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# Examining the Vulnerability of Inhibitory Control to the Impairing Effects of Alcohol

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EXAMINING THE VULNERABILITY OF INHIBITORY CONTROL  
TO THE IMPAIRING EFFECTS OF ALCOHOL

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DISSERTATION

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A dissertation submitted in partial fulfillment of the  
requirements for the degree of Doctor of Philosophy in the  
College of Arts and Sciences  
At the University of Kentucky

By  
Melissa Angelina Miller

Lexington, Kentucky

Director: Dr. Mark Fillmore, Professor of Psychology

Lexington, Kentucky 2014

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## ABSTRACT OF DISSERTATION

### EXAMINING THE VULNERABILITY OF INHIBITORY CONTROL TO THE IMPAIRING EFFECTS OF ALCOHOL

There is growing evidence that acute changes in fundamental mechanisms of impulse control contribute to the transition from social drinking to abusive drinking. One component of impulsivity concerns the ability to inhibit maladaptive behaviors (i.e., inhibitory control). Inhibitory mechanisms are reliably shown to be sensitive to the impairing effects of alcohol, and studies have begun to show that this impairment fails to recover at the same speed as other aspects of behavior. However, the degree to which inhibitory control develops tolerance to alcohol has only been examined under limited conditions. This dissertation consists of three studies examining contexts in which tolerance has been observed for a host of prototypic behaviors, and will compare the degree to which it fails to develop for inhibitory control. Study 1 examined the rate of recovery for inhibitory control compared with other behaviors as blood alcohol concentrations (BACs) declined to zero following a dose of alcohol in 24 social drinkers. Results revealed prolonged alcohol impairment of inhibitory control along the BAC curve, even as BACs approached zero. By contrast, behaviors including reaction time and motor coordination began to show recovery markedly faster, as BACs were still significantly elevated. Study 2 examined the degree to which recent drinking patterns predict acute alcohol impairment from alcohol in a group of 52 drinkers. Recent, heavy consumption predicted less impairment of motor coordination, but bore no relationship to the magnitude of impairment of inhibitory control. Study 3 examined whether increasing the stimulus strength of environmental cues signaling the need to inhibit behavior could reduce alcohol impairment of inhibitory control in 56 participants. Results showed that increasing stimuli strength reduced alcohol impairment of behavioral activation, but actually increased inhibitory failures. Taken together, the findings contribute to the growing body of evidence suggesting that inhibitory control is especially vulnerable to the impairing effects of alcohol compared with other behaviors. Indeed, these studies systematically assessed the pharmacokinetic and environmental factors that contribute to tolerance, indicating that inhibition is disrupted in circumstances under which the response activation is unimpaired. The findings have important implications for understanding the behaviorally-disruptive effects of alcohol.

KEYWORDS: Alcohol, Inhibitory Control, Tolerance, BAC, Intoxication

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EXAMINING THE VULNERABILITY OF INHIBITORY CONTROL  
TO THE IMPAIRING EFFECTS OF ALCOHOL

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## Chapter 1

### INTRODUCTION

The prevalence of alcohol abuse in the United States has increased over the past decade despite considerable concern over its social costs. Alcohol use is particularly prevalent among young adults, with over half of men and women between 18 and 25 years of age reporting frequent consumption (Substance Abuse and Mental Health Services Administration, 2012). Moreover, the typical pattern of alcohol use reported by this demographic is often characterized by periods of heavy alcohol consumption referred to as “binges,” which result from consuming a quantity of alcohol to obtain a blood alcohol concentration (BAC) of 0.08% or higher during a single drinking occasion (NIAAA, 2004). While many young drinkers “age out” of binge drinking, for many, drinking in young adulthood will result in the escalation to heavier drinking and a lifelong problematic drinking and drinking-related problems (e.g., Babor et al., 1992; Zucker, 1987). Such chronic alcohol use and dependence present serious problems on both the societal and individual levels, including unemployment, loss of important personal relationships, and increased risk for accidents and the development of chronic illnesses (e.g., liver cirrhosis). Understanding why individuals persist in abusing alcohol in spite of serious negative costs has been a long-standing focus of substance-abuse researchers.

Impulsivity is one individual characteristic which has received a great deal of attention with regard to its relationship with risky, problematic behaviors, including alcohol abuse. Broadly defined, impulsivity refers to a pattern of under-controlled

behavior in which an individual acts without forethought or consideration of potential negative consequences. Highly impulsive individuals tend to drink more frequently and to engage in binge drinking compared with their less-impulsive peers (Gourdriaan et al., 2007; Marczinski et al., 2007). Notably, prospective studies have shown that impulsivity precedes the onset of drinking, suggesting that it plays a causal role in the development of alcohol abuse. Indeed, longitudinal studies have demonstrated a link between impulsivity, earlier age of onset of drinking, and the transition to alcohol dependence (August et al., 2006).

Although it is important to identify personality factors that are related to drug abuse, such as impulsivity, it is also necessary to understand behavioral mechanisms that underlie these traits. Traditionally, the term impulsivity has been commonly used to refer to a broad range of maladaptive traits, such as inability to wait, heightened sensitivity to reward and insensitivity to punishment, and difficulty withholding responses. More recently, impulsivity is understood as a multi-dimensional construct, consisting of several separate underlying processes (for a review, see de Wit 2008). A wealth of research has identified the ability to inhibit inappropriate actions or behaviors as a fundamental aspect of impulsivity that is particularly relevant to drug abuse. Inhibitory control refers to the ability to inhibit a response that has already been instigated, and this mechanism of behavior affords an individual control over where and when responses are expressed. Thus, the inhibition of behavioral responses is a necessary function for situations in which an individual needs to exert self-restraint and regulation over behavior. As such, deficits in inhibitory control have been implicated in disorders marked by poor self-control, such as antisocial personality, obsessive-compulsive, and attention

deficit/hyperactivity disorders (Barkley, 2006; Nigg 2006) as well as in a wide array of impulsive behaviors including heavy, binge drinking (e.g., Goudriaan et al., 2007; Marcuzinski et al., 2007).

### *Laboratory Models of Inhibitory Control*

Several laboratory tasks have been used to measure inhibitory mechanisms of behavioral control. Stop signal and go/no-go models assess control as the ability to quickly activate and inhibit prepotent (i.e., instigated) responses (Logan 1994; Miller et al. 1991). These tasks employ a reaction time scenario that measures the countervailing tendencies of behavioral activation and inhibition. Figure 1.1. presents a schematic of the cued go/no-go task trials. In this task, “go” and “no-go” targets are presented and participants are required to rapidly respond to go cues and to withhold a response to no-go cues. Prior to the presentation of the target, a cue is presented which will signal the probability of occurrence of the go or no-go targets. For instance, a vertically oriented rectangle signals an 80% likelihood that the subsequent target will be a “go” target (and thus a 20% chance that the target will be “no-go”).

The measure of interest in this task is the number of failures to inhibit a response to no-go targets that were preceded by a “go” cue (i.e., a cue that signaled an 80% likelihood that a “go” target would appear). In this case, the participant is prepared to respond, and must quickly inhibit the response. Activation is measured as the speed of responding to the go-signals and inhibition is assessed by the ability to suppress the response. As such, this model assesses inhibitory control within a context that promotes a strong tendency to respond to a stimulus (i.e., prepotency), thus increasing the difficulty of suppressing that response. Stop signal and go/no-go models of inhibitory control have

been well-validated by laboratory studies. Indeed, inhibitory mechanisms assessed by these models have been shown to be sensitive to inhibitory deficits characteristic of brain injury (Malloy et al. 1993), trait-based impulsivity (Logan et al. 1997), and self-control disorders, such as attention deficit-hyperactivity disorder (ADHD) (Tannok 1998).

#### *Acute Effects of Alcohol on Inhibitory Control and Associated Risks*

Model-based assessments of behavioral inhibition have been used to assess the acute effects of alcohol on inhibitory control (Fillmore 2003, 2007). Such studies have reliably shown that alcohol increases inhibitory failures in a dose-dependent manner (Marczinski & Fillmore, 2003; Fillmore & Weafer, 2004; Fillmore et al., 2005). For example, Marczinski and Fillmore (2003) used a go/no-go task to examine the impairing effect of alcohol on inhibitory control. Participants' inhibitory control was tested under three doses of alcohol: 0.0 g/kg (placebo), 0.45 g/kg, and 0.65 g/kg. The study showed that compared with placebo, the active doses of alcohol increased the likelihood that participants would fail to inhibit responses to no-go targets. Moreover, the findings indicated that the magnitude of impairment increased as a function of dose. That is, following 0.65 g/kg alcohol compared with 0.45 g/kg alcohol, it was increasingly difficult to inhibit or "stop" a prepotent response, as evidenced by more inhibitory failures. Such findings provide evidence that cognitive inhibitory mechanisms of behavioral control are sensitive to the impairing effects of alcohol that could underlie many adverse behavioral effects associated with acute alcohol consumption.

There is growing evidence that these acute changes in fundamental mechanisms of inhibitory control in response to alcohol contribute importantly to the transition from social drinking to abusive drinking (e.g., Fillmore, 2003; 2007; Lyvers, 2000). Inhibitory



mechanisms are required for terminating alcohol use during a drinking episode, and thus, impairment of inhibitory control once drinking has begun compromises the ability to discontinue subsequent drinking. As a result, many drinkers who report intentions to limit their alcohol use fail and instead engage in excessive binge drinking (Collins, 1993). Laboratory studies provide support for this hypothesis. For instance, Weafer and Fillmore (2008) showed that individual differences in the degree to which alcohol impaired inhibitory control predicted ad lib alcohol consumption. Specifically, in this study, individuals who display the greatest impairment of inhibitory control in response to alcohol also consume the most alcohol when given ad-lib access. This finding provides evidence for the association between alcohol-induced disinhibition and alcohol consumption while also highlighting the need to increase our understanding of how acute, alcohol-induced changes in behavioral control can contribute to problem drinking.

#### *Vulnerability of Inhibitory Control to the Impairing Effects of Alcohol*

The notion that inhibitory mechanisms of behavior are especially sensitive to the impairing effects of alcohol compared with other aspects of behavior has been the focus of several studies and help explain why some individuals are unable to stop once drinking has begun. Studies examining the acute effects of alcohol on inhibitory control have found that moderate doses of alcohol selectively impair the ability to inhibit behavior while leaving the ability to activate behavior (i.e., respond quickly) relatively unaffected (Marczinski & Fillmore, 2003; Fillmore & Weafer 2004). Indeed, laboratory studies have found that inhibitory control as measured by the stop signal and cued go/no-go tasks is impaired at moderate doses of alcohol (i.e., approximately 0.45 g/kg alcohol) that yield a blood alcohol concentration (BAC) of approximately 60 mg/100 ml (Marczinski et al.,

2005; de Wit et al., 2000). However, higher doses that yield BACs of approximately 80 mg/100ml are needed to produce impairment of behaviors such as reaction time and psychomotor performance (i.e., Fillmore, 2007; Holloway, 1995).

Studies examining the recovery of alcohol-induced impairment of behaviors also highlight the vulnerability of inhibitory control. The term tolerance refers to the observation that the intensity or magnitude of a response to a drug diminishes following repeated administrations of the drug (Kalant et al., 1971). This effect can also be observed following a single administration of a dose of alcohol. Tolerance can develop during the course of a single drinking episode, which is referred to as acute tolerance. Following alcohol administration, BAC rises rapidly and begins to gradually decline. The rising phase of the BAC curve is referred to as the ascending limb, and the declining phase of the BAC curve is referred to as the declining phase of intoxication. Acute tolerance can be observed by comparing performance during equal BACs on the ascending and descending limbs of intoxication (Kalant et al., 1971). This effect was first documented early last century by Mellanby (1919) who compared the intensity of alcohol impairment at a given BAC on the ascending and descending limbs of the blood alcohol curve. He observed that alcohol-induced ataxia in dogs was less intense at a given BAC during the descending versus the ascending limb of the curve.

Recent studies have shown acute tolerance to the impairing effects of alcohol for several behaviors such as motor coordination, reaction time, and subjective ratings of intoxication (Beirness & Vogel-Sprott, 1984; Schweizer et al., 2004; Fillmore et al., 2005; Fillmore & Vogel-Sprott, 1996; Marcziński & Fillmore, 2009; Schewiezer et al., 2004). In the past, acute tolerance has been considered as a general behavioral adaptation

to a given dose of alcohol and was thought to develop uniformly across behaviors. However, measures of inhibitory control show no acute tolerance to the disinhibiting effects of alcohol (Pihl et al., 2003; Fillmore et al., 2005; Ostling & Fillmore, 2010). For instance, one study examined acute tolerance to alcohol-induced impairment of inhibitory and activational mechanisms of behavioral control (Fillmore et al. 2005). In this study, participants performed two tests on the cued go/no-go task: once on the ascending limb and once on the descending limb of the BAC curve following 0.65 g/kg alcohol. Both tests were performed at comparable BACs. The study showed that alcohol impaired behavioral activation by slowing reaction time and impaired response inhibition by increasing failures to inhibit responses to no-go targets. The study found evidence for acute tolerance for behavioral activation. That is, reaction time performance on the descending limb of the BAC curve had returned to sober levels. However, there was no evidence of acute tolerance for the disinhibiting effects of alcohol. Inhibitory control remained equally impaired on the descending limb as the ascending limb of the BAC curve. These findings highlight another vulnerability of inhibitory control by showing that inhibitory mechanisms appear to be especially slow to recover from the impairing effects of alcohol compared with the impairing effects on the ability to activate behavior.

### *Proposed Studies*

Taken together, there is evidence to suggest that inhibitory mechanisms of behavioral control are especially sensitive to alcohol's impairing effects. However, this possibility has only been examined under limited conditions. This raises questions about additional contexts under which this vulnerability might be evident. The purpose of this dissertation project is to examine the vulnerability of inhibitory control with regard to the

development of tolerance to alcohol's disinhibiting effects. Three experiments are proposed that will examine three contexts in which tolerance has been shown to develop for a host of prototypic behaviors (e.g, motor coordination) and will compare the degree to which it fails to develop for inhibitory control.

First, there is strong evidence that inhibitory control does not develop acute tolerance to the impairing effects of alcohol. Such findings beg the question of when these impairments do show recovery, and how this compares to the rate of recovery of other behaviors that have been shown to develop acute tolerance to alcohol. These questions will be examined by this project by continuing to test the degree to which alcohol impairs inhibitory control as BACs decline to a zero level.

A second context that will be examined is how individual differences in drinker characteristics might contribute to chronic tolerance to alcohol's impairing effects. Evidence has suggested that heavy drinking can result in chronic tolerance to alcohol's impairing effects on the ability to activate behavior. That is, individuals who drink more frequently and in greater amounts display less impairment from alcohol on the ability to execute behavior compared with lighter drinkers. A second experiment is proposed which will examine whether such chronic tolerance will develop for inhibitory mechanisms of behavior as a function of recent drinking habits.

In addition to pharmacological factors that influence tolerance, the environmental contexts in which behaviors are performed under alcohol have been shown to affect the degree of tolerance observed in drinkers (e.g., Vogel-Sprott, 1992). For instance, environmental consequences such as reinforcements that are contingent upon performance can promote behavioral tolerance to alcohol. That is, behavioral tolerance to

alcohol can be facilitated when monetary incentives are made contingent upon resisting its impairing effects (Fillmore & Vogel-Sprott, 1997). Therefore, the third experiment of this proposal will examine the development of environmental tolerance to alcohol's impairing effects by altering the stimulus properties of cues that signal the need to inhibit behavior.

Figure 1.1.

## Cued Go/No-go Task

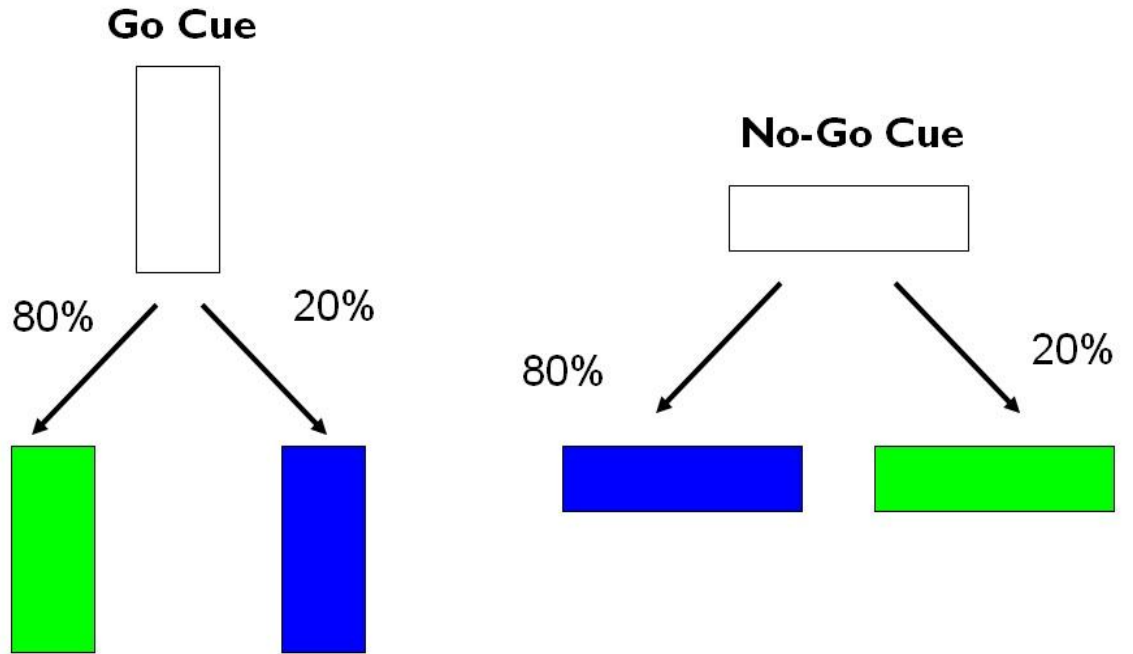


Figure 1.1 Schematic overview of cued go/no-go task, showing go and no-go cues (vertical and horizontal rectangles, respectively) and the likelihood of preceding a go target (green) or a no-go target (blue).

