S+ comparisons, expressed in terms of the percent of change along with the number of participants who exhibited the change.

The CDP SO tests were robustly affected by alcohol and thus provided a particularly strong opportunity for assessing any moderating effect of cigarette smoking. The effects of smoking moderation were observed in most SOT conditions, with the notable exceptions of the eyes-closed conditions in which they were absent (SOT2) or diminished (SOT5). The SOT4 condition (eyes-open, sway-referenced support) was especially sensitive to the effect of smoking, with moderation percent estimates ranging from 75% to 88% across all measures. These results support the hypothesis that smoking does diminish the effects of alcohol and could thereby increase the risk for increased alcohol consumption.

By combining individual conditions in composite measures it was determined that the effects of cigarettes were less prevalent in the eyes-closed conditions, suggesting that the moderation arose primarily from drug-related effects on vision (and perhaps vestibular sensation), rather than on somatosensation (i.e., moderation occurs under conditions in which vision plays a key role in maintaining stability). This is consistent with the scores seen in the Visual ratio calculation (see Figure 9) and the Visual Preference ratio (see Figure 11). From a broader perspective, it can be suggested that

the presence of visual cues may contribute to the combined effects of alcohol and smoking on cognitive processes—particularly those that rely heavily on visual processes (Pomerleau, 1995).

In the tests of MC it was anticipated that the alcohol effects would be especially prominent for the long latency EMG responses (i.e., those involving long loop pathways through the cerebellum and cortices), and that these effects would be partially offset by smoking. Although there were suggestions overall for amplitude and latency effects in the long latency corrective responses involving supra-spinal reflex mechanisms (where they were most expected), the only consistent moderating effect of smoking to emerge was in the toes-up rotation condition in which alcohol led to a substantial and highly consistent decrease in quadriceps EMG amplitude, which was restored 35% by cigarette smoking.

The sensitivity of oculomotor tasks to alcohol identified in the existing literature was the primary reason for including these tests. Although there were robust alcohol effects for most of the pursuit tasks, the optokinetic stimulation test was the only instance where smoking moderation was identified. As suggested earlier, this was expected because of the passive nature of the optokinetic task. In general, it is likely that higher doses of alcohol would be required to fully explicate the effects of smoking cigarettes when using an oculomotor task as the primary measure.

The ratings of subjective effects did not identify robust moderation following cigarette smoking. There was a suggestion that the Sedation scores for A+S+ at t4, t5, and t6 were lower than A+S- (consistent with the hypothesis), but this effect was not robustly evident in all participants (5 out of 6 subjects). It also can be noted that the

A+S+ condition appeared to prolong higher Stimulant scores for t2 and t3 over what was observed in A+S-. Although not clearly present for all study participants (4 out of 6 subjects), this pattern of directional changes is consistent with the proposal of Newlin and Thomson (1990; 2010) that the diminished sensitivity in the offspring of alcoholics is manifested by enhanced stimulation during the ascending limb of the BAC and reduced depressant effects during the descending limb.

Implications for Understanding Mutual Consumption Patterns

The high rate of mutual consumption of alcohol and cigarettes is most likely the result of many behavioral and pharmacological variables (Istvan & Matarazzo, 1984). It cannot be determined if either of these drugs act as a cue to initiate the use of the other in the current paradigm. The addition of a questionnaire to evaluate the level of craving may have helped identify a pattern during testing, but the response patterns for the subjective questionnaire suggests that cigarettes had minimal subjective effects on the stimulating or sedative function of alcohol. The most robust effects for moderating effects of cigarettes occurred in this study at a physiological level.

One possible explanation for the variance in smoking moderation effects across the measures is the contrasting nature of the BAC on each limb. This is most easily detected in subjective measures of mood where alcohol creates a feeling of stimulation on the ascending portion and sedation of the descending portion (Perkins, 1997). If a mechanism of cross-tolerance is primarily contributing to the moderation, then cigarettes would diminish the alcohol effects on the ascending limb (stimulation) and on the descending limb (depression). Although there are exceptions, in the present study the effect of smoking moderation was most readily detected at t2, which corresponded

to the peak or early portion of the descending BAC phase. This increased magnitude of the moderation at the initiation of the descending BAC suggests that the mechanism of cross-tolerance was generally greatest when BAC was highest. However, cigarettes by themselves (or deprivation by itself) had minimal if any effect (restricted largely to high frequency sway power, some oculomotor measures including vertical pursuit, and some EMG data), which further supports the contention that cross-tolerance is the primary mechanism of moderation.

Following the logic developed in the Introduction, a pharmacological mechanism of cross-tolerance provides a tentative explanation for the high rates of smoking among alcoholics. The specific hypothesis tested here is that cigarette smoking diminishes an individuals' sensitivity to alcohol. There are a variety of explanations for the physiological and behavioral interactions of alcohol and nicotine that extend beyond a mechanism of cross-tolerance. Pomerleau (1985) suggested that smoking dampens the level of intoxication through the stimulation of central peptides such as arginine vasopressin. The complexity of these interactions is further underscored by findings that the mesolimbic dopamine pathway moderates the interaction of alcohol and nicotine (Funk, Marinelli, & Le, 2006) and that both substances can moderate the release of dopamine caused by the other (Doyon et al., 2013). The precise nature of the interactions appears moreover to include multiple components that affect the rewarding nature of each drug and the effects on cognitive functioning. The evidence reported here that cigarette smoking can moderate the intoxicating effect of alcohol on some behavioral and physiological measures thus contributes to our understanding of these substances, but in no way exhausts the relevant issues.

Methodological Considerations

It is important to review several methodological considerations while considering the key findings of this experiment. The small sample size and attendant restriction of statistical power must be acknowledged as a limitation of this study. The sample size was regulated by several factors, including available funding and the relatively time-consuming and labor-intensive nature of a multiple dose study of this kind.

A contributing factor was the loss of data from two female participants, who were tested through the entire experimental sequence but subsequently excluded on the basis of data quality issues. As noted above, data from one of these participants (particularly the postural data) were extremely erratic in one of the test sessions, and showed substantial performance abnormalities (including falls) even during the baseline testing. The underlying cause was not determined.

Data from a second female participant were excluded on the basis of self-reports of extreme nausea and discomfort (in addition to a determination that she was unsuited for postural testing on the basis of body mass and associated kinematic factors—a limitation that is not cited in the CDP testing instructions or associated literature). It is noteworthy that two other females were substantially affected by nausea under the combined alcohol and cigarette dosing regimen used here—one of whom vomited during testing and chose to discontinue participation, and a second for whom the relevant session was replaced. Some or all of the data from three of the five females who entered the experiment thus had to be excluded on the basis of nausea-related issues. It is possible that the higher incidence of nausea in the three affected female

participants may point to an unsuccessful attempt to adjust the dosing levels by gender-related factors (although target BAC levels were achieved).

It also may be part of a larger overall pattern, whereby an increase in nausea (albeit quite modest overall) was reported following the combination of alcohol and cigarettes (see Figure 22). The high incidence of nausea in laboratory experiments involving the administration of nicotine, with or without the co-administration of alcohol, has been noted elsewhere (Acheson et al., 2006). It is possible that the vestibular challenges inherent in CDP and oculomotor testing are an exacerbating factor in the present experiment, although that would not account in any obvious way for the higher incidence of nausea in the female participants. The present experiment did not have sufficient power to assess whether the greater prominence of nausea in females reflected a genuine gender-related effect. It should be noted that there are several lines of evidence from other studies demonstrating gender-specific effects, not only on the responses to nicotine and alcohol individually, but on their interactions—including consumption patterns, relative influence of pharmacological and exteroceptive factors, and manifestations in specific physiological and subjective responses (Acheson et al., 2006; Kahler et al., 2012; King, Epstein, Conrad, McNamara, & Cao, 2008; King, McNamara, & Conrad, 2009; Perkins, Fonte, & Grobe, 2000).

The magnitude of the session order effects on the SYNWORK measures of cognitive functions was unanticipated, and served to make the data largely unusable for assessment of alcohol and cigarette effects. Training was given to participants in advance of the first test session with a goal of stabilizing performance, but it was evident that improvement had still not approached asymptote even after completion of

the fourth testing session. Mills and Bisgrove (1983) suggested that measures of cognitive impairment were more sensitive and less variable than sway measures and it was unfortunate that the task chosen to assess cognitive impairments suffered from this weakness.

Some baseline score variability was observed among sessions. The variability can most likely be attributed principally to general day-to-day changes in participant mood, stress, motivation, fatigue, and concentration, as well to differences in variability in drug metabolism and other physiological processes. Participants were instructed to arrive at the lab with a full night of sleep and after having consumed a low-fat lunch, and to have abstained from alcohol or other substances. However, it was not possible to insure compliance. The observed instability is consistent with the findings of Nagoshi and Wilson (1987) that apparently unavoidable day-to-day variability in participant responses poses difficulties for precisely measuring alcohol challenge effects.

Prior to beginning the present study, extensive pilot testing was conducted and special consideration was given to the procedures for administration of both ethanol and nicotine. Due to the physical nature of the tasks performed by the participants it would have been impossible to safely administer the ethanol intravenously, and the emphasis for this early study was in any case on naturalistic consumption patterns. However, the decision to use oral administration made it difficult to control the BAC levels with precision. There also are, as are common, issues regarding the appropriate placebo conditions and the effectiveness of those chosen. It was unlikely that the dosing mixture completely masked the alcohol sessions so the benefits of using a single-blind design to control expectancy effects cannot be confirmed.

Related to this issue is the selection of the relevant control condition for the experimental comparisons. The strength in the design of this study was the ability to compare the results of A-S- and A-S+ so that any nicotine deprivation effects could be isolated. Since the objective of this research was to understand the moderating impact of cigarette smoking on alcohol intoxication it was crucial to insure that baseline conditions were available in which nicotine deprivation was not the major factor. By leveraging both baseline conditions, it was possible to first isolate any effects that could be directly attributed to cigarette smoking and then remove those from the subsequent analysis. The remainder of the statistical analysis was focused primarily on the comparison of A-S+ baseline and the A+S- and A+S+ conditions to identify alcohol effects and any subsequent moderation.

The alcohol dosing was effective in producing BAC levels that were sufficient to yield evidence of intoxication, and to detect the moderating effect of cigarette smoking, without creating intoxication levels that were excessive or dissimilar to what a social drinker might regularly experience. The maintenance dose extended and stabilized the BAC, thus providing an opportunity for additional testing during the intoxicated state and postponed the BAC descending limb. An extremely important observation in this context is that there was no evidence that cigarette smoking had any effect on the BAC levels, and therefore performance changes between two alcohol sessions (A+S-, A+S+) cannot be attributed to variation in the BAC between sessions. This is consistent with the pharmacological explanations of nicotine moderation described above (Davis & deFiebre, 2006; Doyon et al., 2013; Tizabi et al., 2007) and makes a metabolic explanation for the observed moderation less plausible (Parnell, West, & Chen, 2006).

The benefit of using cigarettes for nicotine delivery was that it allowed each participant to raise blood nicotine levels using a typical and accustomed method. A nicotine nasal spray was tested as an alternative delivery modality, but it was determined that the administration produced substantial discomfort, and that this aversiveness would likely create a significant confound. The use of de-nicotinized cigarettes was considered for the placebo conditions as a tool for creating sensory cues of smoking and alleviating elements of nicotine deprivation (Butschky, Bailey, Henningfield, & Pickworth, 1994). However, at the time of this study there was no ready source of de-nicotinized cigarettes, and it was deemed in any case that the relevant comparison at this early stage of investigation was between the act of cigarette smoking versus non-smoking. The role of nicotine *per se* in the findings is an important issue that is reserved for future research.

The alcohol and nicotine delivery mechanisms leave open the respective time courses of their pharmacodynamic effects. Since peak nicotine levels occur within 12 to 14 minutes while smoking a cigarette (Mello, Peltier, & Duncanson, 2013) it is likely that its effects preceded those of alcohol, and it is therefore also possible that some of the moderating effects of the cigarette had dissipated as the nicotine levels decreased. This could be especially relevant for the oculomotor battery of tests, which was first given approximately 32 minutes after the eight-minute dosing period.

Considerations for Future Research

An attempt was made in this research to address some of the methodological limitations that were identified in prior efforts to understand the interaction of alcohol and cigarettes. These limitations included the use of insensitive equipment for measuring

the key posturographic variables, as well as the factors of time of day, participant gender, adequate baselines, inclusion of placebo conditions, and use of ecologically relevant doses. The effectiveness of CDP in assessing alcohol effects was clearly demonstrated, and future efforts would benefit from the use of those procedures. Having now identified the general progression of effects over the course of the BAC, future research also might benefit from a more strategic testing schedule, whereby the number of individual test applications is reduced but introduced at key times. This might reduce the likely routinization of responding to the subjective scales, and eliminate problems associated with prolonged electrode attachment.

The modest sample size of this study created natural challenges for developing inferential statistical models. The within-subjects design was effective in eliminating individual variations in responses to the alcohol and cigarette dosing, but due to the extensive time required in the lab for each condition it proved difficult to ascertain and recruit a group of participants. More participants should be used in future efforts and the A-S- could be eliminated from the counter-balancing to reduce participant fatigue. This would also serve to relieve the testing burden on participants, and ease some of the difficulties recruiting participants with sufficient time to dedicate to the multi-session protocol.

Contributing to the power issues was the loss of two female participants because of data quality issues, including the prominence of nausea that affected three of the five females who enrolled in the study. The possible underlying causes, and solutions, would benefit from an additional pilot study. The nausea seemed particularly to involve the combination of drinking and smoking. Possible solutions might include a less

regimented (or more extended) consumption period, use of other mixers for the alcohol beverage, use of smaller or less heavily nicotine cigarettes, and recruitment of individuals with a history of heavier smoking. It also is possible that alternative modes of nicotine delivery would eliminate nausea. Use of lower doses of alcohol might also be considered, although this would lead to a corresponding reduction in effect sizes and elimination of opportunity to observe interactions with smoking.

Much of the prior research in this area has used static measures of postural stability, measures which in this study were the least sensitive to the effects of smoking moderation in most cases (i.e., SOT1 and SOT2). Having demonstrated the robust sensitivity of the CDP procedures to the subtle effects of the alcohol and smoking, there are expansive opportunities to reassess the nuanced patterns of moderation. This includes further investigation by age, gender, and genetic risk for alcoholism. In addition, there is an opportunity to more extensively isolate the influence of dose for both alcohol and nicotine with a dose-ranging study. The strength of the findings in the present research supports the use of CDP in any assessment of alcohol, cigarettes (nicotine), or their mutual interactions in future research.