Figure 1.2.

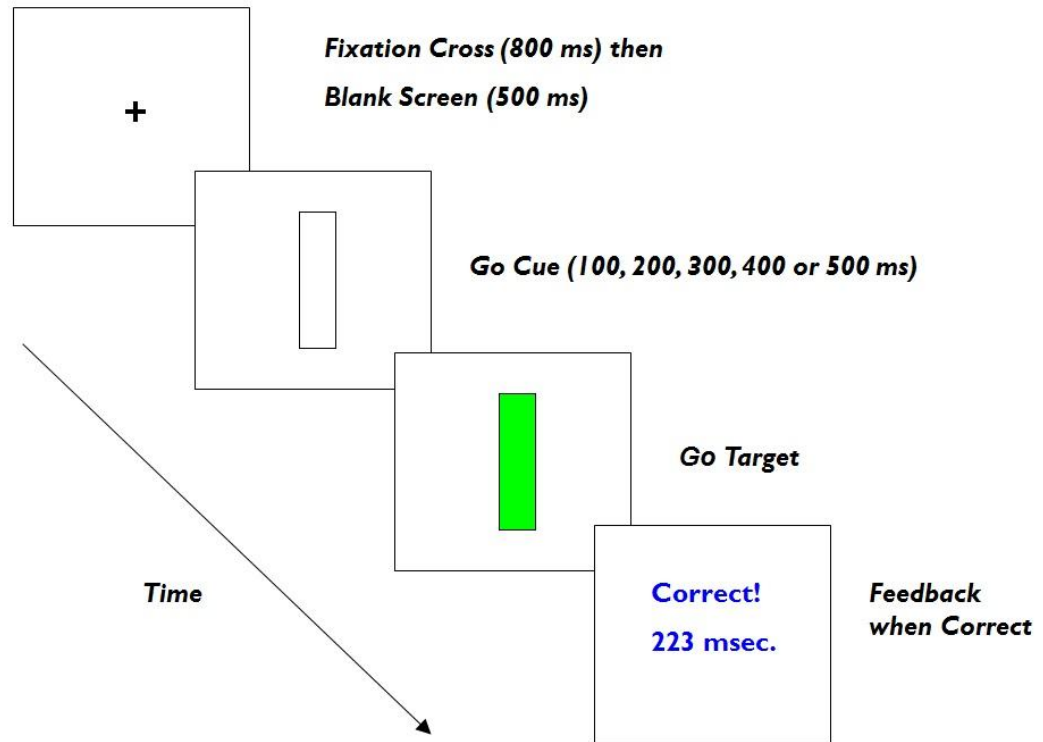


Figure 1.2. Schematic of a “go” condition trial of the cued go/no-go task. In this trial, a fixation point is presented followed by the presentation of a “go cue” (a horizontal rectangle) signaling an 80% likelihood that a “go target” will appear (a green rectangle). When the go target is presented, the participant executes the response as quickly as possible, and the computer provides feedback immediately following the response.

Figure 1.3

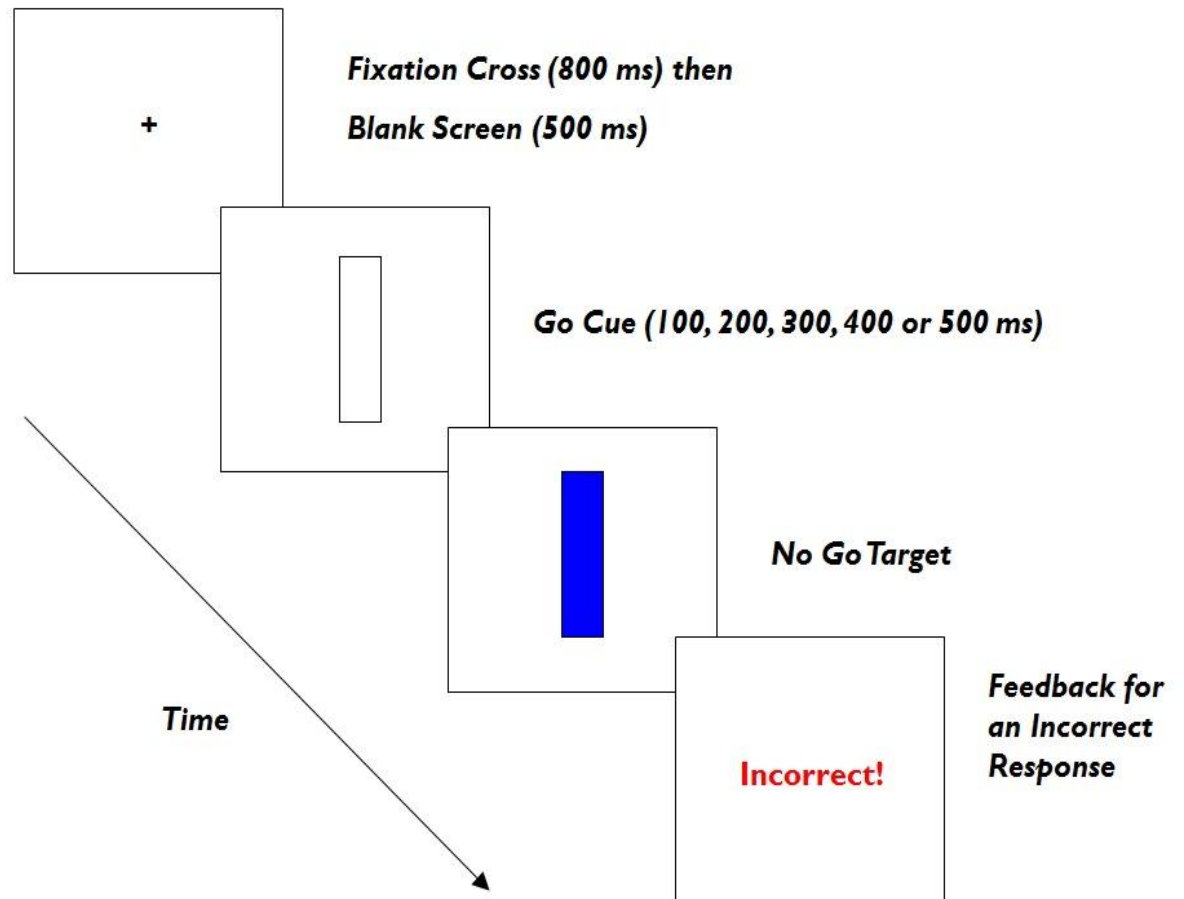


Figure 1.3. Schematic of an inhibitory failure on a “no-go” condition of the cued go/no-go task. In this trial, a fixation point is presented followed by the presentation of a “go cue” (a horizontal rectangle) signaling an 80% likelihood that a “go target” will appear. However, a no-go target is presented (blue rectangle). The participant makes an inhibitory error by responding to the blue rectangle, and receives feedback regarding the incorrect response.



## Chapter 2

### PROTRACTED IMPAIRMENT OF IMPULSE CONTROL

#### UNDER AN ACUTE DOSE OF ALCOHOL: A TIME-COURSE ANALYSIS

(STUDY 1; Miller & Fillmore)

#### Introduction

The prevalence of alcohol abuse in the United States has increased over the past decade despite considerable concern over its social costs. Alcohol use is particularly prevalent among young adults, with over half of men and women between 18 and 25 years of age reporting frequent alcohol use (Substance Abuse and Mental Health Services Administration, 2004). Moreover, the typical pattern of alcohol use reported by this demographic is often characterized by periods of heavy alcohol consumption referred to as “binges,” which are usually defined as consuming five or more drinks during a single occasion (Wechsler & Nelson, 2001). There is growing evidence that acute changes in fundamental mechanisms of impulse control contribute importantly to the transition from social drinking to abusive drinking (e.g., Fillmore, 2003; 2007; Lyvers, 2000). As such, researchers have sought to gain a better understanding of how mechanisms of impulsivity operate to promote the abuse of alcohol.

One fundamental component of impulsivity concerns the ability to inhibit inappropriate or maladaptive actions or behaviors. Inhibitory control refers to the ability to inhibit a response that has already been instigated (see Logan & Cowan, 1984). This mechanism of behavior affords an individual control over where and when responses are expressed. Thus, the inhibition of behavioral responses is a necessary function for situations in which an individual needs to exert self-restraint and regulation over behavior. As such, deficits in inhibitory control have been implicated in a wide array of

impulsive behaviors including heavy, binge drinking (e.g., Goudriaan et al., 2007; Marczinski et al., 2007). Human laboratory studies have employed stop-signal and cued go/no-go models to evaluate behavioral control as the ability to quickly activate and inhibit prepotent (i.e., instigated) responses (Logan 1994; Miller et al., 1991). These models are based on reaction time tasks requiring individuals to quickly activate a response to a go-signal and inhibit a response to stop or no-go signals. Studies have shown that these mechanisms of behavioral control are sensitive to the disruptive effects of alcohol. Indeed, alcohol increases inhibitory failures and slows response activation in a dose-dependent manner (Fillmore, et al., 2005; Fillmore & Weafer, 2004). However, studies provide evidence that inhibitory mechanisms are more sensitive to alcohol's impairing effects compared with response activation. For example, studies have consistently found that inhibitory control is impaired at relatively low blood alcohol concentrations (BAC) that fail to slow response times (e.g., Fillmore & Vogel-Sprott, 1999; de Wit et al., 2000).

Studies examining the speed with which behaviors recover from alcohol's impairing effects have also provided evidence of the sensitivity of inhibitory mechanisms to the drug's effects (e.g., Fillmore et al., 2005; Ostling & Fillmore, 2010; Fillmore & Weafer, 2012). The term tolerance refers to the observation that the intensity of a behavioral response to a drug diminishes with repeated administrations of the drug (Kalant et al., 1971). Although alcohol tolerance can develop as a function of chronic, heavy consumption, it can also be observed following a single dose of alcohol. Acute tolerance refers to the diminished response to alcohol during the time-course of a single dose. This effect was first documented early last century by Mellanby (1919), who

compared the intensity of alcohol impairment at a given BAC on the ascending and descending limbs of the blood alcohol curve. He observed that alcohol-induced ataxia in dogs was less intense at a given BAC during the descending versus the ascending limb of the BAC curve. This acute tolerance might be due to an adaptive process occurring during physiological exposure to the drug over time (e.g., Kalant et al, 1971).

In humans, acute tolerance to the impairing effects of alcohol has been observed for several behaviors such as motor coordination, reaction time, and subjective ratings of intoxication (Beirness & Vogel-Sprott, 1984; Schweizer et al., 2004; Fillmore et al., 2005; Fillmore & Vogel-Sprott, 1996; Marczynski & Fillmore, 2009; Schewiezer et al., 2004). In the past, acute tolerance was thought to develop uniformly across behaviors. However, several laboratory studies have failed to observe the development of acute alcohol tolerance for measures of inhibitory control (e.g., Fillmore et al., 2005; Ostling & Fillmore, 2010; Fillmore & Weafer, 2012). In one such study, Fillmore et al. (2005) compared the development of acute tolerance to the impairing effects of alcohol on response activation to the impairing effects on response inhibition. Participants performed the cued go/no-go task twice: once on the ascending limb and once on the descending limb of the BAC curve following 0.65 mg/kg alcohol. Both tests were performed at comparable BACs of approximately 80 mg/100 ml. The study showed that alcohol impaired behavioral activation by slowing reaction time and impaired response inhibition by increasing failures to inhibit responses to no-go targets. With regard to acute tolerance, the study found rapid recovery of behavioral activation. That is, reaction times measured on the descending limb of the blood alcohol curve had returned to sober levels. However, inhibitory control remained as impaired on the descending limb as it

was on the ascending limb of the blood alcohol curve. Such findings show that inhibitory mechanisms are especially slow to recover from the impairing effects of alcohol.

Evidence that inhibitory control fails to recover from alcohol's impairing effects at the same rate as other behaviors begs the question of when impaired inhibitory mechanisms return to sober levels. Prolonged impairment of inhibitory mechanisms along the descending limb of the BAC curve could play an important role in the development of alcohol abuse. Drinkers might be prone to engaging in continued impulsive action even as BACs decline, such as resuming alcohol consumption, resulting in excessive binge drinking in a situation. No work has systematically extended the time-course analysis of the disinhibiting effects of alcohol along the BAC curve to determine when behavioral impairment might show full recovery. Thus, the present study compared the recovery of alcohol-induced impairment of inhibitory control with the recovery of other behaviors that have demonstrated acute tolerance to alcohol. The study employed an extended time-course approach to examine the recovery of inhibitory control, reaction time, motor coordination, and ratings of subjective intoxication following a dose of 0.65 g/kg alcohol as drinkers' BAC descended from a peak of approximately 80 mg/100 ml to a near-zero level. As a control, performance was also tested following a placebo dose. Consistent with our previous research (e.g., Fillmore et al., 2005; Ostling & Fillmore, 2010), it was hypothesized that reaction time, motor coordination, and subjective intoxication would display acute tolerance to the effects of alcohol, and that complete recovery would also be evident once BACs returned to near-zero levels. However, we predicted that there would be no evidence of acute tolerance for inhibitory control, and

that given this lag in recovery, we might fail to observe complete recovery of this impairment as BACs approach zero.

## Methods

### *Participants*

Twenty-four individuals (12 men and 12 women) between the ages of 21 and 29 (mean age = 23.2,  $SD = 2.6$ ) participated in this study. Volunteers were recruited by flyers, posters, and newspaper/online advertisements seeking adults for studies of the effects of alcohol on cognitive functions. Volunteers were screened using health questionnaires and a medical history interview. Volunteers who reported any contraindication to alcohol, impaired cardiovascular functioning, seizure, head trauma, or central nervous system (CNS) tumors, were excluded from participation. Volunteers were also asked about past histories or present diagnoses of psychiatric disorder (i.e., Axis I, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [DSM-IV, American Psychiatric Association, 2000]). Participants who reported a diagnosis of a DSM-IV Axis I disorder, past or present use of psychotropic medication, and/or past or present participation in counseling or therapy were also excluded from participation.

Volunteers had to report drinking at least once per month in an amount of at least two drinks to participate. Volunteers who reported alcohol dependence, as determined by a score of 5 or higher on the Short-Michigan Alcoholism Screening Test (S-MAST; Selzer et al., 1975) were excluded from the study. Any other high-risk indicators of alcohol dependence, including prior treatment for an alcohol use disorder or conviction for driving under the influence also precluded participation. With regard to other drug use, the majority of the sample reported using caffeine ( $n = 20$ ). Thirteen participants

reported smoking cigarettes in the amount of less than a pack of cigarettes a day. Nine reported occasional past month use of marijuana on a less-than-weekly basis. No other drug use in the past month, including stimulants, opiates, or cocaine, was reported. Participants were in good health with no contraindications to drinking. The University of Kentucky Medical Institutional Review Board approved the study, and participants received \$85.

### *Materials and Measures*

*Personal drinking habits questionnaire (PDHQ; Vogel-Sprott, 1992).* This questionnaire provided three measures of the quantity and frequency of typical consumption: the number of drinking occasions per week, the typical drinks consumed per drinking occasion, and the typical BAC attained during a drinking episode. Typical BAC was calculated based on self-reported number of drinks usually consumed in a drinking episode, the type of alcohol usually consumed (beer, wine, or liquor), and the typical hourly duration of the drinking episode. This information, along with gender and weight in kilograms, was entered into an anthropometric formula to calculate peak BAC obtained during the typical drinking episode of each participant (McKim, 2007).

*Cued go/no-go task* Inhibitory control was measured using a computerized cued go/no-go model used in previous research (e.g., Marczinski & Fillmore, 2003; Fillmore et al. 2005) and was operated by E-Prime experiment generation software (Schneider et al., 2002). A trial began with a fixation point (+) for 800 ms, followed by a blank screen for 500 ms. A rectangular-shaped cue was then displayed for one of four randomly occurring stimulus onset asynchronies (SOAs = 100, 200, 400, and 800 ms) before a go or no-go signal appeared for 1000 ms. If the rectangle turned green (the go signal) subjects were to

make a computer key press as quickly as possible and if the rectangle turned blue (the no-go signal) they were to inhibit any response. A test consisted of 250 trials with 700 ms inter-trial intervals and required 15 minutes to complete.

The orientation of the rectangular cue signaled the probability that a go or no-go signal would appear. A vertically-oriented rectangle (height = 7.5 cm, width = 2.5 cm) turned green on 80% of the trials and turned blue on 20% of the trials. A horizontally-oriented rectangle (height = 2.5 cm, width = 7.5 cm) turned green on 20% of the trials and turned blue on 80% of the trials. Therefore, vertical and horizontal-oriented rectangles operated as go and no-go cues, respectively. The measure of interest was the proportion ( $p$ ) of inhibition failures to no-go signals in the go cue condition. Greater  $p$ -inhibition failures indicate poorer inhibitory control (i.e., disinhibition). Presentation of the go cue increases response preparation (i.e., produces a response prepotency), making it more difficult to inhibit a response when the no-signal unexpectedly appears. The disinhibiting effects of alcohol are most evident in this cue condition (Marczinski and Fillmore, 2003).