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APPENDIX A

Telephone Screener

ALCOHOL/TOBACCO TELEPHONE SCREENER

Name: _____

Date Screened: _____

Telephone #: _____

No Yes

1. How old are you? _____

Is the person younger than 21 or older than 30?

___ ___^{***}

2. Do you have any illness that could affect your memory
or the way you think?

___ ___^{***}

If yes describe: _____

3. Have you ever been tested for the HIV (AIDS) virus?

___ ___

A. When was the test performed? Month/Year ___/___

B. Was the test positive?

___ ___^{***}

4. Do you have any life threatening illness?

___ ___^{***}

If yes describe: _____

5. Did you ever have neurosurgery? _____ ^{***}

A. What was the surgery for? _____

B. How old were you? _____

6. Have you ever had a head injury with loss of consciousness? _____ ^{**}

A. How many times? _____

B. Type of injury Minutes Unconscious Age

7. Have you ever had fits or seizures? _____ ^{**}

A. What were they attributed to? _____

B. How often do these seizures occur? _____ times per _____

C. Are you taking any medication for these seizures? _____ ^{**}

List medications: _____

8. Have you ever had any other illnesses such as diabetes, asthma,
high blood pressure, arthritis, or liver disease? _____ ^{**}

List: _____ Age: _____ When? ____/____

List: _____ Age: _____ When? ____/____

9. Have you ever had any type of surgery? _____ *

List: _____ Age: _____ When? ____/____

List: _____ Age: _____ When? ____/____

List: _____ Age: _____ When? ____/____

10. Have you ever used IV drugs? _____ **

List: _____ Age: _____ When? ____/____

List: _____ Age: _____ When? ____/____

11. Do you have any eye problems not corrected by glasses or contact lenses? _____ *

A. Describe: _____

B. Is the problem in both eyes? _____

C. Do you wear glasses or contact lenses? _____

12. Do you have any problems with your hearing, despite a hearing aid? _____ *

A. Describe: _____

B. Do you wear a hearing aid? _____

C. Describe your hearing without a hearing aid (circle one):

Excellent Very good Good Fair Poor

13. Do you have trouble with dizziness, vertigo, or motion sickness? _____ **

A. Describe: _____

14. Do you have any physical handicaps or injuries that affect the way you walk or move your body? _____ **

A. Describe: _____

15. Are you currently taking prescription medication? _____ *

Tranquilizers (e.g., Valium, Xanax, Librium) _____

Antidepressants (e.g., Elavil, Wellbutrin, Prozac) _____

Neuroleptics (e.g., Compazine, Haldol, Lithium, Thorazine) _____

Methadone _____

Antabuse _____

Others _____

16. Are you a regular smoker? _____

Would it bother you to have to abstain from smoking during the experiment, which could last 3-5 hours? _____ **

Now I need to ask you a few questions about your alcohol use.

17. Do you drink alcoholic beverages? _____ **

About how many drinks do you have per week? _____

18. Do you have any concerns about your drinking habits? _____ **

19. After you started drinking regularly did you ever become tolerant to alcohol. That is you drank a great deal more in order to get an effect? ___ ___**

20. Have you ever felt guilty about your drinking? ___ ___**

21. Have you wanted to quit or cut down on drinking three or more times? ___ ___**

22. While drinking, has one or two drinks of alcohol ever caused you to:

A. Flush or blush - that is, your face and hands felt hot and your face turned red? ___ ___

B. Break out into hives? ___ ___

C. Feel very sleepy? ___ ___

D. Have nausea? ___ ___

E. Have headaches, or head pounding or throbbing ___ ___

F. Have heart palpitations, where your heart beat so hard you could feel it? ___ ___

23. Does anyone in your immediate family have a problem with alcohol (this would include you mother, father, sisters, and/or brothers)? ___ ___**

24. Would you object to completing a detailed psychiatric history? ___ ___***

Key: *** = Definite exclusions ** = Probable exclusion * = Possible exclusion

APPENDIX B

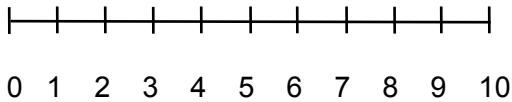
Revised Biphasic Alcohol Effects Scale (R-BAES)

Date: _____

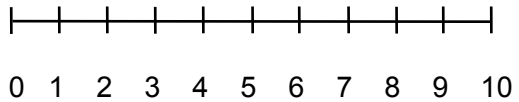
I.D. #: _____

The following adjectives describe feelings that some people have at various times. On a scale from 0 to 10, with 0 being “not at all” and 10 being “extremely,” please rate the extent to which each of these adjectives describes your feelings AT THE PRESENT TIME.

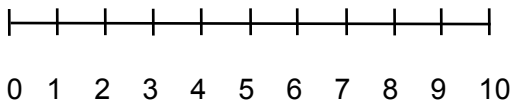
Difficulty Concentrating



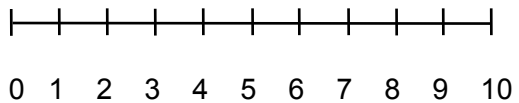
Energized



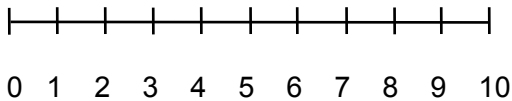
Down



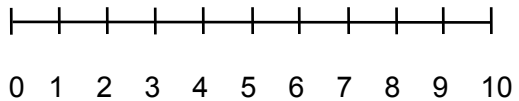
Excited



Elated



Heavy Head



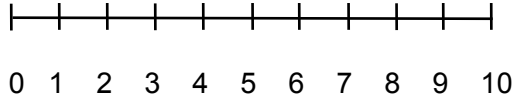
Inactive



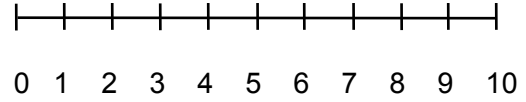
Stimulated



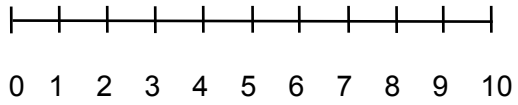
Sedated



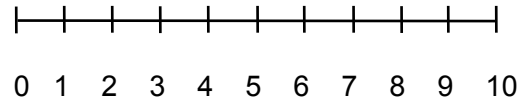
Talkative



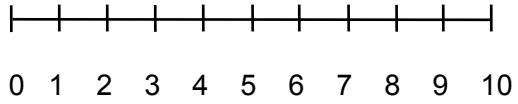
Slow Thoughts



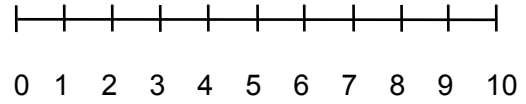
Up



Sluggish



Vigorous



APPENDIX C

Nicotine Effects Scale

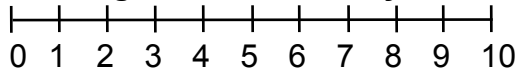
NES _____

Date: _____

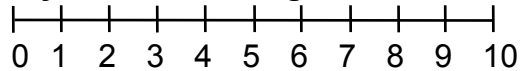
I.D. #: _____

The following adjectives describe feelings that some people have at various times. On a scale from 0 to 10, with 0 being "not at all" and 10 being "extremely," please rate the extent to which each of these adjectives describes your feelings AT THE PRESENT TIME.