*Two-choice reaction time (RT) task.* Reaction time (RT) was measured by a computerized choice RT task which was operated using E-prime Experiment Generation software (Schneider et al., 2002) and performed on a personal computer. Participants are required to respond as quickly and accurately as possible to the presentation of targets on the screen. The letters X and O serve as the targets, and participants must press the (‘) key in response to the letter O and the (/) key in response to the letter X. A test contains 90 trials. Each trial consisted of the following sequence of events (a) a fixation point (+) displayed for 800 ms; (b) a blank white screen displayed for one of three stimulus onset

asynchronies (SOAs = 100, 400, and 900 ms); (c) the stimulus presented for 1,000 ms or until the response occurred; (d) a feedback screen that presented in a random order. A test required approximately 5 minutes to complete.

*Grooved Pegboard* Motor coordination was measured by a grooved pegboard task (Lafayette Instruments, Lafayette, IN). The pegboard task consists of a 5 by 5 inch metal surface that contains 25 “keyhole shaped” holes arranged in five rows of five holes each. Each of these holes has a large rounded side and a smaller, square side (a groove). The orientation of the groove in each hole varies such that no two adjacent holes have the same orientation. Participants are required to pick up the pegs one at a time and place them in the holes, filling in one row at a time until all 25 holes have been filled (i.e., one trial). The time to complete a trial (in seconds) is the measure of interest. A test consisted of four trials. The average completion time of the four tests was the dependent measure.

*Subjective Intoxication* The degree of subjective intoxication is measured on a visual analogue scale (VAS). Participants rate their degree of subjective intoxication by placing a vertical line at the point representing the extent to which they ‘feel intoxicated’ on a 100-mm horizontal line ranging from 0 mm “not at all” to 100 mm “very much.”

#### *Procedure*

Participants were tested individually in the Behavioral Pharmacology Laboratory of the Department of Psychology between 10 a.m. and 6 p.m. Sessions were scheduled at least 24 hours apart and were completed within a two week time period. Participants were instructed to fast for four hours prior to each session, as well as to refrain from consuming alcohol or any psychoactive drugs for at least 24 hours before all sessions. Prior to each session, participants provided urine samples and were tested for drug



metabolites including amphetamine, barbiturates, benzodiazepines, cocaine, opiates, and tetrahydrocannabinol (On Trak Teststiks, Roche Diagnostics Corporation, Indianapolis, IN, USA) and in women, human chorionic gonadotropin (hCG hormone), to verify that they were not pregnant (Mainline Confirms HGL, Mainline Technology, Ann Arbor, MI, USA). Any participants who tested positive for recent drug use or for pregnancy were excluded from participating. Breath samples were also provided at the beginning of each session to verify a zero BAC.

*Familiarization session.* After providing informed consent, participants provided proof of age to verify that they were at least 21 years old. They completed questionnaires concerning health status, drinking habits, and demographic characteristics. Finally, they performed shortened versions of each test to become acquainted with the task requirements.

*Test Sessions.* Performance was tested under two doses of alcohol: 0.0 g/kg (placebo) and 0.65 g/kg. Each dose was administered during a separate test session, and dose order was counterbalanced across participants. Participants were blind to the doses they received at each session. Sessions were separated by a minimum of one day and a maximum of one week. The alcohol dose was calculated on the basis of body weight and administered as absolute alcohol mixed with three parts carbonated soda divided equally into two glasses. Participants had two minutes to finish each glass, and the glasses were served four minutes apart. The placebo consisted of a volume of absolute alcohol that matched the total volume of the 0.65 g/kg alcohol drink. A small amount (3 ml) of alcohol was floated on the surface of the beverage. It was sprayed with an alcohol mist that resembles condensation and provides a strong alcoholic scent as the beverage is

consumed. Previous research has shown that individuals report that this beverage contains alcohol (Fillmore & Vogel-Sprott, 1998).

Subjects were tested on the cued go/no-go, choice RT, and pegboard tasks and completed the subjective rating scale at three times: 30 minutes (time 1), 90 minutes (time 2), and 320 minutes (time 3) after drinking began. Based on prior studies of the active alcohol dose (e.g., Marczinski & Fillmore, 2003; Fillmore & Vogel-Sprott, 1998), subjects were expected to obtain a BAC of 65 mg/100 ml at 30 (time 1) minutes that would continue to rise to an approximate peak of 80 mg/100 ml at 60 minutes, and descend back to 65 mg/100 ml by 90 minutes (time 2). Based on the average rate of BAC decline per minute, BACs were predicted to return to near zero levels by 320 minutes after drinking (time 3). BAC was measured at 30-minute intervals throughout the session, including immediately prior to and immediately following each test. The intervals were as follows: 30, 60, 90, 120, 150, 180, 210, 240, 270, 290, and 320 minutes after drinking began. Breath samples were also obtained at these times during the placebo session ostensibly to measure subjects' BACs. Participants remained at leisure in a waiting room and were provided with a light snack as their BACs fell between time 2 and time 3. After the final test (time 3), they were provided with transportation home. After the final session they were paid and debriefed.

#### *Criterion measures*

*Inhibitory Control.* Response inhibition was measured as participants' failures to inhibit responses to no-go targets (failure of response inhibition). Failure of response inhibition was measured as the proportion ( $p$ ) of no-go targets in the go cue condition in which a participant failed to inhibit a response (i.e.,  $p$ -inhibition failures)

*Reaction Time.* The two-choice RT task measured participants' RT as the mean RT to targets in milliseconds, with fewer milliseconds indicating faster RTs.

*Motor Coordination.* The grooved pegboard task measured motor coordination as the time in seconds required to insert all of the pegs into the board averaged across the four trials. Faster mean completion times indicated greater motor coordination.

*Subjective Intoxication.* Greater degree of intoxication was indicated by higher ratings on the subjective intoxication VAS.

#### *Data analyses*

All dependent measures were analyzed by 2 dose (0.0 g/kg and 0.65 g/kg) X 3 time (times 1, 2, and 3) repeated-measures analyses of variance (ANOVA). Acute tolerance to alcohol was tested by *a priori* simple effects comparisons of time 1 and time 2 following 0.65 g/kg using pairwise *t* tests. Planned comparisons of performance at time 3 between placebo and alcohol conditions were also used to determine if complete recovery was evident as BACs approached zero following the active dose.

## Results

### *Drinking habits*

Subjects reported drinking 1.8 ( $SD = 0.8$ ) days per week and consuming 5.3 ( $SD = 2.4$ ) drinks per occasion. Subjects reported typically drinking to a BAC of 82.6 ( $SD = 44.4$ ) mg/100 ml. Two-sample *t* tests revealed that men drank more frequently than women ( $p < 0.05$ ). Men reported drinking 2.2 ( $SD = 0.6$ ) days per week compared to 1.5 ( $SD = 0.8$ ) for women. Men also reported consuming more drinks per drinking occasion compared with women ( $p < 0.01$ ), with men typically consuming 6.8 ( $SD = 2.3$ ) drinks and women consuming 3.8 ( $SD = 1.6$ ) drinks. However, once body weight differences

were taken into account, there were no significant differences between men and women with respect to the typical BACs attained per drinking episode,  $p = 0.07$ .

#### *Blood alcohol concentrations*

No detectable BACs were observed following placebo. Figure 1 plots the mean BACs following alcohol when BACs were obtained. The figure shows that BACs ascended to a peak of 75.4 mg/100 ml ( $SD = 12.7$ ) at 60 minutes after drinking began. Potential gender differences were examined by a 2 (gender) X 3 (time) ANOVA. No main effect or interaction involving gender was observed ( $ps > 0.30$ ). There was a main effect of test, owing to the higher BACs at times 1 and 2 compared with time 3. Indeed, for the entire sample, the mean BAC at time 1 (30 minutes), BAC was 59.9 mg/100 ml ( $SD = 15.9$ ). At time 2 (90 minutes) the mean BAC was 61.6 mg/ 100 ml ( $SD = 10.8$ ). A paired-sample  $t$  test revealed no difference in BAC at time 1 versus time 2,  $p = 0.5$ . At test 3, the mean BAC (320 minutes), the mean BAC was 11.7 mg/ 100 ml ( $SD = 10.1$ ).

#### *Task performance*

*Inhibitory Control* Figure 2 shows the mean p-inhibition failures on the cued go/no-go task following placebo and alcohol for the three tests. The figure shows greater inhibitory failures in response to alcohol compared with placebo for each test. A 2 (dose) X 3 (time) repeated-measures ANOVA of p-inhibition failures revealed a significant main effect of dose,  $F(1, 23) = 12.02$ ,  $p < 0.01$ ,  $\eta^2 = 0.34$ . There was no main effect of time,  $F(2, 46) = 0.58$ ,  $p = 0.56$ ,  $\eta^2_{\text{partial}} = 0.02$ , nor an interaction,  $F(2, 46) = 0.88$ ,  $p = 0.42$ ,  $\eta^2_{\text{partial}} = 0.04$ . Planned comparison tests confirmed that at time 1, alcohol significantly increased inhibitory failures compared with placebo,  $t(23) = 2.83$ ,  $p < 0.01$ , and that this impairment remained at time 2 (the descending limb),  $t(23) = 2.08$ ,  $p <$

0.05. A planned test also compared performance at time 1 at time 2 following alcohol. This test revealed no difference in inhibitory failures between time 1 and time 2 following alcohol,  $p = 0.83$ , indicating no acute recovery of inhibitory control from the ascending to descending limb. Finally, a comparison of inhibitory failures at time 3 between placebo and alcohol conditions revealed that there were still significantly more errors following alcohol compared with placebo at this time,  $t(23) = 2.39$ ,  $p < 0.05$ .

*Reaction Time* Figure 3 plots the mean RTs on the two-choice reaction time for each test following placebo and alcohol. A 2 (dose) X 3 (time) repeated-measures ANOVA revealed a significant main effect of dose,  $F(1, 23) = 8.19$ ,  $p < 0.01$ ,  $\eta^2_{\text{partial}} = 0.26$ , a main effect of time,  $F(2, 46) = 9.52$ ,  $p < 0.001$ ,  $\eta^2_{\text{partial}} = 0.29$ , and an interaction,  $F(2, 46) = 4.11$ ,  $p < 0.05$ ,  $\eta^2_{\text{partial}} = 0.15$ . Planned comparison tests confirmed that at time 1, alcohol significantly slowed RTs compared with placebo,  $t(23) = 3.34$ ,  $p < 0.001$ . However, following alcohol, RTs were significantly faster at time 2 compared with time 1,  $t(23) = 2.24$ ,  $p < 0.05$ . Moreover, at time 2, RTs following alcohol did not differ from RTs following placebo,  $p = 0.24$ . Finally, a comparison of RT at time 3 between placebo and alcohol also confirmed that there was no significant difference in RTs at this time,  $p = 0.17$ .

*Motor Coordination* Figure 4 plots the mean time to complete the pegboard task in seconds for each test following placebo and alcohol. A 2 (dose) X 3 (time) repeated-measures ANOVA revealed a main effect of time,  $F(2, 46) = 36.25$ ,  $p < 0.001$ ,  $\eta^2 = 0.61$ , and an interaction,  $F(2, 46) = 23.04$ ,  $p < 0.001$ ,  $\eta^2 = 0.50$ . There was no main effect of dose,  $F(1, 23) = 3.64$ ,  $p = 0.07$ ,  $\eta^2 = 0.14$ . Planned comparison tests showed that at time 1, alcohol significantly slowed completion time compared with placebo,  $t(23) = 4.55$ ,  $p <$

0.001. There was a significant decrease in completion time from time 1 to time 2 following alcohol,  $t(23) = 3.50, p < 0.001$ , indicating acute tolerance. At time 2, there was no statistical difference observed in completion time between alcohol and placebo,  $p = 0.06$ , indicating acute recovery of motor coordination on the descending limb. Finally, a comparison at time 3 between placebo and alcohol also showed no significant difference in completion time,  $p = 0.09$ .

*Subjective Intoxication* Figure 5 plots the mean subjective intoxication ratings for each time following placebo and alcohol. A 2 (dose) X 3 (time) repeated-measures ANOVA of ratings revealed a main effect of dose,  $F(1, 23) = 33.03, p < 0.001, \eta^2 = 0.59$ , of time,  $F(2, 46) = 32.63, p < 0.001, \eta^2 = 0.59$ , and an interaction,  $F(2, 46) = 23.87, p < 0.001, \eta^2 = 0.51$ . Planned comparison tests revealed that alcohol increased intoxication ratings compared with placebo at time 1,  $t(23) = 5.56, p < 0.001$ , and time 2,  $t(23) = 5.49, p < 0.001$ . There was also a significant decrease in ratings from time 1 to time 2 following alcohol,  $t(23) = 5.20, p < 0.001$ . Finally, a comparison at time 3 between placebo and alcohol showed no significant difference in intoxication ratings,  $p = 0.08$ .

#### *Reliability/Stability of Task Measures*

The degree to which each task reliably assessed participants' performance over time during a session was also tested. For each task, we analyzed the intraclass correlation coefficient (Cronbach's Alpha) based on performance at each of the three testing times following placebo. Cronbach's alphas for inhibitory control, motor coordination, and reaction time measures were 0.78, 0.98, and 0.98, respectively. These results confirm high test-retest reliability of each measure, and that the individual

differences among participants' performance level on a task showed a high degree of consistency over tests within the session.

### Discussion

The present study sought to determine the degree to which alcohol-induced impairment of inhibitory control recovers as BACs decline to a near zero level. Inhibitory control was measured by performance on a cued go/no-go task in a group of young adult, social drinkers. Subjects also performed tasks measuring reaction time and motor coordination, and provided subjective ratings of intoxication. Subjects performed all tasks in response to placebo and 0.65 g/kg alcohol, and performance was tested at three time points after drinking: at comparable BACs of approximately 65 mg/100 ml on the ascending and descending limbs of the blood alcohol curve, and then over five hours after drinking began, when BACs were nearly zero.

The study showed that alcohol significantly impaired performance on all tasks and increased subjective ratings of intoxication on the ascending limb of the BAC curve compared with placebo. Acute tolerance was observed for RT, motor coordination, and subjective intoxication. That is, comparisons of performance at comparable BACs on the descending versus ascending limb of the BAC curve showed significant decreases in impairment of RT and motor coordination and a reduction in ratings of intoxication. This recovery continued to the third test of performance, as BACs approached zero. By contrast, we observed no evidence of acute tolerance for inhibitory control. Indeed, alcohol continued to increase inhibitory failures on the descending limb to the same general degree as was observed on the ascending limb, which is consistent with previous findings from our laboratory (Fillmore et al., 2005; Ostling & Fillmore, 2010; Fillmore &

Weafer, 2012). Although this study design did not permit a straightforward approach to formally test whether the time by dose interaction significantly differed by measure, the effect size for the time by dose interaction for inhibitory control was considerably smaller compared with the other measures. Moreover, not only had the disinhibiting effects of alcohol failed to recover on the descending limb, but the study showed that at time 3, nearly five hours after drinking, inhibitory control remained significantly impaired at a magnitude similar to the degree of impairment observed much earlier under the dose during times 1 and 2.

This study is the first to examine whether alcohol-induced deficits of inhibitory control fully recover as BACs decline to zero. It is not clear why drinkers remained substantially disinhibited in the study despite having near-zero BACs. There is a growing body of research that suggests that inhibitory control is especially sensitive to the disruptive effects of alcohol compared with other behavioral functions. This sensitivity is especially evident when examining the development of tolerance to alcohol impairment. With regard to chronic tolerance, it is generally assumed that heavier drinkers should display reduced reactions to a dose of alcohol (i.e., tolerance), whereas lighter drinkers should be more affected by the same dose. While this is the case for measures, such as RT, motor coordination, and subjective intoxication, we fail to observe tolerance to the disinhibiting effects of alcohol as a function of recent, heavy consumption (i.e., Marcziński et al., 2007; Miller et al., 2012). Moreover, as shown by the present study and by others, within a single drinking episode, inhibitory control fails to adapt to and recover from the impairing effects of an acute dose of alcohol (Fillmore et al., 2005; Ostling & Fillmore, 2010; Fillmore & Weafer, 2012). What is new from the present research is that



we have provided additional evidence showing that alcohol-induced impairment of inhibitory mechanisms continues even after BACs become essentially negligible after drinking.

It is unlikely that the persistent impairment of inhibition observed after five hours post-alcohol was the result of boredom or fatigue, as participants' response activation and psychomotor performance recovered fully by this time. Moreover, the testing regime was not arduous for the subjects as they were required to complete the test battery only three times during the entire test session with ample time between tests. Instead, the prolonged impairment of inhibitory control might represent a protracted pharmacological/physiological effect of alcohol. In fact, there is some evidence to suggest that the effects of alcohol on cognition and behavior can be observed the day following alcohol consumption, long after alcohol has been eliminated from the body (for a review, see Prat et al., 2008). However, evidence for the hangover effect has generally been inconsistent. For example, several studies have failed to show any protracted impairment from alcohol on simple, psychomotor skills, such as RT and coordination (e.g., Chait & Perry, 1994; Finnigan et al., 1998; Kruisselbrink et al., 2006). A lack of prolonged impairment of motor performance is consistent with our current findings that showed the initial alcohol-induced impairments of these behaviors began to recover early during the time-course on the descending limb of the curve even while BACs were still elevated (i.e., > 50 mg/100 ml). By contrast, prolonged, day-after impairments have been observed for more complex behaviors, such as those requiring divided and/or sustained attention (Finnigan et al., 2005; Roehrs & Roth, 2001). However, to date, no work has shown whether alcohol-induced impairments of inhibitory mechanisms of behavioral

control are subject to such a “day-after” hangover effects. The protracted impairment of inhibitory control observed in the present study could suggest that cognitive operations involving the inhibition of actions are likely to show protracted impairments from alcohol, possibility even day-after impairments, such as carryover or hangover effects. Such a possibility awaits to be examined.

To better understand why alcohol has such protracted effects on inhibitory control compared with other aspects of behavior, it is important to consider the neural underpinnings of behavioral control. Event-related human brain potentials (ERPs) have been used to identify the neural mechanisms underlying cognitive processes, including inhibitory control. To do this, ERPs are recorded as participants perform a cued go/no-go task. Findings have shown that the successful inhibition of responses on the task generates heightened P3 (or P300) waves located at midline central sites (i.e., Bokura et al., 2001; Falkenstein et al., 1999; Kok et al., 2004), whereas reduced P3 waves are associated with disinhibition (e.g., Bauer and Hesselbrock, 1999; Iacono et al., 2003; Patrick et al., 2006). What is more, P3 waves are consistently reduced following moderate doses of alcohol (Barthalow et al., 2003; Rorhbaugh, et al., 1987). Indeed, Easdon et al. (2005) have shown that a moderate dose of alcohol increased inhibitory failures and reduced P3 amplitudes specifically in instances when participants exhibited inhibition failures. Given that the P3 component of the ERP has been of particular interest in the study of alcohol abuse and inhibition, a potential extension of this work would be to continue to record ERPs throughout the time course of the BAC curve. This would provide an important psychophysiological counterpart to the present study’s

behavioral findings, and offer insight into the duration of alcohol's effects on neural functioning even as BACs begin to dissipate.

There are some potential limitations of the current study which might inform future research. First, the study's sample was comprised of primarily college-aged, young adults. The sample reported consuming an average of 5.3 drinks per drinking occasion, and 12 participants (50% of the sample), reported drinking to a 0.08% BAC on a regular basis. These habits are typical of this demographic (e.g., Johnston et al., 2010), and do not reflect abnormally heavy, or dependent drinkers. Moreover, regression analyses revealed no relationship between any of the drinking habits we measured (frequency, quantity, and typical BAC) and the degree to which inhibitory control was impaired by alcohol ( $ps > 0.36$ ). That said, future work might be aimed toward extending the present findings to populations with different patterns of consumption.

Another possible limitation of this study is that we only focused on one aspect of behavioral control (i.e., the ability to inhibit a prepotent response). However, our findings raise the question of whether alcohol results in a prolonged impairment across of broad range of inhibitory functions. Indeed, alcohol has been shown to impair other aspects of inhibitory control, such as mechanisms of attentional control. In these studies, alcohol disrupts attentional control, resulting in a decreased ability to direct attention from distractions (Fillmore et al. 2000; Abroms and Fillmore 2004). Moreover, such impairments in mechanisms of attentional control have also been implicated as a factor that might contribute to alcohol abuse (Tarter et al 2004; Blume et al 2005). As such, it is important to examine whether alcohol-induced impairments of attentional control also fail to recover from alcohol's disinhibiting effects along the timecourse of the BAC

curve. Moreover, such a possibility will also provide assurance that the failure of recovery that we have observed in the present study is related not only to inhibitory failures on a go/no-go task, but to the general construct of inhibitory mechanisms of behavioral control.

Finally, it is important to consider the implications of such a prolonged impairment of inhibitory mechanisms following alcohol consumption. In particular, the results might lead to a better understanding of the impulsive behavior and poor decision making commonly observed under alcohol. Studies suggest that alcohol-induced impairment of inhibitory control contributes to alcohol abuse by promoting excessive or binge drinking (e.g., Marczyński et al., 2007; Weafer & Fillmore, 2008), and alcohol-induced disinhibition is also related to other impulsive, aggressive, and socially inappropriate behaviors (Fillmore 2003, 2007; Jentsch & Taylor, 1999). Thus, the recovery of behavioral activation following a dose of alcohol coupled with continued impairment of inhibitory mechanisms might result in the prolonged display of impulsive behavior even as BACs decline considerably. For example, following an initial drink, individuals might decide to extend a drinking session, leading to a binge episode given that they feel sober and detect no impairment of motor coordination, yet continue to be significantly disinhibited. Additionally, other risky decisions might follow, such as decisions to drive or engage in risky sexual or other aggressive behaviors. As such, future studies aimed at better identifying the mechanisms by which this prolonged impairment of impulse control persists will prove beneficial.

Figure 2.1

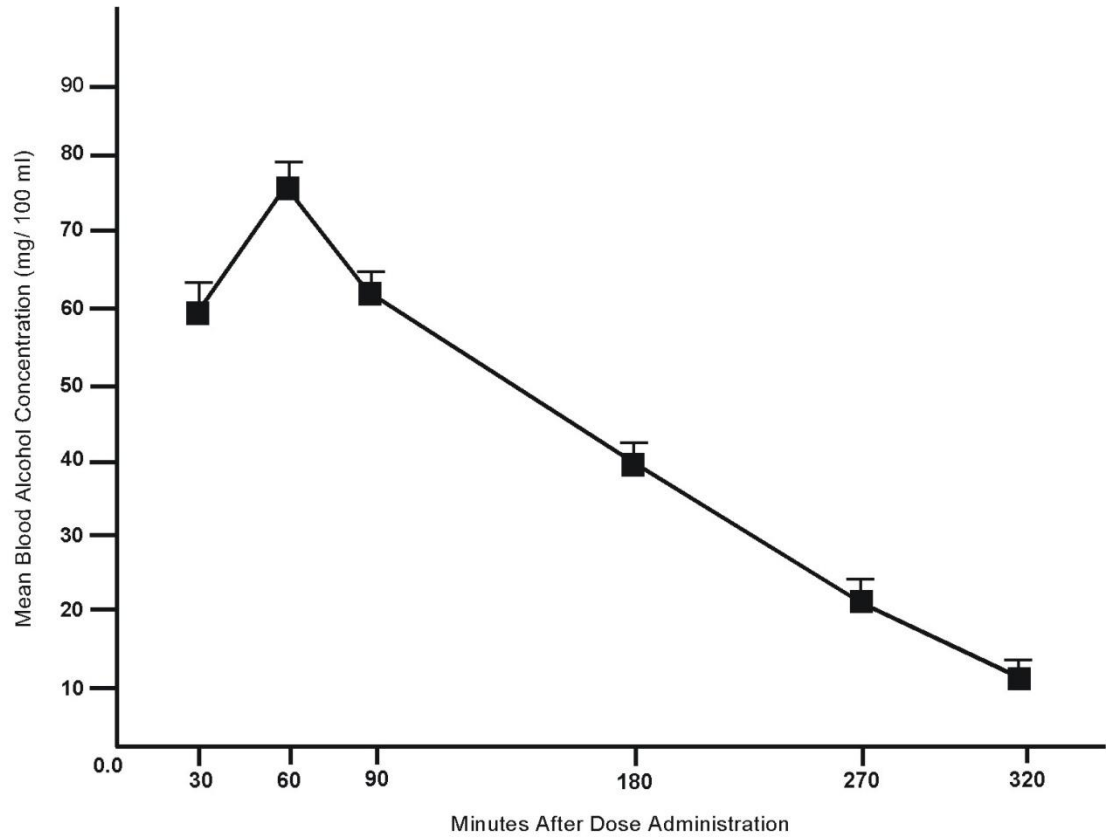


Figure 2.1. Mean blood alcohol concentrations (BAC) following 0.65 g/kg alcohol at intervals when breath samples were obtained. Capped vertical lines show standard error of the mean.

Figure 2.2

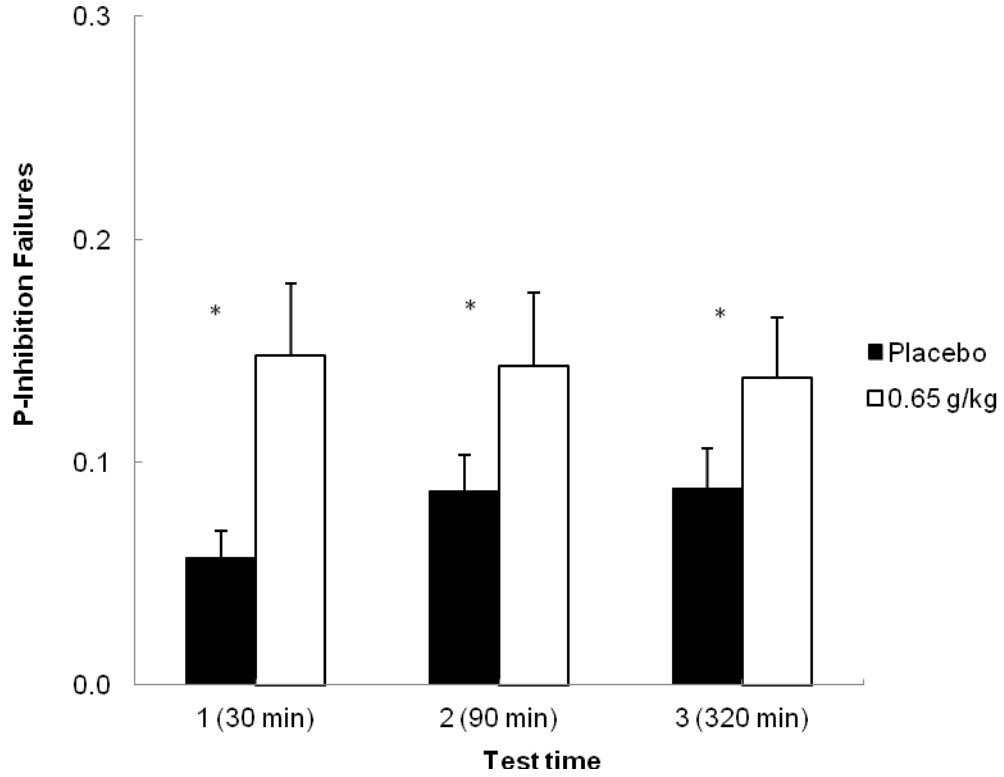


Figure 2.2. Mean proportion of failures to inhibit responses on the cued go/no-go task at each test time in response to placebo and alcohol. Capped vertical lines show the standard error of the mean. Asterisks (\*) indicate a significant increase in inhibitory failures from placebo to alcohol,  $p < 0.05$ .

Figure 2.3

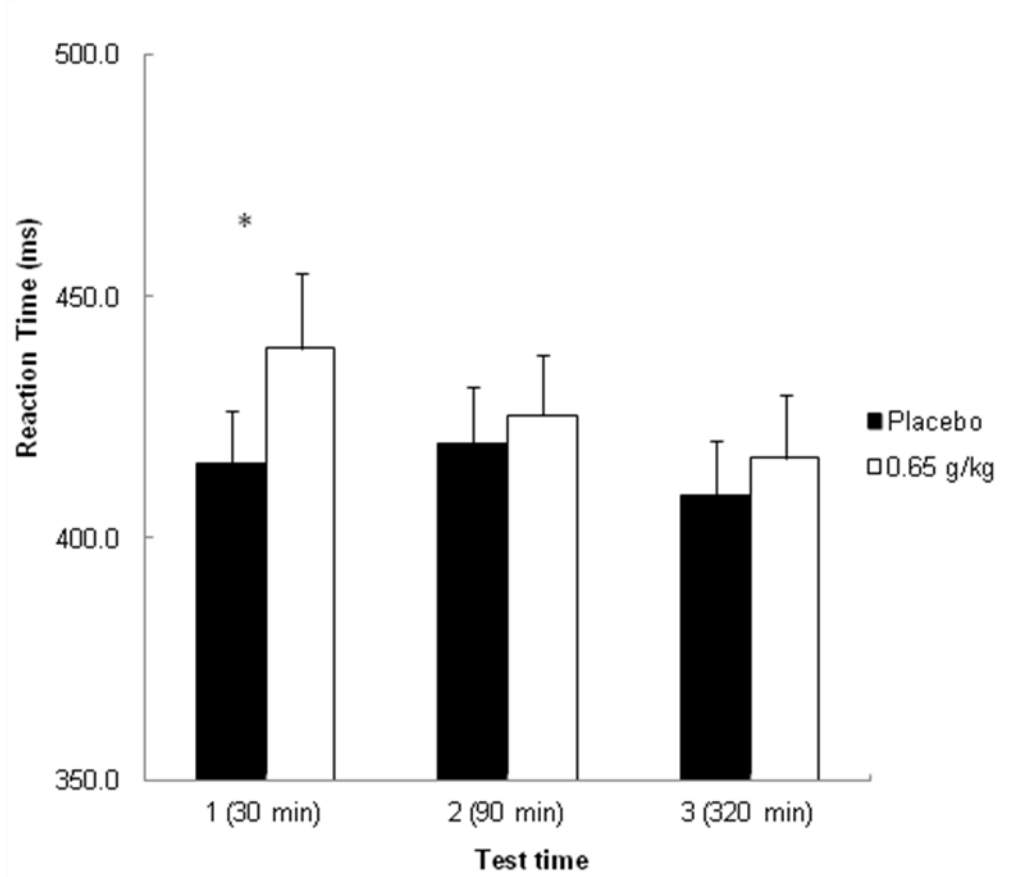


Figure 2.3. Mean reaction time (RT) in milliseconds during the choice reaction time task at each test time in response to placebo and alcohol. Capped vertical lines show the standard error of the mean. Asterisks (\*) indicate a significant increase in RT from placebo to alcohol,  $p < 0.001$ .

Figure 2.4.

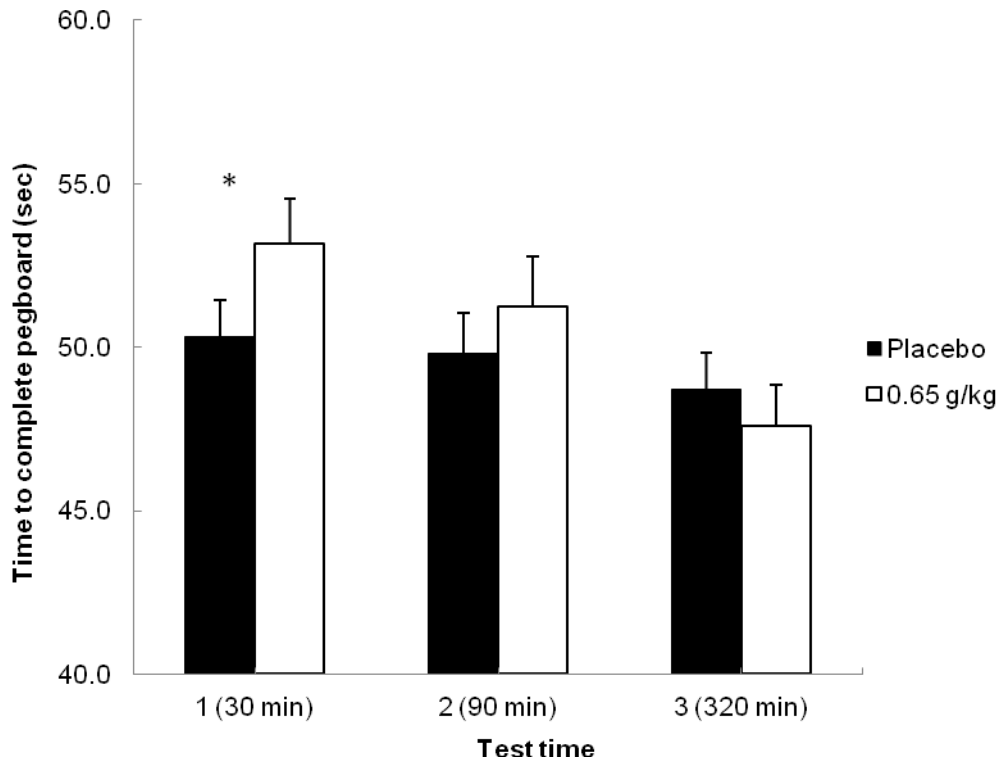


Figure 2.4. Mean time to complete the pegboard task (in seconds) at each test time in response to placebo and alcohol. Capped vertical lines show the standard error of the mean. Asterisks (\*) indicate a significant increase in completion time from placebo to alcohol,  $p < 0.001$ .



Figure 2.5.