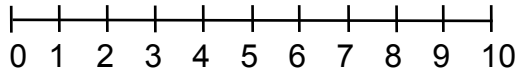
I feel lightheaded or dizzy



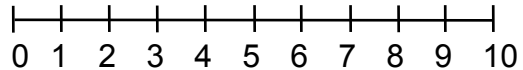
My heart is beating faster



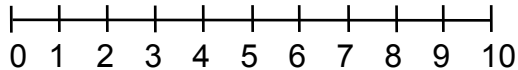
I feel high



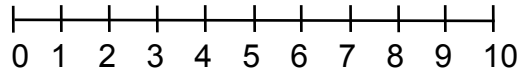
I feel satisfied



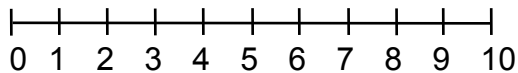
I feel nauseated



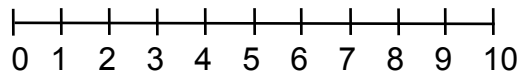
I feel alert and awake



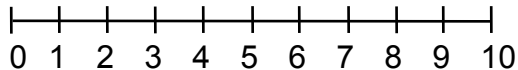
I feel anxious or tense



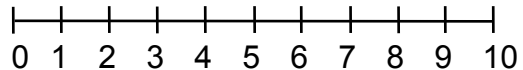
I feel calm and relaxed



I feel stimulated



I am able to concentrate



APPENDIX D

Timeline Follow Back Consumption Questionnaire

INSTRUCTIONS FOR COMPLETING THE TIMELINE DRINKING CALENDAR

Using the attached calendar, we would like you to reconstruct your drinking for the time period indicated on the calendar. This is not a difficult task, especially when you use the calendar for reference. We have found calendars useful in helping people recall their drinking. The following are instructions and tips for completing the calendar:

INSTRUCTIONS

1. It is important that for each day listed on the calendar, there is a number indicating the number of drinks you consumed. In reporting your total daily consumption, we would like you to report it in **STANDARD DRINKS**.
2. On the days you did not drink any alcoholic beverages mark those days with an "0".
3. On the days that you did consume a beverage containing alcohol, write in the total number of **Standard Drinks** that you drank on those days. This includes combined beverage use. For example, if you drank a glass of wine with dinner and a drink containing 1-1/2 oz. of hard liquor after dinner, you would count that as 2 standard drinks for that day. **The important thing is to make sure that something is filled in for each day.**

4. The purpose of the calendar is to get as accurate a picture of what your drinking has been like for the indicated time period, in terms of the number of drinking days and number of drinks per day, we would like you to be as accurate as possible. However, if you cannot recall exactly whether or not you consumed an alcoholic beverage on Monday or Thursday of a certain week, or whether it was the during the first, second or third week, **do give it your best effort.**

HELPFUL HINTS

- A. If you have an **appointment book** or a **daily diary** available, you can **use** it to help you recall your drinking.
- B. As you will notice **standard holidays days are marked on the calendar** to help your recall; you can also write in special holidays such as birthdays, vacations, celebrations.
- C. Some people have **regular drinking patterns** and this can help in filling out the calendar. For example, you may have a **weekend/weekday change** in your drinking or your drinking may be different depending on the season, or whether you are on vacation or a business trips.

APPENDIX E

Medical Screener

PHYSICAL EXAM

NAME: _____ I.D.#: _____

1. SPONTANEOUS NYSTAGMUS

A. In the light

- 1. _____ Absent
- 2. _____ Present-Right
- 3. _____ Present-Left

2. GAZE NYSTAGMUS

A. Right Gaze

B. Left Gaze

C. Vertical Gaze

1. _____ Absent

1. _____ Absent

1. _____ Absent

2. _____ Present

2. _____ Present

2. _____ Present

____ Right

____ Right

____ Right

____ Left

____ Left

____ Left

____ Upbeat

____ Upbeat

____ Upbeat

____ Downbeat

____ Downbeat

____ Downbeat

3. POSITIONAL NYSTAGMUS

A. Body Right

1. _____Absent

2. _____Present

____Right

____Left

____Upbeat

____Downbeat

B. Body Left

1. _____Absent

2. _____Present

____Right

____Left

____Upbeat

____Downbeat

4. HALLPIKE INDUCED NYSTAGMUS

1. _____Negative

2. _____Positive-Head Hang Left

3. _____Positive-Head Hang Right

4. _____Positive-Head Hang Center

Score Dominant Position for the following characteristics

1. Latency _____(0-20 seconds)

2. Fatigue _____(1-30 seconds)

3. Habituation _____(1st-5th trial)

5. FINGER-NOSE

1. _____Normal

2. _____Abnormal-Left Hand

3. _____Abnormal-Right Hand

7. RAM

6. HEEL-SHIN

1. _____Normal

2. _____Abnormal-Left Foot

3. _____Abnormal-Right Foot

8. ROMBERG

1. _____ Normal
2. _____ Abnormal-Left Hand
3. _____ Abnormal-Right Hand

1. _____ Negative
2. _____ Positive

9. TANDEM ROMBERG

1. _____ Negative
2. _____ Positive

10. GAIT

1. _____ Normal
2. _____ Abnormal (describe)

11. PURSUIT

1. _____ Normal
2. _____ Saccadic
3. _____ Absent

12. SACCADES

1. _____ Normal
2. _____ Dysmetric
3. _____ Slow
4. _____ Disconjugate

13. HEADSHAKE NYSTAGMUS

1. _____ Absent
2. _____ Present-Left Beat
3. _____ Present-Right Beat

14. HEADSHAKE VISUAL ACUITY

1. _____ Normal
2. _____ Abnormal

15. REFIXATION SACCADES

- 1. _____None
- 2. _____Head-Left
- 3. _____Head-Right
- 4. _____Bidirectional

16. OTOLOGIC (check all that apply)

- 1. _____Normal
- 2. _____TM Perforation
- 3. _____Otorrhea
- 4. _____TM Immobility
- 5. _____Other, specify:

Physicians Signature: _____ Date: _____

APPENDIX F

Pre-Test Screener

ALCOHOL PRE-TESTING SCREEN

Name: _____ Date: _____

- | | <u>No</u> | <u>Yes</u> |
|---------------------------------------|-----------|--------------------|
| 1. Is the breathalyzer test positive? | ___ | ___ ^{***} |

2. When did you last use:

	<u>Date</u>	<u>Amt.</u>	<u>Never</u>		
Alcohol	_/_/_	___	___	___	___
Marijuana	_/_/_	___	___	___	___
Hallucinogens	_/_/_	___	___	___	___
Methadone	_/_/_	___	___	___	___
Tranquilizers	_/_/_	___	___	___	___
Antidepressants	_/_/_	___	___	___	___
Neuroleptics	_/_/_	___	___	___	___

Other prescribed or over the counter medicines (e.g., aspirin, cough medicine, antihistamines)?