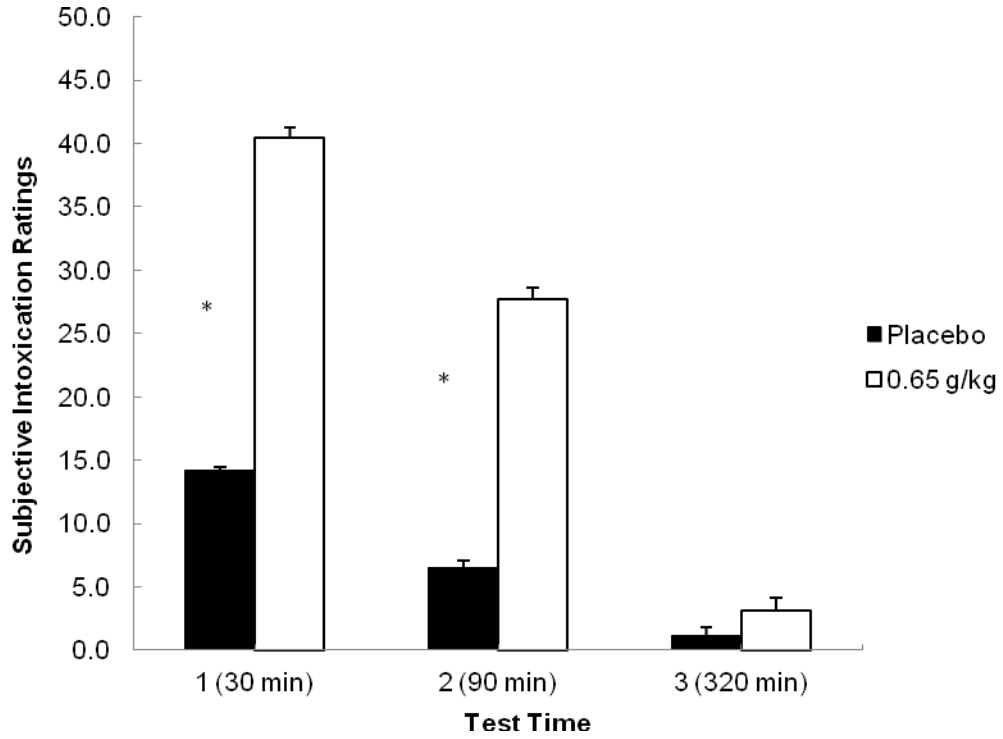


Figure 2.5. Mean subjective intoxication ratings (1 – 100) at each test time in response to placebo and alcohol. Capped vertical lines show the standard error of the mean. Asterisks (\*) indicate a significant increase in intoxication ratings from placebo to alcohol,  $p < 0.001$ .

## Chapter 3

### LACK OF TOLERANCE TO THE DISINHIBITING EFFECTS OF ALCOHOL IN HEAVY DRINKERS

(STUDY 2; Miller, Hays & Fillmore)

#### Introduction

Alcohol tolerance is observed as a diminished response to a given dose as a function of repeated administrations of the drug. As tolerance develops, higher doses of alcohol are needed to reinstate the initial effect. Thus, alcohol tolerance has become recognized as a factor that may contribute to alcohol abuse and dependence by encouraging the use of higher doses (American Psychiatric Association 1994). It is generally assumed that heavier drinkers should display reduced reactions to a dose of alcohol (i.e., tolerance), whereas lighter drinkers should be more affected by the same dose. Indeed, these assumptions are supported by laboratory research. Early studies compared alcohol responses in healthy adults to those displayed by alcohol-dependent individuals who were in treatment (Goldberg 1943; Mendelson and Mello 1966; Nathan et al. 1971). These studies found that alcohol-dependent drinkers displayed less behavioral impairment to alcohol compared with healthy controls. More recent studies have also shown that tolerance can be observed in relation to the drinking habits of non-dependent, “social drinkers,” such that those who drink frequently and engage in binge drinking display less impairment than lighter, infrequent drinkers (e.g., Fillmore and Vogel-Sprott 1995; Holdstock et al. 2000; Townshend and Duka 2005; Brumback et al 2007). Taken together, the evidence suggests that tolerance may be readily influenced by recent drinking patterns which do not necessarily reflect alcohol abuse or dependence.

Although such evidence might suggest that tolerance is a ubiquitous phenomena produced by a history of heavy consumption, the evidence to date has focused almost exclusively on measures of motor performance, such as body sway, hand steadiness, and visuo-motor tracking. However, in recent years there have been major advancements in the identification of specific behavioral and cognitive processes by which alcohol impairs self-regulation, and comparatively little is known about the development of tolerance to alcohol impairment of these mechanisms. Human laboratory studies have employed stop-signal and cued go/no-go models to evaluate behavioral control as the ability to activate and inhibit prepotent (i.e., instigated) responses (Logan and Cowan 1984; Miller et al. 1991; Logan 1994). These models are based on reaction time tasks that require individuals to quickly activate a response to a go-signal and inhibit a response when a stop or no-go signal occurs. Studies show that these mechanisms of behavioral control are sensitive to the disruptive effects of alcohol. Following administration, alcohol increases inhibitory failures and slows response activation in a dose-dependent manner (Fillmore et al. 2005; Fillmore and Weafer 2004). Moreover, alcohol-induced impairments in inhibitory control have been linked to abuse potential. Studies suggest that acute impairments of inhibition might reduce the ability to terminate drinking behavior during a drinking episode, thus resulting in excessive, binge drinking (Fillmore 2003; 2007). As such, it is important to determine if recent drinking patterns might also affect tolerance to alcohol impairment of inhibitory control.

The purpose of the present study was to examine the relationship between recent drinking habits and the degree to which alcohol impairs drinkers' inhibitory mechanisms of behavioral control. The study examined a large group of non-dependent adult drinkers

who reported a wide range of drinking habits (both quantity and frequency). Behavioral effects were tested in response to a moderate dose of alcohol (0.65 g/kg) and a placebo (0.0 g/kg). In addition to examining inhibitory control, the study also included a measure of motor coordination, which has shown tolerance as a function drinking habits in previous research (e.g., Fillmore and Vogel-Sprott 1996; Schweizer et al. 2004; Fillmore et al. 2005).

## Methods

### *Participants*

Fifty-two adult drinkers (25 men and 27 women) between the ages of 21 to 33 (mean age = 23.6,  $SD = 3.3$ ) participated in this study. The sample was comprised of 7 African-American, 1 Asian, and 45 Caucasian participants. Volunteers who self-reported head trauma, a diagnosis of a psychiatric disorder, or current substance abuse disorder were excluded from participation. Volunteers who reported alcohol dependence, as determined by a score of 5 or higher on the Short-Michigan Alcoholism Screening Test (S-MAST; Seltzer et al. 1975) were also excluded.

Potential volunteers had to report drinking at least once per month in an amount of at least two drinks to participate. With regard to other drug use, the majority of the sample reported using caffeine ( $n = 44$ ). Those who use caffeine reported drinking caffeinated beverages an average of 4.9 ( $SD = 2.4$ ) days per week. Twelve participants reported smoking cigarettes. Out of those who reported smoking, one participant reported smoking more than a pack of cigarettes (i.e., 20 cigarettes) a day while the others ( $n = 11$ ) reported smoking less than a pack of cigarettes a day. 8 participants reported some past month use of marijuana. No other drug use in the past month, including stimulants,

opiates, or cocaine, was reported. All participants were in good health with no contraindications to alcohol consumption. The University of Kentucky Medical Institutional Review Board approved the study, and participants received \$85.

### *Materials and Measures*

*Cued Go/No-Go Task.* Response inhibition was measured using a cued go/no-go task that has been used in previous research (e.g., Fillmore et al. 2005; Marcziński and Fillmore 2003). E-Prime experiment generation software (Schneider et al. 2002) was used to operate the task, which was performed on a computer. Cues provide preliminary information regarding the type of imperative target stimulus (i.e., go or no-go) that is likely to follow, and the cues have an 80% probability of signaling the correct target (thus on 20% of these trials, the cue will precede an incorrect target). Participants were instructed to press the forward (/) slash key on the keyboard as soon as a go (green) target appeared and to suppress the response when a no-go (blue) target was presented. Key presses were made with the right index finger. To encourage quick and accurate responding, feedback was presented to the participant during the inter-trial interval by displaying the words *correct* or *incorrect* along with the RT in milliseconds. A test required approximately 15 minutes to complete.

*Grooved Pegboard Task.* Motor coordination was measured by a grooved pegboard task (Lafayette Instruments). The task consists of a 5 X 5 inch board that contains 25 holes arranged in five rows of five holes each. The holes are “keyhole” shaped and the pegs fit into them as a key would fit into a lock. Using their dominant hand, participants take pegs from a tray one at a time and fit them in the holes, filling in each row at a time from left to right. Extra pegs are available to replace any dropped pegs

during the trial. A trial is complete after all holes are filled. The time to complete a trial (in seconds) is the measure of interest. A test consists of four trials.

*Timeline follow-back (TLFB; Sobell and Sobell, 1992).* The TLFB provides an assessment of drinking habits over the past 3 months. Four measures of drinking habits for the past 3 months were obtained: (1) total number of drinking days for that period (*drinking days*), (2) total number of drinks consumed in that period (*total drinks*), (3) total number of days in which participants reported feeling drunk (*drunk days*) and (4) total number of days on which binge drinking occurred (*binge days*). A binge was defined as drinking an amount of alcohol sufficient to elevate a subject's BAC to 0.08% (80 mg/100 ml) or higher (NIAAA, 2004). To determine the number of binge days, an estimate of BAC was calculated based on the number of drinks consumed, the type of alcohol consumed, the time span in hours spent drinking, and gender and body weight. This was done using well-established, valid anthropometric-based BAC estimation formulae which assume an average clearance rate of 15 mg/dl per hour of the drinking episode (Watson et al. 1981; McKim 2007).

#### *Procedure*

Volunteers were told that the purpose of the experiment was to study the effects of alcohol on cognitive and behavioral tasks. Sessions were conducted in the Behavioral Pharmacology Laboratory of the Department of Psychology and participants were tested individually. Before test sessions, participants were instructed to fast for four hours and to abstain from alcohol for 24 hours. Prior to sessions, participants provided urine samples that were tested for drug metabolites, including amphetamine, barbiturates, benzodiazepines, cocaine, opiates, and tetrahydrocannabinol (On Trak Teststicks, Roche

Diagnostics Corporation, Indianapolis, IN) and pregnancy in the female participants (Mainline Confirms HGL, Mainline Technology, Ann Arbor, MI). A zero BAC was verified for participants from breath samples. Participants completed an intake session to provide background information and to become acquainted with laboratory procedures and the behavioral tasks.

*Test sessions.* Task performance was tested under two doses of alcohol: 0.0 g/kg (placebo) and 0.65 g/kg. Each dose was administered during a separate test session, and dose order was counterbalanced across participants. Sessions were separated by a minimum of one day and a maximum of one week. Alcohol doses were calculated on the basis of body weight and administered as absolute alcohol mixed with three parts carbonated soda. The placebo dose (0.0 g/kg) consisted of a volume of carbonated mix that matched the total volume of the 0.65 g/kg alcohol drink. A small amount (3 ml) of alcohol was floated on the surface of the beverage. It was sprayed with an alcohol mist that resembled condensation and provided a strong alcoholic scent as the beverage was consumed. Previous research has shown that individuals report that this beverage contains alcohol (Fillmore and Vogel-Sprott 1998). Drinks were consumed in six minutes. Following 0.65 g/kg alcohol, a peak BAC of 80 mg/100 ml was expected to occur approximately 60 minutes after drinking (Fillmore and Vogel-Sprott 1998).

Participants were tested on the ascending limb of the BAC curve. Thirty minutes after drinking began, they performed the 20 minute test battery, which consisted of the cued go/no-go and grooved pegboard tasks. BACs were measured at 30 and 50 minutes post-drinking (i.e., before and after testing occurred). Breath samples were also obtained

at these times during the placebo session ostensibly to measure BACs. After testing, participants received a meal and were released once their BAC fell below 20 mg/100 ml.

#### *Criterion measures*

Failures of response inhibition were measured as the proportion of no-go targets in which a participant failed to inhibit a response. The measure of interest was the proportion ( $p$ ) of inhibition failures in the go cue (i.e., prepotent) condition. Greater  $p$ -inhibition failures indicate poorer inhibitory control (i.e., disinhibition). The pegboard task measured motor coordination as the number of seconds required to fit all of the pegs into the board averaged across the four trials. Longer mean completion times indicated poorer motor coordination.

#### *Data Analyses*

Dependent measures were analyzed by one-way repeated measures analyses of variance (ANOVA) testing the main effect of dose (0.0 g/kg vs. 0.65 g/kg) on performance. Initially, all analyses were conducted with gender and dose order (placebo first vs. alcohol first) as between-subjects factors. There were no significant main effects or significant interactions involving gender or dose order for any of the dependent measures of interest. Therefore, all subsequent analyses presented were collapsed across gender and dose order.

The relationship of each drinking habit measure to the degree of alcohol impairment on inhibitory control and motor coordination was tested by regression analyses. For each regression, the individual drinking habit measure from the TLFB was entered as the independent (i.e., predictor) variable, and the magnitude of the alcohol effect on each behavioral measure (motor coordination, inhibitory control) was the



dependent measure. To determine the magnitude of alcohol effects, impairment scores were calculated by subtracting each participant's performance score following placebo from his or her score following 0.65 g/kg alcohol. The impairment score for motor coordination was calculated by subtracting the task completion time following placebo from the completion time following alcohol such that larger scores indicated greater impairment. For inhibitory control, impairment scores were calculated by subtracting *p*-failures following placebo from *p*-failures following alcohol such that larger impairment scores indicated greater impairment of inhibitory control.

## Results

### *Blood Alcohol Concentrations*

BACs in the active dose condition were analyzed by a 2 (gender) X 2 (time) mixed-design ANOVA. No main effect or interaction involving gender was observed ( $p > 0.10$ ). There was a main effect of time,  $F(1, 50) = 20.5, p < 0.01$ , owing to an increase in BAC on the ascending limb of the BAC curve when testing occurred. For the entire sample, the mean BAC was 76.2 mg/100 ml ( $SD = 21.2$ ) at the beginning of the test (30 minutes after drinking) and 84.9 mg/100 ml ( $SD = 14.4$ ) at the conclusion of the test (50 minutes after drinking). No detectable BACs were observed under the placebo condition.

### *Alcohol Effects*

Alcohol increased the mean *p*-inhibition failures from 0.088 ( $SD = 0.12$ ) to 0.132 ( $SD = 0.11$ ). For motor coordination, alcohol increased the mean time needed to complete the task from 52.2 sec ( $SD = 6.77$ ) to 55.5 sec ( $SD = 8.00$ ). The effects of alcohol on inhibitory control and motor coordination were analyzed by individual, one-way repeated measures ANOVAs. Significant main effects of dose on performance were

found for both  $p$ -inhibition failures,  $F(1, 51) = 13.1, p < 0.01$ , and pegboard performance,  $F(1, 51) = 26.1, p < 0.001$ .

#### *Drinking habits and alcohol impairment*

Table 1 presents participants' drinking habits as reported on the TLFB. As the table shows, there was substantial variation with regard to the frequency and quantity of consumption reported. Some participants reported infrequent, light drinking (e.g., drinking less than twice a month over the past 3 months, and never binge drinking). Others reported drinking frequently (e.g., consuming alcohol on 86 out of the past 90 days) and in consistently large amounts (e.g., binge drinking on nearly one-third of the past 90 days).

To test the relationship between drinking habits and alcohol impairment, zero-order regression analyses of each drinking habit measure onto the drinkers' alcohol impairment scores for motor coordination and for inhibitory control were performed. For motor coordination, each drinking habit measure bore a significant negative relationship to the degree of motor impairment observed in response to alcohol ( $ps < 0.01$ ). Figure 1 plots the relationships between alcohol impairment of motor coordination and subjects' drinking habits. The figure shows that impairment was inversely related to the drinkers' levels of recent alcohol consumption. Specifically, those who reported drinking the most days and in the greatest quantities were the least impaired and those who reported drinking less frequently and in lower quantities were most impaired.

In contrast to motor impairment, none of the drinking habits bore a significant relationship with the degree of impaired inhibitory control displayed by participants ( $ps > 0.21$ ). Figure 2 plots the individual differences in impaired inhibitory control. Some

drinkers displayed considerable increases in inhibitory failures under alcohol, whereas others showed little or no impairment. However, unlike motor coordination, the figure shows that recent heavy drinking was not associated with reduced impairment of inhibitory control.

The possibility that drinking history is related to baseline performance of motor coordination and inhibitory control was also tested. Separate regression analyses were performed by regressing each drinking habit measure on the mean  $p$ -inhibition and motor coordination score following placebo. The analyses revealed no significant relationships between any of the drinking habit measures and motor coordination ( $ps > 0.08$ ) or inhibitory control ( $ps > 0.46$ ) following placebo.

Finally, to determine whether individual differences in baseline skill on the behavioral tasks (i.e., performance under placebo) influenced the degree of alcohol impairment displayed, individual regression analyses were used to test the relationships between placebo performance scores and the impairment scores for inhibitory control and motor coordination. The analyses revealed no significant relationships between baseline performance and impairment for motor coordination ( $p = 0.81$ ) or for inhibitory control ( $p = 0.09$ ). Thus, it appears that the impairment scores we calculated were not influenced by individual differences in skill on the behavioral measures.

#### *Drinking habits and BAC*

Extended periods of heavy drinking can activate additional enzymes, such as the microsomal ethanol oxidizing system, to hasten the metabolism of alcohol resulting in faster elimination and lower BACs. The possibility that such metabolic tolerance could account for the observed relationship between heavy drinking and reduced motor

impairment was examined by determining the degree to which individual differences in drinkers' BACs during testing were related to their drinking habits. Tests of zero-order correlations showed that neither BAC at the beginning of testing (30 min) or at the conclusion of testing (50 min) bore a significant relationship with any drinking habit measure ( $p > 0.27$ ).