_____	_/_/_	___	___	___	___
_____	_/_/_	___	___	___	___

3. Do you smoke cigarettes? _____

About how many cigarettes have you had so far today? _____

When did you have your last cigarette? _____

4. Have you had any caffeine since lunch? _____

5. When did you finish your last meal?

Time: _____ Content: _____

Key: *** = Definite exclusions

** = Probable exclusion

* = Possible exclusion

APPENDIX G

Testing Timeline Worksheet

ID#: _____ AGE: _____ SEX: _____

HEIGHT: _____ WEIGHT: _____ TEST DATE: _____

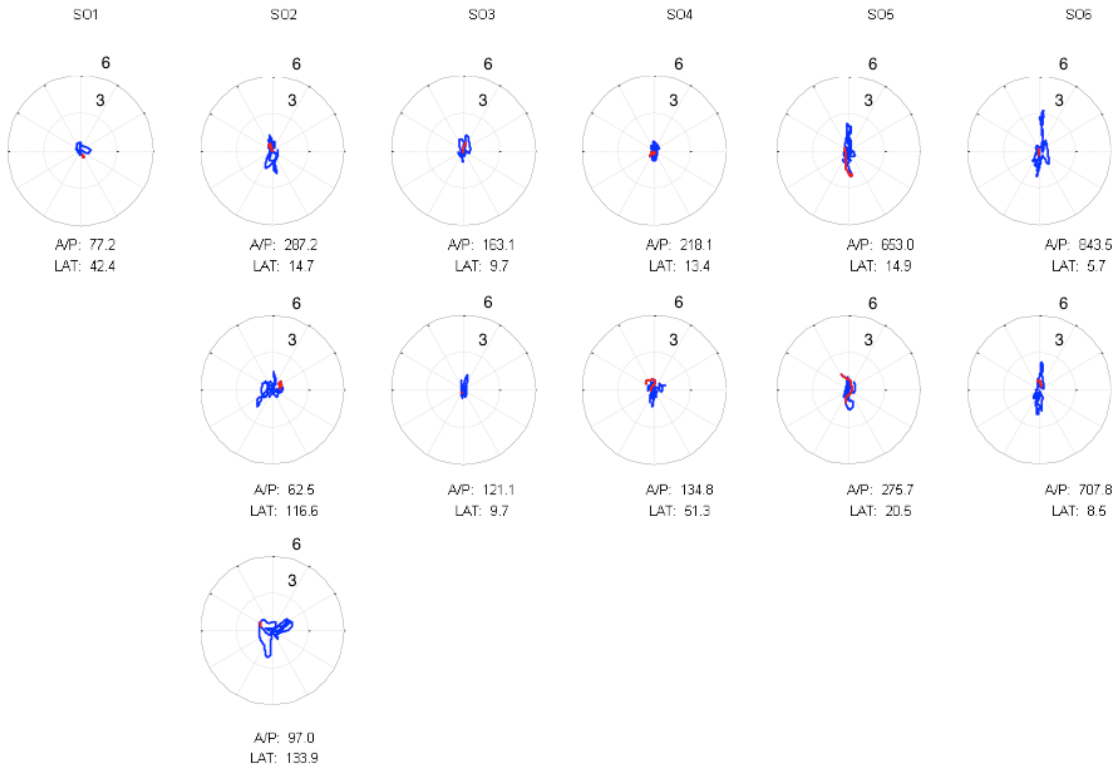
TIME OF DAY	TEST DURATION	TIME RE ACTUAL	TEST
_____		_____	Medical Examination
_____		_____	Eye Exam Left _____ Right _____
_____		_____	Consumption History
_____		_____	Equitest Prep
_____	0:00	-0:45 _____	BACb _____
_____	0:00	-0:45 _____	ENGb _____
_____	0:25	-0:20 _____	SOB
_____	0:32	-0:13 _____	MCb
_____	0:39	-0:06 _____	SHSb
_____	0:40	-0:05 _____	SYNWORK
_____	0:45	0:00 _____	CONSUME BEVERAGE/CIGARETTE (4 cups at 2 min intervals)
_____	0:53	0:08 _____	RINSE MOUTH WITH TAP WATER
_____	1:05	0:20 _____	BAC1 _____
_____	1:05	0:20 _____	SHS1 _____
_____	1:07	0:22 _____	SO1
_____	1:15	0:30 _____	BAC2 _____
_____	1:17	0:32 _____	MC1
_____	1:25	0:40 _____	BAC3 _____
_____	1:27	0:42 _____	ENG1 _____ BAC4 _____
_____	1:45	1:00 _____	BAC5 _____
_____	1:45	1:00 _____	SHS3
_____	1:45	1:00 _____	CONSUME BEVERAGE/CIGARETTE (4 cups at 2 min intervals)
_____	1:53	1:08 _____	RINSE MOUTH WITH TAP WATER
_____	1:59	1:14 _____	SYNWORK
_____	2:05	1:20 _____	BAC6 _____
_____	2:05	1:20 _____	SHS4 _____
_____	2:07	1:22 _____	SO2
_____	2:15	1:30 _____	BAC7 _____
_____	2:17	1:32 _____	MC2
_____	2:25	1:40 _____	BAC8 _____
_____	2:25	1:40 _____	SHS5
_____	2:27	1:42 _____	ENG2 _____ BAC9 _____
_____	2:45	2:00 _____	BAC10 _____
_____	2:45	2:00 _____	SHS6
_____	2:45	2:00 _____	CONSUME CIGARETTE
_____	2:59	2:14 _____	SYNWORK
_____	3:05	2:20 _____	BAC11 _____
_____	3:05	2:20 _____	SHS7
_____	3:07	2:22 _____	SO3
_____	3:15	2:30 _____	BAC12 _____
_____	3:17	2:32 _____	MC3
_____	3:25	2:40 _____	BAC13 _____
_____	3:25	2:40 _____	SHS8

_____	3:27	2:42 _____	ENG3	_____ BAC14 _____
_____	3:45	3:00 _____	BAC15 _____	
_____	3:45	3:00 _____	SHS9	
_____	3:59	3:14 _____	SYNWORK	
_____	4:15	3:30 _____	BAC16 _____	
_____	4:15	3:30 _____	SHS10	
_____	4:45	4:00 _____	BAC17 _____	
_____	4:45	4:00 _____	SHS11	
_____	4:59	4:14 _____	SYNWORK	
_____	5:15	4:30 _____	BAC18 _____	

_____		_____	BACe _____	

APPENDIX H

Sway Area Illustration



Examples of the sway paths and associated estimates of AP and lateral sway area for a single participant 80 min after the administration of alcohol.

APPENDIX I

SYNWORK

SYNWORK is a computer-based test of performance that presents four tasks concurrently. The screen is divided into four quadrants, which include a Sternberg memory task, an arithmetic task, a visual-monitoring task, and an auditory-monitoring task (Elsmore, 1992).