### Discussion

This study examined the development of chronic tolerance to alcohol's impairing effects on motor coordination and inhibitory control as a function of recent drinking habits. The results revealed significant relationships between drinkers' recent patterns of alcohol consumption and the degree to which alcohol impaired their motor coordination. These were negative relationships, such that heavier, more frequent drinking and more binge drinking episodes predicted less alcohol impairment of motor coordination. This is in accord with the notion that the quantity and frequency of recent alcohol consumption can contribute to the development of chronic tolerance. However, drinking habits bore no relationship to the degree of alcohol impairment of inhibitory control. These results suggest that heavy alcohol use can lead to tolerance to the drug's motor impairing effects, but not to its disinhibiting effects.

A failure to observe a relationship between drinking habits and the degree to which alcohol impaired subjects' inhibitory control cannot be due to limited range in drinking habits or to a lack of sensitivity of inhibitory control to the impairing effects of alcohol in this study. Participants' drinking habits were carefully assessed over a sustained period of time using a 90 day assessment tool, the timeline follow-back. A wide range of drinking behavior both in terms of typical quantity and frequency of consumption was

observed. Indeed, this range of consumption was sufficient to display a relationship with the degree to which alcohol impaired the subjects' motor coordination. With regard to the sensitivity of our behavioral assessments, we observed significant alcohol impairment of both motor coordination and inhibitory control in response to the dose tested. Moreover, we observed substantial variation in the degree to which subjects were impaired on both tasks.

It is not clear why inhibitory control might fail to develop tolerance to the impairing effects of alcohol as a function of recent heavy drinking. There is a growing body of research that suggests that inhibitory control might be especially vulnerable to the disruptive effects of alcohol compared with other behavioral functions. For example, studies show that inhibitory control is impaired at BACs that are insufficient to impair other behavioral functions, such as reaction time (Fillmore and Vogel-Sprott 1999; de Wit et al. 2000). Alcohol-induced impairment of inhibitory control also fails to show acute recovery (i.e. acute tolerance) within a single drinking session. Studies have shown that impaired motor coordination and reaction time display acute tolerance while response inhibition remains impaired from the ascending to the descending limb (e.g., Fillmore et al. 2005; Ostling and Fillmore 2010). The current findings build upon this earlier work by suggesting that the lack of acute tolerance to alcohol observed in inhibitory control might contribute to the lack of chronic tolerance found in the present study.

A lack of tolerance to alcohol's disinhibiting effects might also contribute to heavy, binge drinking. Many drinkers report intentions to limit their alcohol consumption only to fail and drink excessively, fueling the notion that alcohol reduces control over

consumption in some individuals (Collins 1993). Thus, impairment of inhibitory mechanisms from an initial dose of alcohol could compromise the ability to stop subsequent administrations of alcohol in a drinking situation, resulting in a binge episode. A failure of inhibitory control to adapt to the impairing effects of alcohol even after sustained heavy use might pose a potential risk for impulsive, disinhibited behavior.

The present study focused on one aspect of behavioral control (i.e., the ability to inhibit a prepotent response). However, the findings raise questions about how tolerance might fail to develop to alcohol impairment on a broad range of inhibitory functions. For instance, another component of disinhibition is attentional control, which refers to the ability to ignore irrelevant information. Researchers have identified inhibitory mechanisms that gate the influence of irrelevant information (Houghton and Tipper 1994). Alcohol has been shown to impair these inhibitory mechanisms, resulting in a decreased ability to direct attention from distractions (Fillmore et al. 2000; Abroms and Fillmore 2004). Moreover, such impairments in mechanisms of attentional control have also been implicated as a factor that might contribute to alcohol abuse (Tarter et al 2004; Blume et al 2005). As such, it is important to examine whether alcohol-induced impairments of attentional control also fail to develop tolerance as a function of frequent, heavy drinking. Such a possibility remains to be examined.

As with all correlational studies, this study cannot demonstrate a specific causal-relationship between recent, heavy consumption and tolerance to alcohol's impairing effects on motor coordination. It is reasonable to suggest that the observed relationship between drinking habits and the degree to which alcohol impaired motor coordination is evidence of the physiological development of tolerance as a function of more frequent,

heavy consumption. Indeed, there was wide variation in the drinking patterns in this sample, with heavier drinkers consuming alcohol in vastly greater amounts and with more frequency than lighter drinkers. As such, it is likely that the reduced impairment or motor coordination by heavier drinkers was observed as tolerance. However, other possible explanations for the observed results remain. For instance, it might be the case that for some, a reduced response to alcohol might actually precede heavy drinking. In fact, it has been suggested that differences in the degree to which alcohol impairs behavior represent “behavioral markers” that are related to other factors, such as a family risk of alcoholism, that contribute to the development of alcohol-related problems (e.g., Eng et al 2005; Chung and Martin, 2009). Specifically, it might be the case that a low-level of responding to alcohol might predict later alcohol abuse and dependence, as the drinker must consume more alcohol to achieve the desirable effects (Shuckit, 2009). The present findings are consistent with this notion, in that the low level of impairment shown by some of the drinkers in the sample might promote the heavy drinking that they report.

Finally, it is also possible that other factors might contribute to the degree to which individuals display tolerance. Some factors that differentiate heavier from lighter drinkers include demographics such as age, gender, and socioeconomic status, with those who drink more heavily and use drugs being more likely to be male, younger, and of a lower socioeconomic status than lighter, social drinkers (e.g., Stinson et al 2005). Illicit drug use is another factor that might be related to alcohol tolerance. Many drinkers, particularly those who report heavy, problematic consumption, also engage in regular illicit drug use, such as cocaine and methamphetamine (i.e., Kandel and Yamaguchi 1993; Degenhardt et al. 2001; Wagner and Anthony 2002). Studies suggest that alcohol

tolerance also might be enhanced by a history of co-administration with stimulant drugs (e.g., Fillmore 2003). The sample in our study was comprised of relatively young drinkers who reported little to no use of other drugs. Thus, we could not examine the relation between of alcohol impairment and history of illicit drug use. Given that alcohol tolerance may contribute to abuse by encouraging the use of escalating doses, it is important to determine how alcohol tolerance might be affected by a history of co-administration with other drugs.



Table 3.1  
*Descriptive statistics for drinking habits over the past 90 days as reported on the  
 Timeline Follow-Back (TLFB)*

	Mean	SD	Minimum	Maximum
<u>Measure</u>				
Drinking Days	26.9	17.7	5.0	86.0
Total Drinks	120.5	94.3	20.0	371.0
Binge Days	10.3	10.0	0.0	34.0
Drunk Days	9.1	7.6	0.0	27.0

Figure 3.1

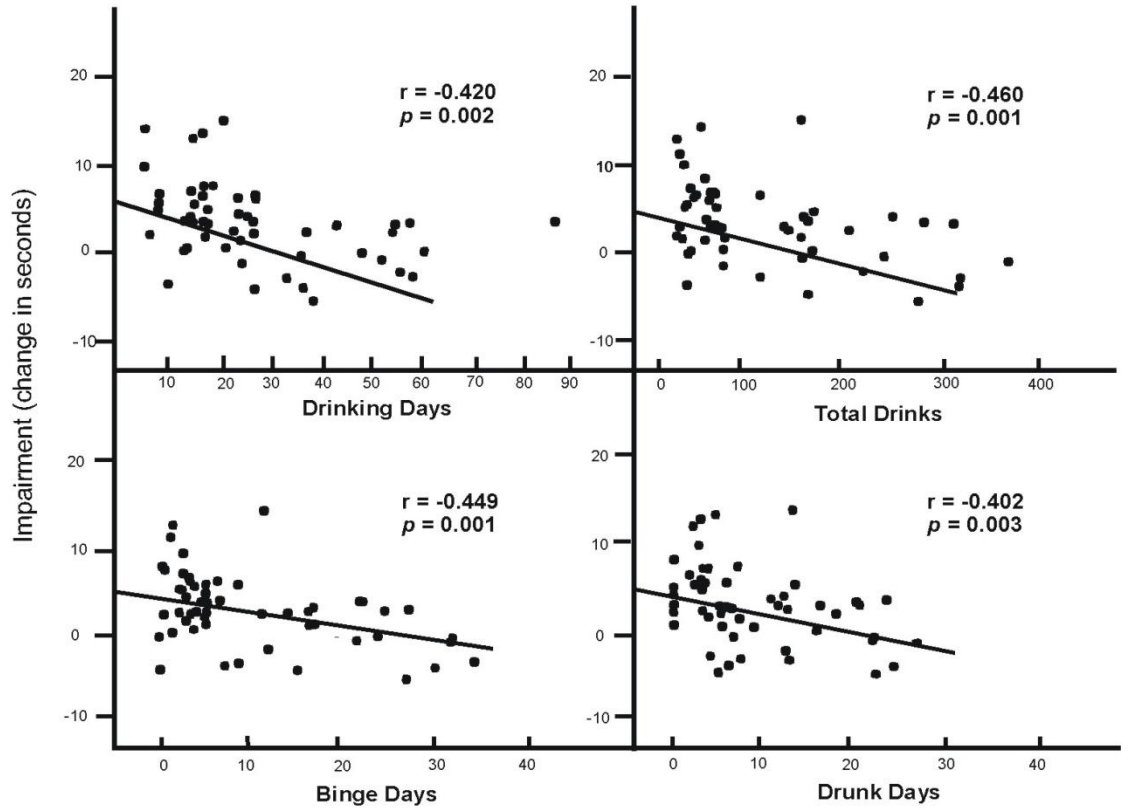


Figure 3.1. Scatter plot of the relationship between drinking habit measures and the change in performance on the grooved pegboard task under placebo to 0.65 g/kg alcohol. Impairment is expressed as an increase in the time (in sec) to complete the test under alcohol versus placebo. The least-squares regression lines are derived from a simple linear regression of each drinking habit measure and the change in performance score. Pearson r correlation coefficients and  $p$  values are presented for each relationship.

Figure 3.2

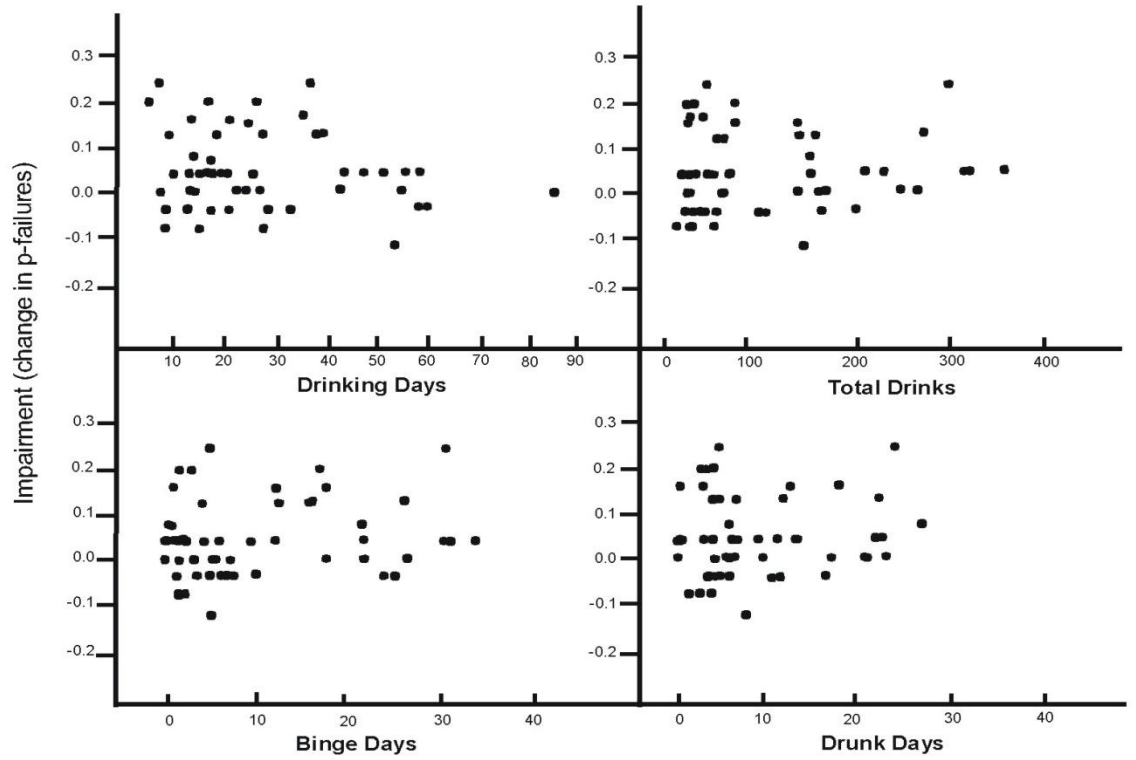


Figure 3.2. Scatterplot of the relationship between drinking habits and the changes in p-failures under placebo and 0.65 g/kg alcohol. Impairment is expressed as an increase in p-failures under alcohol versus placebo.

## Chapter 4

### CAN THE USE OF MULTIPLE STOP SIGNALS REDUCE THE DISINHIBITING EFFECTS OF ALCOHOL?

(STUDY 3; Miller & Fillmore)

#### Introduction

Considerable laboratory research indicates that alcohol impairs a range of skills relevant for everyday activities. Alcohol has been shown to slow simple and complex reaction time, decrease steadiness, impair motor coordination, and reduce the ability to inhibit action (Laberg and Loberg, 1989; Holloway, 1995; Fillmore, 2007). A general determinant of the magnitude of alcohol impairment is the drinker's blood alcohol concentration (BAC) at the time of testing, with impairment increasing as a function of BAC (Holloway, 1995). However, other factors also contribute to the degree of alcohol impairment observed. Intensity of alcohol impairment also depends on the demands of the behavioral functions being examined. Indeed, alcohol impairment intensifies as a function of task demand and complexity (Maylor et al., 1992). Activities that are the most sensitive to the impairing effects of alcohol are those that require drinkers to divide their attention across multiple stimuli (e.g., Steele and Josephs, 1990; Fillmore, 2007). For example, some divided attention tasks require individuals to respond to information presented visually while engaged in a simultaneous listening task. It has been shown that performance on such tasks is more sensitive to the disruptive effects of alcohol compared with performance on simpler tasks with fewer demands. In fact, divided attention performance can be significantly impaired at BACs as low as 20 mg/100 ml (Moskowitz and Robinson, 1998; Holloway, 1995).

Despite evidence that the impairing effects of alcohol can be especially pronounced in environments that require dividing attention across multiple stimuli, some circumstances have been identified whereby the presentation of multiple stimuli can actually facilitate performance. The “redundant signal effect” (RSE) refers to the phenomenon by which individuals respond more quickly and accurately when information is presented as redundant stimuli (e.g., stimuli simultaneously presented aurally and visually), rather than as a single stimulus presented to either modality alone (Todd, 1912). RSE has most commonly been examined in studies of reaction time (RT) and response accuracy (e.g., Miller, 1982; Gondan et al., 2005; Kim et al., 2012). In these studies, participants are required to respond quickly to information presented as either a visual (e.g., a color) or an auditory stimulus (e.g., a tone). RTs to these individual stimuli are then compared with RT to the stimuli when presented simultaneously, as bimodal, redundant signals. Findings indicate that RT to bimodal, redundant signals is faster than RT to either of the single-modal signals. These findings are somewhat counterintuitive given that performance is typically hindered when attention is divided across two modalities. However, the ability to detect and respond to features of a stimulus is markedly enhanced when information about the stimulus is derived simultaneously from more than one sensory input. Although the neurophysiological mechanisms underlying the redundant signal effect are not entirely clear, the effect appears to involve specialized multisensory neurons in the superior colliculus and association cortex that allow for intersensory activation between the visual and auditory channels at some level of processing prior to responding (e.g., Miller, 1986; Mordkoff and Yantis, 1991; Schroger and Widmann, 1998; Stein, 1998; Cavina-Pratesi et al., 2001).

Given evidence that responses are facilitated by redundant signals, it might be the case that redundant signals can also ameliorate the slowing effects of alcohol on RT. To explore this possibility, we examined the extent to which redundant signals reduced the slowing effects of alcohol on RT in healthy adults (Fillmore, 2010). Participants performed a two-choice RT task in which they were required to press a key in response to a stimulus. Stimuli were presented as visual (i.e., letters), auditory (i.e., tones), or redundant signals (i.e., a letter and a tone presented simultaneously). Performance was tested under three alcohol doses: 0.65 g/kg, 0.45 g/kg and placebo (0.0 g/kg). Redundant signals produced faster RT compared with either of the unimodal signals. Alcohol slowed RT to all stimuli. However, the speed advantage produced by the redundant stimuli was maintained at BACs above 80 mg/100 ml. Evidence for an RT advantage to bimodal stimuli under alcohol is important because it challenges the assumption that alcohol impairment is intensified in multi-stimulus environments.

To date, the ability of redundant signals to reduce impairment under alcohol has only been examined with regard to behaviors that involve the execution of actions (e.g., RT, response accuracy). However, alcohol is also well-recognized for its impairing effects on response inhibition. Stop-signal and cued-go/no-go tasks have been used to examine the ability to inhibit prepotent (i.e., instigated) responses (Logan and Cowan, 1984; Miller et al., 1991; Logan, 1994). These tasks require participants to quickly respond to a go signal and to inhibit a response when a stop or no-go signal is presented. Alcohol studies using these tasks find that the drug reliably increases failures to inhibit responses to stop-signals in a dose-dependent manner (Marczinski and Fillmore, 2003; Fillmore et al., 2005). Moreover, alcohol-induced disruptions of inhibitory control have

been linked to risky behaviors such as excessive binge drinking in humans and laboratory animals (Poulos et al., 1998; Weafer and Fillmore, 2008). As such, it is important to determine whether redundant signals might potentially reduce the impairing effects of alcohol on the ability to inhibit action.