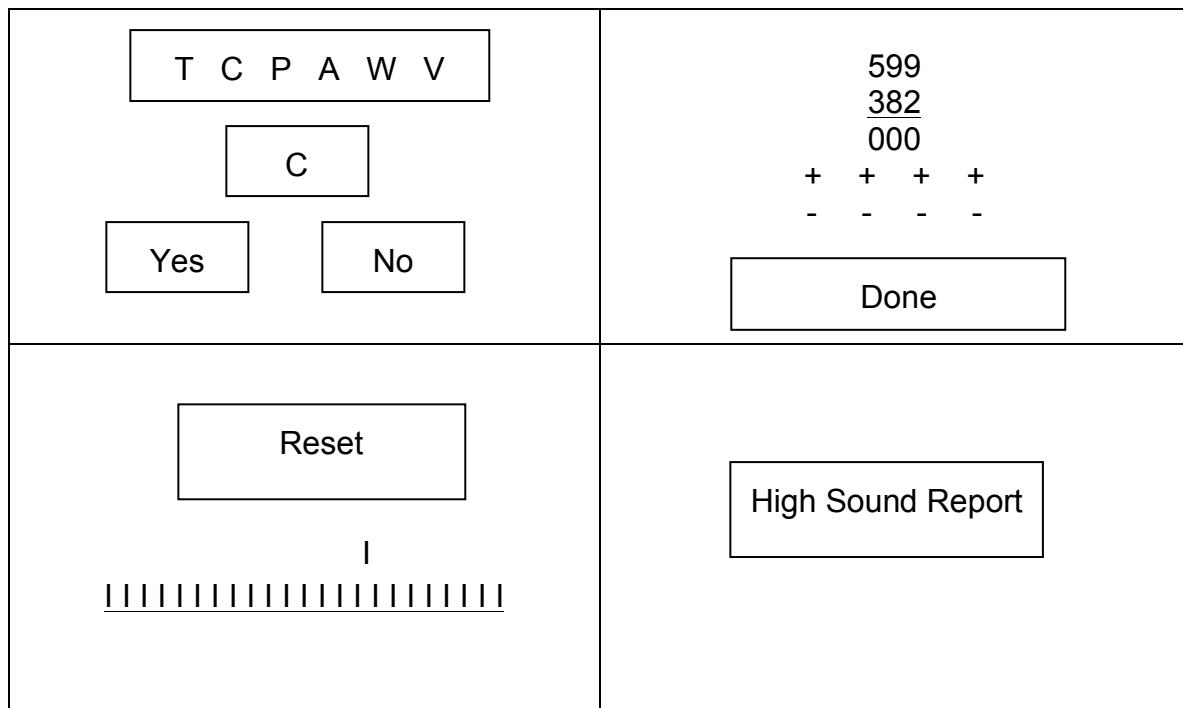


Figure A25. SYNWORK screen layout.

The Sternberg memory task presented a list of six letters at the beginning of the task that could be retrieved later with a penalty. Probe letters were then displayed every 20 seconds for 5 seconds. Participants responded by clicking on the “YES” or

“NO”. The probe letter was removed after 5 seconds or a response, whichever came first. The probability of the probe letter matching the stimulus set was .5.

The arithmetic task was displayed throughout the task. Three digit numbers were chosen randomly from 100 to 999. Participants then used "+" and "-" buttons to manipulate the digits below each column and clicked on “DONE” when finished. There were no time limits but incorrect answers resulted in a score deduction.

The visual monitoring task required participants to reset a pointer before it reached the end of a scale. The pointer moved from the center of the scale horizontally for 100 pixels in either direction (201 total pixels) and a rate of 200 msec per pixel. The pointer returned to the center when participants clicked on the reset button. The score was proportional to the distance of the pointer from the center with the maximum points being awarded in the final 10 percent of the scale. Points were deducted for each second the pointer was at the edge of the scale.

In the auditory monitoring task participants responded only to high pitch tones. Tones were presented at a 5 second interval. The low pitch tone was 1046 Hz and the high pitch tone was 1319 Hz. Following a high pitch tone, which was presented 20% of the time, participants clicked a button labeled "High Tone Report". Responses were accepted until the onset of the next tone but points were deducted for omissions.

SYNWORK provides a log file that details performance during each test, which in addition to other measures includes score and reaction time. A 45-minute training session preceded the first session so that participants were able to develop performance strategies, in an attempt at minimizing additional training effects over the course of the experiment.

Measures of cognitive activity, derived from the SYNWORK task, demonstrated very little sensitivity to alcohol and cigarettes, and the effects could not be distinguished from training effects that emerged after repeated exposure to the task, both within and across test sessions. Scores were generally lower in the alcohol conditions while cigarettes tended to decrease the latency of response and increase the percent correct. There was a considerable amount of variation between participants in overall performance. There was a time effect in the overall score ($F=6.32, p<.001$), which made any potential sensitivity measures unreliable for this analysis.

The peak of the BAC was accompanied by a sharp decrease in performance on the Sternberg task. Surprisingly, the lowest scores were often found in the placebo condition. In general, the scores in the cigarette conditions were higher than the alcohol-only condition.

There was consistent improvement in performance on the arithmetic and auditory monitoring portions of the task for all condition towards the end of each session. The gauge monitoring score was lowest for the alcohol/cigarette condition, but it could not be distinguished from the order effects.

APPENDIX J

Smoking Effects

As described in the Results section, the A-S+ session was chosen as the preferred baseline for use in assessing the magnitude of the effects of alcohol administration. However, in the presence of substantial influences of nicotine, such a strategy is clearly not appropriate. Alcohol and smoking interactions were not analyzed for moderation effects when primary smoking effects were identified in both A+S+ vs. A+S- and A-S+ vs. A-S- comparisons. Once a smoking effect was identified the measure was excluded from additional analysis for alcohol effects due to the challenges in isolating moderating effects of cigarettes in the A+S+ condition from the direct effect of the nicotine. The present study was focused on the moderating effects of cigarette smoking during acute alcohol intoxication, and the primary data analysis was isolated to the measures that were consistent with that objective. However, the emergence of smoking effects created some interesting patterns that by themselves could warrant additional investigation. As described below there are several instances where smoking had a primary effect and there are instances where alcohol appears to moderate the smoking effect.

In the CDP analysis the low frequency measures were effective at distinguishing alcohol effects and the corresponding moderation caused by cigarettes. However, it was determined that the high frequency measures were extremely sensitive to smoking. This was not surprising based on literature (reviewed in the Introduction) that identified tremor following cigarette smoking. It is likely in the current research that smoking induced a tremor that was high frequency in nature (Bhidayasiri & Tarsy, 2012) and the

alcohol actually reduced the high frequency movements. There is evidence that even modest doses of alcohol can reduce tremor by 30% (Landauer, 1981). The posturography analyses provide support for this finding.

Table A15 presents high frequency (2.0-5.0 Hz) sway in the lateral, AP, and shear dimensions for the different SOT conditions. In this Table, the effects of smoking with alcohol absent (A-S+ vs. A-S-) and present (A+S+ vs. A+S-) are displayed. Robust smoking effects (particularly in the lateral dimension) in the absence of alcohol are apparent for the majority of SOT conditions (with the exception of SOT6). Following alcohol consumption, some evidence for increased high frequency body sway associated with smoking also was obtained for SOT1 and the two eyes closed conditions (SOT2 and SOT5). Figures A26-A28 display the composite SOT scores for high frequency lateral, AP, and shear body sway. Inspection of these figures confirms substantial differences between the A-S+ and A-S- sessions. Clearly, smoking accentuates high frequency body sway and does not moderate the effect of alcohol in this case.

Table A15. Summary of smoking effects in high frequency spectral power for sensory organization test results at t2 + t3.