There is some evidence that redundant inhibitory signals can enhance inhibitory control in the sober state (i.e., Cavina-Pratesi et al., 2001; Gondan et al., 2005; Gondan et al., 2010). However, the possibility that redundant signals can ameliorate the impairing effects of alcohol on inhibitory control is uncertain. Inhibitory control appears especially vulnerable to the disruptive effects of alcohol. For instance, studies show that inhibitory control is impaired at low BACs that do not slow RT (Fillmore and Vogel-Sprott, 1999; de Wit et al., 2000). Alcohol-induced impairments of inhibition also persist longer following a dose than other behaviorally impairing effects, and drinkers show little tolerance to the disinhibiting effects of the drug despite a history of heavy drinking (Fillmore and Vogel-Sprott, 1995; Fillmore et al., 2005; Miller et al., 2012). Such vulnerability to alcohol impairment raises questions about whether redundant signals can improve response inhibition under alcohol to the same extent that they enhance response activation under the drug.

Drinkers encounter rich stimuli in their environments which require them to process multi-sensory signals that direct behavior. Thus, the present study provides a laboratory analysis of how drinkers respond to bimodal stimuli by examining whether the impairing effects of alcohol on inhibitory control might be altered by the presentation of redundant inhibitory signals. The effect of redundant inhibitory signals was tested by comparing response inhibition to a visual no-go signal presented alone or accompanied

by a redundant auditory no-go signal. To test the possibility that redundant inhibitory signals could strengthen inhibition and reduce the disinhibiting effects of alcohol, performance was tested following both placebo (0.0 g/kg) and a moderate dose of alcohol (0.65 g/kg alcohol). The effect of redundant activation signals on alcohol impairment of response activation was also assessed in the study.

## Method

### *Participants.*

Fifty-six adults between the ages of 21 and 33 (mean age = 23.1,  $SD = 3.0$ ) participated in this study. Volunteers were recruited by flyers, posters, and newspaper advertisements seeking adults for studies of the effects of alcohol on cognitive functions. Volunteers were screened using health questionnaires and a medical history interview. Those who reported any contraindication to alcohol, impaired cardiovascular functioning, seizure, head trauma, central nervous system (CNS) tumors, or past histories of psychiatric disorder (i.e., Axis I, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition [DSM-IV]*) were excluded from participation. Those who reported alcohol dependence, as determined by a score of 5 or higher on the Short-Michigan Alcoholism Screening Test (S-MAST; Selzer et al., 1975) were also excluded. Any other high-risk indicators of alcohol dependence, including prior treatment for an alcohol use disorder or conviction for driving under the influence also precluded participation.

Volunteers had to report drinking at least once per month in an amount of at least two drinks to participate. With regard to other drug use, the majority of the sample reported using caffeine ( $n = 47$ ). Thirteen participants reported smoking cigarettes in the amount of less than a pack of cigarettes a day. Nine reported some past month use of



marijuana. No other drug use in the past month, including stimulants, opiates, or cocaine, was reported. Participants were in good health with no contraindications to drinking. The University of Kentucky Medical Institutional Review Board approved the study, and participants received \$85.

### *Materials and Measures*

*Cued Response Inhibition Task.* Response inhibition was measured using a computerized cued go/no-go model used in previous research (e.g., Marcziński and Fillmore, 2003; Fillmore et al. 2005) and was operated by E-Prime experiment generation software (Schneider et al., 2002). A trial began with a fixation point (+) for 800 ms, followed by a blank screen for 500 ms. A rectangular-shaped cue was then displayed for one of four randomly occurring stimulus onset asynchronies (SOAs = 100, 200, 400, and 800 ms) before a go or no-go target appeared for 1000 ms. If the rectangle turned green (go target) subjects were to make a computer key press as quickly as possible. If the rectangle turned blue (no-go target) they were to inhibit a response. A test consisted of 250 trials with 700 ms inter-trial intervals and required 20 minutes to complete.

The orientation of the rectangular cue signaled the probability that a go or no-go target would appear. A vertically-oriented rectangle (height = 7.5 cm, width = 2.5 cm) turned green on 80% of the trials and turned blue on 20% of the trials. A horizontally-oriented rectangle (height = 2.5 cm, width = 7.5 cm) turned green on 20% of the trials and turned blue on 80% of the trials. Therefore, vertical and horizontal-oriented rectangles operated as go and no-go cues, respectively. The measure of interest was the proportion ( $p$ ) of inhibition failures to no-go targets in the go cue condition. Presentation of the go cue increases response preparation (i.e., produces a response prepotency),

making it more difficult to inhibit a response when the no-go target unexpectedly appears. The disinhibiting effects of alcohol are most evident in this cue condition (Marczinski and Fillmore, 2003), and poorer inhibitory control is indicated by greater p-inhibition failures (i.e., disinhibition).

There were two versions of this task containing either single or redundant no-go targets. For the single version, the signal to inhibit a response was the single, visual stimulus (the color blue), as described above. In the redundant version (Figure 4.1), the no-go target (blue) was always coupled with the simultaneous presentation of a brief 1200 Hz auditory tone.

*Cued Response Activation Task.* RT was measured by a simple cued response task operated by E-prime Experiment Generation software (Schneider, et al., 2002). Participants first saw a rectangular shaped cue that was displayed for one of four randomly occurring SOAs (100, 200, 400, or 800 ms). On half the trials, the cue turned green for 1000 ms, followed by a 700 ms inter-trial interval. Participants were instructed to respond as quickly as possible to the target by pressing the forward slash (/) key. The orientation of the cue (upright vs. flat) signaled the probability that the target would appear on a given trial. An upright cue (valid cue) correctly signaled the onset of the target on 80% of the trials. Thus, valid cues allowed participants to prepare to respond, which speeds RT. The target followed the flat cue on only 20% of the trials (invalid cue). On these trials, participants are unprepared to respond, which slows their RT to the unexpected appearance of the target. Response activation was measured as the mean RT to targets in this invalid cue condition because RT to non-cued stimuli is more sensitive to alcohol's slowing effects on behavior than responses to the cued stimuli (Marczinski

and Fillmore, 2003). A test was comprised of 250 trials and required 20 minutes to complete. Responses less than 100 ms and greater than 1000 ms were excluded. These outliers were infrequent, occurring on average less than 0.25% of the trials for which a response was observed (i.e., less than one trial per test).

There were two versions of this task containing either single or redundant go targets. For the single version, the signal to activate a response was a single, visual stimulus (the color green), as described above. In the redundant version, the signal (green) was always coupled with the simultaneous presentation of a brief 1200 Hz auditory tone (Figure 4.2).

*Timeline follow-back.* The timeline follow-back (TLFB; Sobell and Sobell, 1992) assessed the typical quantity and frequency of weekly drinking over the past 3 months. Two measures of drinking habits were obtained: (1) frequency; the average number of drinking occasions per week, and (2) quantity; the average number of standard drinks per drinking occasion.

*Subjective Intoxication* Participants rated their degree of subjective intoxication on a visual analog scale by placing a vertical line at the point representing the extent to which they “feel intoxicated” on a 100-mm horizontal line ranging from 0 mm “not at all” to 100 mm “very much.”

#### *Procedure*

Participants were individually tested in the Behavioral Pharmacology Laboratory of the Department of Psychology between 10 a.m. and 6 p.m. Sessions were scheduled at least 24 hours apart and were completed within two weeks. Participants were instructed to fast for four hours prior to each alcohol session, and to refrain from consuming alcohol

or any psychoactive drugs for at least 24 hours before sessions. Prior to each session, subjects provided urine samples that were tested for drug metabolites including amphetamine, barbiturates, benzodiazepines, cocaine, opiates, and tetrahydrocannabinol (On Trak Teststicks, Roche Diagnostics Corporation, Indianapolis, IN, USA) and in women, human chorionic gonadotropin (hCG hormone), to verify that they were not pregnant (Mainline Confirms HGL, Mainline Technology, Ann Arbor, MI, USA). Any participants who tested positive for recent drug use or for pregnancy were excluded from participating. Breath samples were also provided at the beginning of each session to verify a zero BAC.

*Familiarization session.* After providing informed consent, subjects provided proof of age to verify that they were at least 21 years old. They completed questionnaires concerning health status, drinking habits, and demographic characteristics. Half of the participants ( $n = 28$ ) were assigned to complete the cued response inhibition task, and the other half were tested on the cued response activation task. For each of these test conditions, half of the participants ( $n = 14$ ) were tested in the single condition, and the other half were tested in the redundant condition. Assignment to task and condition was random with the constraint that each of the four groups was comprised of an equal number of 7 men and 7 women. Participants performed a familiarization test in their respective conditions.

*Test Sessions.* Performance was tested under two doses of alcohol: 0.0 g/kg (placebo) and 0.65 g/kg. Doses were administered during separate test sessions, and dose order was counterbalanced across participants. Sessions were separated by a minimum of one day and a maximum of one week. The alcohol dose was calculated on the basis of

body weight and administered as absolute alcohol mixed with three parts carbonated soda. The placebo dose (0.0 g/kg) consisted of a volume of carbonated mix that matched the total volume of the 0.65 g/kg alcohol drink. A small amount (3 ml) of alcohol was floated on the surface of the beverage. It was sprayed with an alcohol mist that resembled condensation and provided a strong alcoholic scent as the beverage was consumed. In similar studies, individuals report that this beverage contains alcohol (Fillmore and Vogel-Sprott, 1998). Drinks were consumed in six minutes. Following 0.65 g/kg alcohol, a peak BAC of 80 mg/100 ml was expected to occur approximately 60 minutes after drinking (Fillmore and Vogel-Sprott, 1998).

Testing occurred on the ascending limb of the BAC curve. Task performance was tested 40 minutes after drinking began, and concluded at 60 minutes post-drinking (i.e., near the peak BAC following the active dose), at which point participants completed the subjective intoxication ratings. BACs were measured at 40 and 60 minutes post-drinking (i.e., before and after testing and completion of subjective intoxication ratings). Breath samples were also obtained at these times during the placebo session ostensibly to measure BAC. After testing, participants received a meal and were released once their BAC fell below 20 mg/100 ml.

#### *Data Analyses*

For the two groups tested on the cued response inhibition task, a 2 Dose (0.0 g/kg vs. 0.65 g/kg) X 2 Target Condition (single vs. redundant) ANOVA of p-inhibition failures tested the effects of alcohol and target condition on their inhibitory control. For the two groups tested on the cued activation task, the effects of dose and target condition were examined by a 2 (Dose) X 2 (Target Condition) ANOVA of their RT scores. For

both behavioral inhibition and activation, the effect of alcohol in each target condition was tested by planned comparison *t* tests contrasting performance under alcohol to performance following placebo. Initially, all analyses were conducted with gender as a factor. There were no significant main effects or interactions involving gender for either inhibitory failures or RT. Therefore, all analyses excluded gender as a factor.

## Results

### *Demographics and drinking habits*

Table 4.1 presents the ages and drinking habits for participants in each of the four target condition groups. A one-way ANOVA revealed no significant differences in age among the four groups,  $F(3, 52) = 1.15, p = 0.34$ . The mean age for the entire sample was 23.1 ( $SD = 3.02$ ) years. With regard to drinking habits, a one-way ANOVA showed no target condition group differences in the weekly frequency,  $F(3, 52) = 0.60, p = 0.62$ , or quantity of consumption,  $F(3, 52) = 1.14, p = 0.34$ . For the entire sample, mean weekly frequency of drinking was 1.99 ( $SD = 1.22$ ), and the mean typical quantity per occasion was 4.67 drinks ( $SD = 2.28$ ).

*Blood Alcohol Concentrations* A 4 (target condition group) X 2 (time) ANOVA of BACs following 0.65 g/kg alcohol revealed no significant main effect of group, or a group X time interaction ( $ps > 0.14$ ). A main effect of time was obtained due to the rise of BACs during the session,  $F(1, 52) = 45.39, p < 0.001$ . The entire sample's mean BACs at 40 and 60 min post-drinking were 83.1 mg/100 ml ( $SD = 18.94$ ) and 93.7 mg/100 ml ( $SD = 20.33$ ), respectively. No detectable BAC was observed following placebo administrations.

*Cued Response Inhibition* Figure 4.3 shows the mean p-inhibition failures to the single and redundant targets on the cued go/no-go task. The 2 (dose) X 2 (target condition) ANOVA revealed a significant main effect of dose,  $F(1, 26) = 14.04, p < 0.01, \eta^2 = 0.33$ . There was no significant effect of target condition,  $F(1, 26) = 0.08, p = 0.93, \eta^2 = 0.01$ , or a dose X condition interaction,  $F(1, 26) = 2.95, p = 0.10, \eta^2 = 0.07$ . Planned comparison tests showed that compared with placebo, alcohol significantly increased p-inhibition failures in the redundant target condition,  $t(13) = 3.11, p < 0.01, d = 0.83$ , and in the single target condition,  $t(13) = 2.12, p < 0.05, d = 0.56$ .

*Cued Response Activation* Figure 4.4 shows the mean RTs in the single and redundant target conditions in the cued response activation task. A 2 (dose) X 2 (target condition) ANOVA revealed significant main effects of dose,  $F(1, 26) = 15.24, p < 0.01, \eta^2 = 0.21$ , and target condition,  $F(1, 26) = 59.92, p < 0.001, \eta^2 = 0.72$ . No significant interaction was observed,  $F(1, 26) = 2.59, p = 0.12, \eta^2 = 0.01$ . Planned comparisons showed that alcohol significantly slowed RT compared with placebo in both the single,  $t(13) = 3.03, p < 0.01, d = 0.34$ , and the redundant conditions,  $t(13) = 2.78, p < 0.05, d = 0.74$ . Two sample  $t$  tests comparing the target conditions revealed significantly faster RTs in the redundant condition following both placebo,  $t(26) = 8.03, p < 0.001, d = 3.00$  and alcohol,  $t(26) = 6.66, p < 0.001, d = 2.52$ .

*Subjective intoxication* A 4 (target condition) X 2 (dose) ANOVA of subjective intoxication ratings revealed no significant main effect of target condition, or a condition X dose interaction ( $ps > 0.25$ ). A main effect of dose was obtained due to higher ratings of intoxication in response to 0.65 g/kg alcohol compared with placebo,  $F(1, 52) = 212.57, p < 0.001, \eta^2 = 0.79$ . For the entire sample, the mean ratings of subjective

intoxication following placebo and alcohol were 12.0 ( $SD = 14.9$ ) and 57.0 ( $SD = 20.9$ ), respectively.

## Discussion

The present study sought to determine whether redundant stimuli might reduce the impairing effects of alcohol on response inhibition and activation. Previous work has shown that redundant activation signals can improve the speed and accuracy of responding and that such facilitation can be observed following alcohol (e.g., Fillmore, 2010). Indeed, in the current study, drinkers responded more quickly to redundant, visual-auditory activation signals compared with single signals. Moreover, although alcohol slowed RT in both redundant and single target conditions, the RT speed-advantage in the redundant condition was maintained even under 0.65 g/kg. In fact, RT in the redundant condition was considerably faster than RT in single target condition, regardless of the dose condition. Thus, redundant signals had a robust facilitating effect on RT even following a dose of alcohol which was sufficient to impair (i.e., slow) RT.

The study also showed that alcohol impaired inhibitory control by increasing inhibitory failures in both the single and redundant target conditions. However, unlike RT, redundant signals did not enhance inhibitory control in either the sober or intoxicated states. In fact, the magnitude of alcohol impairment in the redundant condition was larger than the degree of impairment in the single target condition. Thus, not only did redundant signals fail to improve inhibitory control, but they may possibly contribute to greater alcohol impairment of inhibition compared with single inhibitory signals.

To date, the majority of research on the redundant signal effect has focused on the execution of actions (e.g., speeding RT). Although a few studies of response inhibition



have shown facilitating effects of redundant signals in sober adults (i.e., Cavina-Pratesi et al., 2001; Gondan et al., 2005), no research has explored the possibility that redundant signals could ameliorate alcohol-induced deficits of inhibitory control. The current finding that redundant inhibitory signals do not reduce impairment under alcohol is contrary to findings on response execution and raises questions about why redundant inhibitory signals failed to reduce the disinhibiting effects of alcohol.

A possible explanation for this finding concerns alcohol's effects on information processing capacity. Evidence suggests that alcohol impairs behavioral control by reducing the drinker's capacity to process information from multiple sources, particularly when the information signals that behaviors should be inhibited (Moskowitz and De Pre, 1968; Medina, 1970; Steele & Southwick, 1985; Fillmore and Van Selst, 2002; Bartholow et al., 2003). Any alcohol-induced capacity limitation in the present study could have limited the ability to effectively integrate information, especially when the information is presented to two or more modalities (visually and aurally). Such an account raises the possibility that redundant inhibitory signals could actually ameliorate alcohol impairment if presented to the same modality (e.g., two visual signals), thereby placing less demand on information processing. Indeed, RSE in the execution of responses is often demonstrated using redundant signals within the same modality (Marzi et al., 1996; Murray et al., 2001). A logical next step in this new area of research is to test the possibility that such single-modal redundant signals could improve inhibitory control, particularly under alcohol.