		Smoking Effect (A-S-/A-S+)			Alcohol Effect (A-S+/A+S+)		
		Effect Size	n-sub	p-value	Effect Size	n-sub	p-value
SOT1	Lateral	1.4275	6	0.00001	0.8234	5	0.01
	AP	0.9121	5	0.0265	1.0271	6	0.0063
	Shear	0.2332	3	0.2177	0.3209	5	0.0779
SOT2	Lateral	1.2011	5	0.0071	0.6779	4	0.0742
	AP	0.9959	4	0.0369	1.0683	6	0.024
	Shear	0.6862	5	0.0404	0.3299	4	0.2069
SOT3	Lateral	1.4222	6	0.0055	0.4538	5	0.0935
	AP	1.2273	6	0.0073	0.8804	5	0.0329
	Shear	0.5009	4	0.1206	0.1297	4	0.3298
SOT4	Lateral	1.3643	6	0.0072	0.4908	4	0.2161
	AP	1.4226	5	0.0116	0.056	3	0.4629
	Shear	0.9283	6	0.0188	0.0424	4	0.4671
SOT5	Lateral	1.1923	6	0.002	0.7544	5	0.0119
	AP	0.8191	5	0.0204	0.6957	4	0.0449
	Shear	0.689	4	0.0327	0.7284	4	0.0396
SOT6	Lateral	0.7882	5	0.0634	0.0409	3	0.4728
	AP	0.2861	4	0.1931	0.2314	3	0.3888
	Shear	0.3556	5	0.1118	0.2728	3	0.3539
Composite	Lateral	1.2326	6	0.0021	0.5266	5	0.0652
	AP	0.9439	6	0.0005	0.6411	4	0.0558
	Shear	0.5655	5	0.0188	0.304	3	0.1499
EyeOpen	Lateral	1.2505	6	0.0021	0.4318	5	0.1275
	AP	0.962	6	0.0001	0.5207	4	0.1114
	Shear	0.5045	6	0.023	0.1915	3	0.2629
EyeClosed	Lateral	1.1967	6	0.0035	0.7161	5	0.0229
	AP	0.9075	6	0.0168	0.882	5	0.0158
	Shear	0.6876	5	0.0191	0.5292	4	0.0918

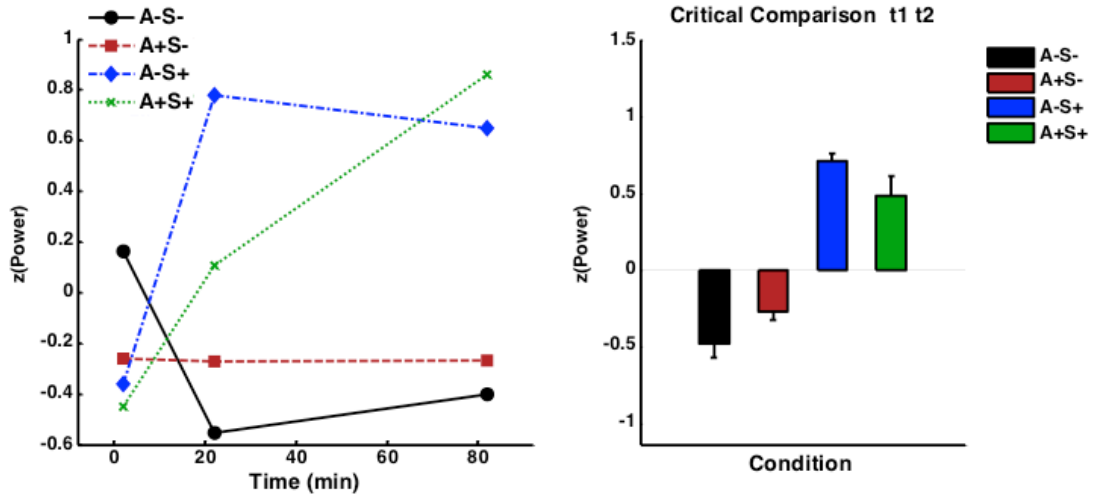


Figure A26. High frequency spectral power in lateral direction for SOT5 with comparison at t1 + t2 (smoking effect).

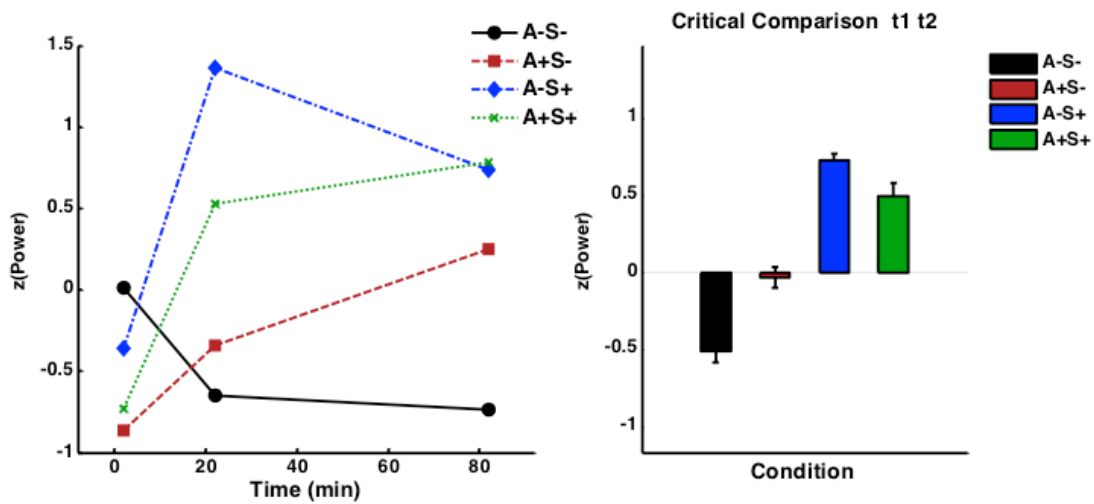


Figure A27. Composite high frequency spectral power in lateral direction with comparison at t1 + t2 (smoking effect).

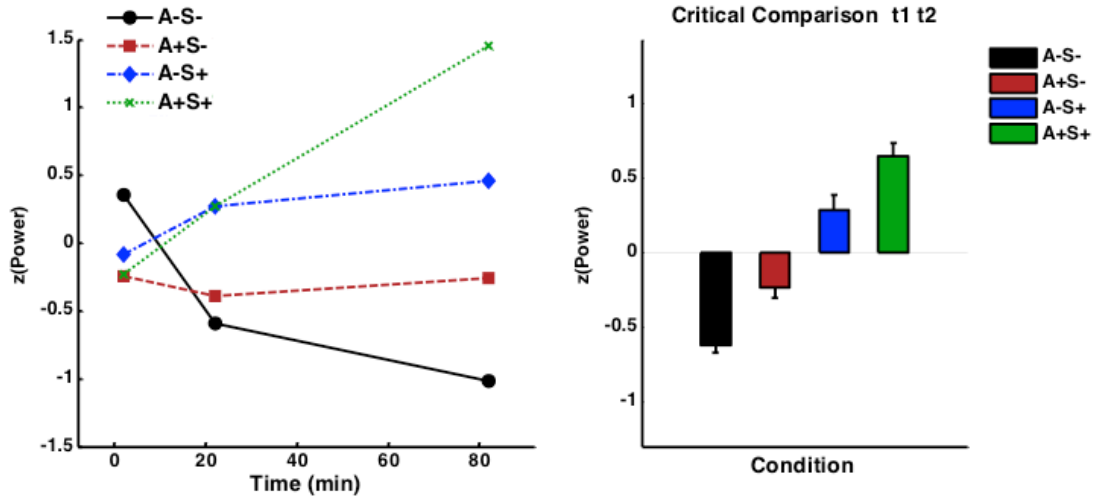


Figure A28. Composite high frequency spectral power in AP direction with comparison at t1 + t2 (smoking effect).

The MC tasks that included translation movements were generally most affected by cigarette smoking, which contributed to their exclusion from the primary analysis. Three EMG responses were evaluated. First, early tibialis responses were quantified by first identifying the maximum response in a window from 75-130 msec, and the onset latency was identified as the last zero-crossing preceding this maximum. The amplitude for the early tibialis response was then measured as the area in a 50 msec window commencing at the latency onset point. Second, the amplitude of the mid-latency tibialis response was measured as the area in a window from 200-300 msec, and the latency was estimated as the last zero-crossing preceding the maximum amplitude in this window. Finally, the amplitude of the quadriceps response was measured as the area in a window from 150-250 msec, and the latency was estimated as the last zero-crossing preceding the maximum amplitude in this window.

The forward and backward translation MC conditions (see Table A16 and A17, respectively) provide some evidence of main effects of smoking. In a few cases, cigarette consumption increased the latency and amplitude of specific EMG responses. This pattern of results was particularly evident for the quadricep response following a forward platform translation (see figure A29).

Table A16. Forward translation at t1 + t2.

		Smoking Effect (A-S-/A-S+)			Alcohol Effect (A-S+/A+S+)		
		Effect Size	n-sub	p-value	Effect Size	n-sub	p-value
Early Tibialis	Latency	0.6009	4	0.162	0.8178	5	0.0431
	Amplitude	1.1647	5	0.0361	0.7268	4	0.1183
Mid Tibialis	Amplitude	1.363	4	0.0503	0.5736	4	0.2526
Quad	Amplitude	1.9456	6	p=0.0005	1.1958	6	p=0.0146

Table A16. Backward Translation at t1+t2.

		Smoking Effect (A-S-/A-S+)			Alcohol Effect (A-S+/A+S+)		
		Effect Size	n-sub	p-value	Effect Size	n-sub	p-value
Early Gastroc	Amplitude	1.1067	5	0.0149	0.4303	4	0.281

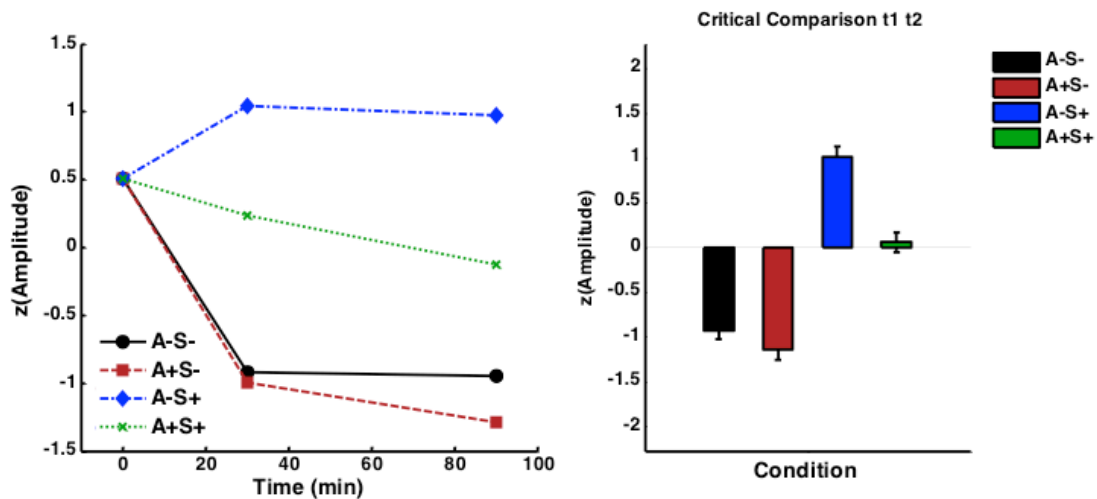


Figure A29. Forward translation quadricep amplitude with comparison at t1 + t2 (smoking effect).

At the current alcohol dose, the most reliable oculomotor measures were associated with the optokinetic stimulation condition, which is a passive task that is reflexive in nature. For the active tasks (i.e., smooth pursuit and saccades) the participants were required to focus their attention and actively engage. In many of the alcohol conditions, the participants seemed to lose attentional focus to the point where the data were not usable. Although less robust than the posturography and EMG effects, a tendency towards improved vertical smooth pursuit performance can be seen in the EOG data (see Table A18 and Figure A30). Smoking cigarettes appeared to improve focus and attention so that there was a clear benefit from nicotine.

Table A18. Vertical Smooth Pursuit at .4Hz at t1 + t2.

	Smoking Effect (A-S-/A-S+)			Alcohol Effect (A-S+/A+S+)		
	Effect Size	n-sub	p-value	Effect Size	n-sub	p-value
Coherence	0.2139	3	0.2754	0.8008	3	0.0618
RMS	0.3611	3	0.2438	0.3252	3	0.2734
SNR	0.5581	4	0.1091	0.3565	3	0.2167
Intrusion Ratio	0.8859	5	0.0355	0.5531	4	0.1865
Composite	0.6017	5	0.0811	0.4116	4	0.15

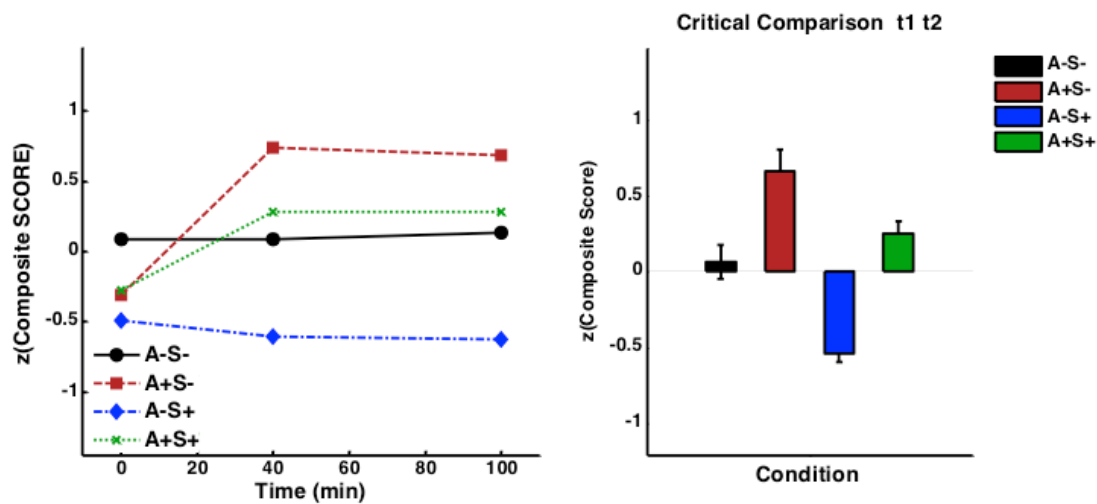


Figure A30. Vertical smooth pursuit composite with comparison at t1 + t2 (smoking effect).

It is important to note that the participants for this study were smokers and evidence of smoking effects in the absence of alcohol cannot be unambiguously interpreted. In this case the obtained effects may be due either to: 1) the direct effects of smoking; or 2) the reduction of withdrawal symptoms in smokers required to abstain from smoking during a test session lasting several hours. However, in either case, it is clearly inappropriate to estimate the magnitude of alcohol effects using the A-S+ session as a baseline. Furthermore, there is some evidence that cigarettes reduce the

magnitude of the alcohol effects in the EMG (see Figure A29) and EOG (see Figure A29) measures, but it is clear that cigarette smoking tends to *increase* high frequency body sway, whether or not alcohol has been consumed.