It should be noted that this study did not examine responses to "go" and "no-go" signals that were presented as an auditory stimulus alone. There were two reasons for this

omission. First, responses to simple auditory stimuli do not differ from responses to simple visual stimuli in these types of tasks. Studies of response activation find that RTs to auditory stimuli are similar to visual stimuli, and that redundant signals show comparable improvement over single signals regardless of their modality (Cheng et al., 2010; Fillmore, 2010). Second, the tasks used in the study examined response inhibition and activation using a cued response model in which an initial stimulus (e.g., a rectangle) provided preliminary information that a specific response would be required on a given trial. This allowed us to examine inhibitory control when there was a response prepotency by first presenting a go cue following by a no-go signal. The cues were visual stimuli (i.e., rectangular shapes in one of two orientations). Visual go cues generally do not increase the pre-potency of responses to auditory signals (Miller et al., 1991). Thus, to ensure the response prepotency effects across target condition, we compared only target conditions that involved visual signals (visual and visual + auditory).

Additionally, this study only examined the effect of redundant signals on alcohol impairment of behavioral effects on the ascending limb of the BAC curve. We know, however, that the magnitude of impairment observed on the descending limb is not always the same as that on the ascending limb, even when BACs are comparable. Indeed, studies examining acute tolerance to the impairing effects of alcohol compare performance on tasks at comparable BACs on the ascending and descending limb. Acute tolerance is observed as a reduction in alcohol impairment on the descending limb of the BAC curve compared with the ascending limb, and has been shown to develop for several behaviors, including reaction time (i.e., Fillmore et al., 2005; Fillmore & Vogel-Sprott, 1996). However, several studies have failed to observe the development of acute

alcohol tolerance for measures of inhibitory control (e.g., Fillmore et al., 2005; Ostling & Fillmore, 2010; Weafer & Fillmore, 2012). Given that drinkers will encounter multi-sensory demands even as BACs decline, it is also important to consider how redundant signals might affect alcohol impairment of activation and inhibitory mechanisms on the descending limb of the BAC curve.

Finally, it is important to consider the ecological relevance of studying drug effects in the context of redundant environmental signals. Common technologies (e.g., cars, navigation systems, phones, and computers) are becoming increasingly complex in their ability to deliver information to the user. One aspect of this complexity concerns the ability of these devices to provide redundant information to two or more modalities (e.g., visual readouts accompanied by verbal prompts and/or information). The tacit assumption is that such redundant information should have facilitating effects on behavior. However, little is known about how such redundant information affects behaviors in the drugged state, when information processing capacity is compromised in some manner. Indeed, the present findings suggest that acts of control, such as the inhibition of behavior, could be disrupted by such redundant information when an individual is intoxicated. As such, it is important to understand how alcohol and other drugs affect not only simple stimulus-response behaviors, but also the ability to execute behavioral control in contexts where information is presented redundantly to two or more modalities. The present study provides a useful model to begin such research.

Table 4.1

*Descriptive statistics and drinking habits for the groups of participants who completed the single and redundant target conditions in the go/no-go and cued activation tasks, n=14 per group.*

Target condition	Go Response Inhibition Task				Cued Activation Task			
	Single		Redundant		Single		Redundant	
Men: Women	7:7		7:7		7:7		7:7	
	M	(SD)	M	(SD)	M	(SD)	M	(SD)
Age (years)	22.6	(3.3)	22.1	(1.5)	24.0	(3.3)	23.6	(3.9)
Frequency	1.7	(1.0)	1.8	(0.9)	2.3	(1.6)	2.1	(1.2)
Quantity	4.7	(2.3)	3.7	(1.2)	5.2	(2.8)	5.0	(2.4)
SMAST score	0.9	(1.9)	0.1	(0.5)	0.3	(0.7)	0.3	(1.1)

*Frequency = typical number of drinking days per week*

*Quantity = mean number of standard drinks consumed per drinking occasion*

Figure 4.1

## Redundant Cued Activation Task

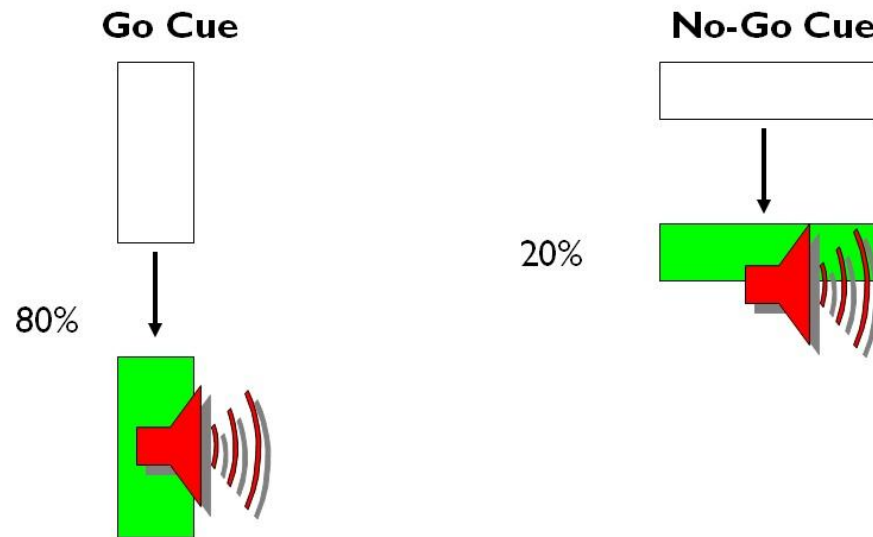


Figure 4.1. Schematic of the redundant condition of the cued activation task. The figure shows go and no-go targets (vertical and horizontal rectangles, respectively), and their likelihood of preceding a go target (a green rectangle). In this redundant condition, the go target is paired with an auditory tone.

Figure 4.2.

## Redundant Cued Response Inhibition Task

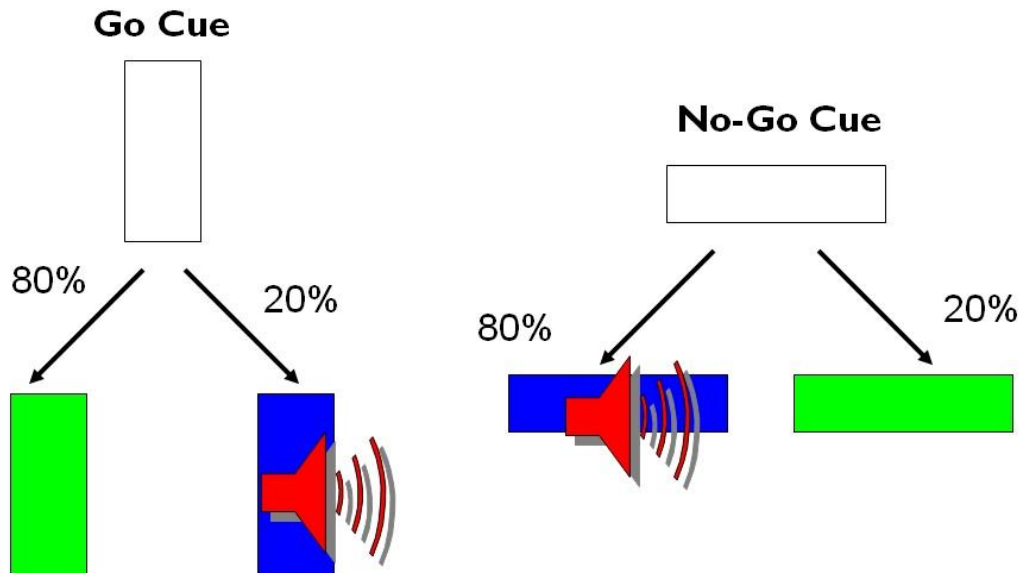


Figure 4.2. Schematic of the redundant condition of the cued response inhibition task.

The figure shows go and no-go cues (vertical and horizontal rectangles, respectively) and their likelihood of preceding a go target (green) or a no-go target (blue). As can be seen, in this redundant condition, no-go targets are simultaneously paired with an auditory tone.

Figure 4.3

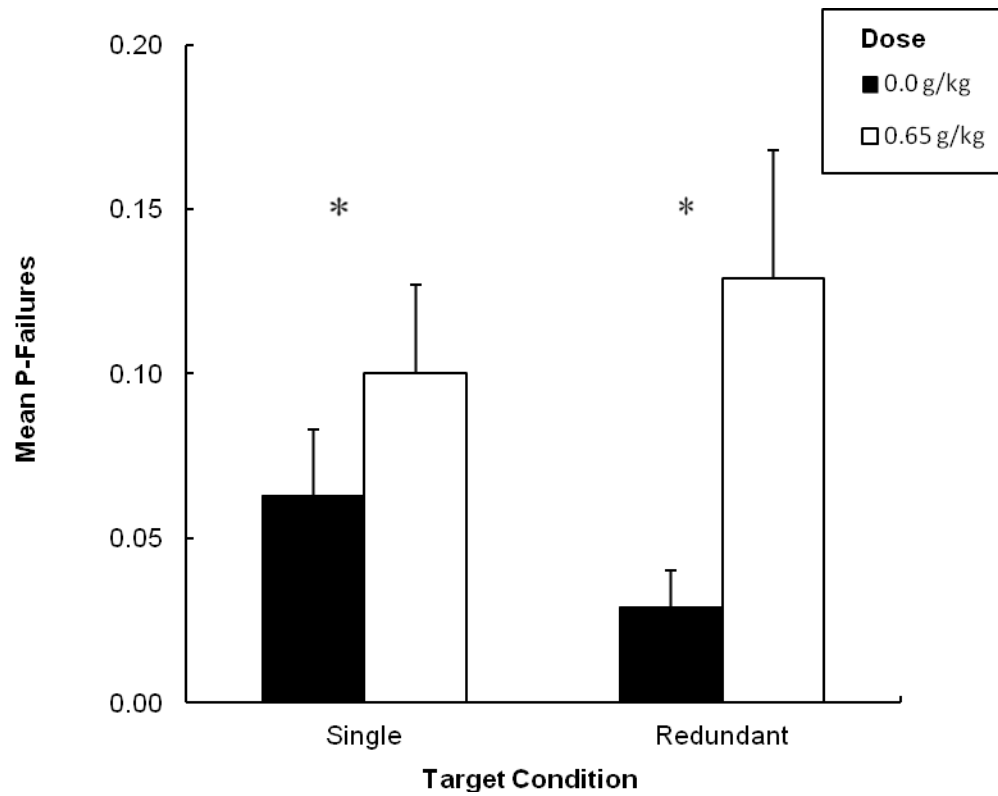


Figure 4.3. Mean p-failures on the go/no-go task following 0.0 g/kg (placebo) and 0.65 g/kg alcohol for those in the single and redundant inhibitory signal groups. Capped vertical lines show *SEMs*. Asterisks indicates significant difference in p-failures under alcohol compared with placebo,  $p < 0.01$ .

Figure 4.4.

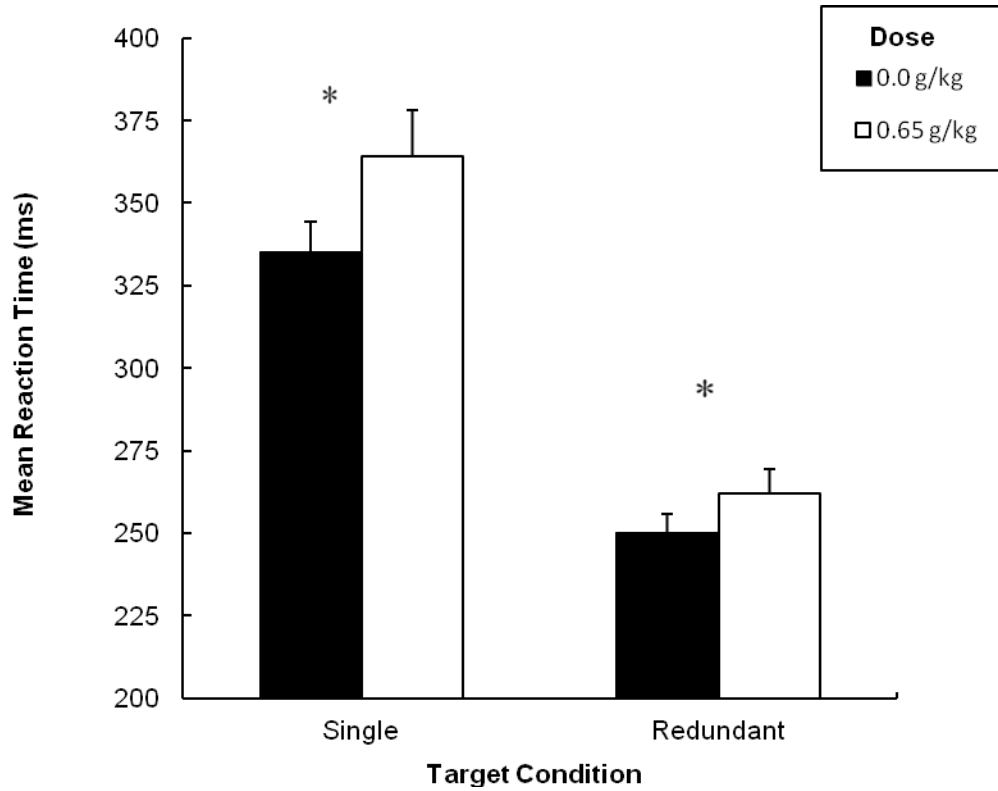


Figure 4.4. Mean RT in milliseconds on the cued response activation task following 0.0 g/kg (placebo) and 0.65 g/kg alcohol for those in the single and redundant activation signal groups. Capped vertical lines show *SEMs*. Asterisks indicate significant difference in RT under alcohol compared with placebo,  $ps < 0.001$ .



## Chapter 5

### GENERAL DISCUSSION

This dissertation examined the development of alcohol tolerance for inhibitory mechanisms of behavioral control in three contexts in which tolerance has been shown to develop for a host of other prototypic behaviors. Study 1 examined the rate of recovery of inhibitory control and other behaviors in response to alcohol along the BAC curve to test the hypothesis that inhibitory control would not fully recover from alcohol's impairing effects as BACs approached zero. Results showed that alcohol-induced impairments of inhibitory control persisted nearly five hours after drinking occurred, as BACs approached zero. By contrast, performance on tasks measuring reaction time, motor coordination, and ratings of subjective intoxication displayed full recovery by this time. Study 2 tested the hypothesis that chronic tolerance to alcohol's impairing effects as a function of recent alcohol consumption would be observed for motor coordination, but that no such relationship between drinking habits and alcohol-induced impairment of inhibitory control would be observed. Indeed, the results provided evidence for tolerance for motor coordination, such that recent frequent, heavy consumption was associated with less alcohol impairment compared with lighter drinking. By contrast, drinking habits bore no such relationship to the degree of alcohol impairment of inhibitory control, indicating a lack of tolerance. Finally, study 3 aimed to determine whether increasing the signal strength of stimuli indicating the need to inhibit responses (i.e., by presenting them as bimodal, redundant signals) would reduce the degree to which alcohol impaired inhibitory control. It was hypothesized that redundant signals would reduce the degree to which alcohol impaired response execution, but would have no such protective effects on

response inhibition. The results showed that, unlike the enhancing effects of redundant activation signals on response time, redundant inhibitory signals did not improve inhibitory control in either the sober or intoxicated states. Instead, following alcohol, redundant inhibitory signals appeared to contribute to even more pronounced impairment of inhibition compared with single inhibitory signals.

Taken together, these studies provide additional, compelling evidence that inhibitory mechanisms of behavioral control do not develop tolerance to the impairing effects of alcohol under the same contexts for which tolerance is observed for other behaviors. This was observed through examinations of both the pharmacological and environmental factors that influence alcohol tolerance. The results of these three studies consistently showed that the degree to which alcohol impairs behaviors such as behavioral activation and motor coordination can be reduced as a result of pharmacological and environmental circumstances, whereas these factors have no such effect on inhibitory mechanisms. Together, the findings contribute to the growing body of literature suggesting that inhibitory control is particularly sensitive to the impairing effects of alcohol compared with other aspects of behavior, and have implications for understanding the behaviorally-disruptive effects of the drug.

#### *Implications of the Findings*

The patterns of impairment and recovery revealed by the results of this dissertation improve our understanding of the relationship between alcohol-induced disinhibition and the problematic behaviors often displayed by intoxicated drinkers. For instance, the findings are consistent with previous findings suggesting that alcohol differentially impairs inhibitory and activation mechanisms (e.g., de Wit et al., 2000;

Fillmore & Vogel-Sprott, 1999; 2000; Mulvihill et al., 1997). Evidence for a lag in tolerance for inhibitory versus activational mechanisms suggests that, as blood alcohol declines, drinkers' response inhibition remain disrupted, despite having unimpaired ability to activate responses (e.g., Pihl et al., 2003; Schweizer et al., 2004). The term "activational bias" has been used to describe the observation that acute tolerance following a single administration of alcohol develops readily for the activation of behavior while inhibitory mechanisms remain impaired on the descending limb of the BAC curve. Now, with the current findings, we see evidence for this activational bias in additional contexts: as BACs approach zero, following recent heavy, consumption, and in the presence of increased strength of stimuli indicating the need to activate or inhibit a response (i.e., redundant signals). This additional support for an activation bias of alcohol disruption and recovery has meaningful implications for understanding some of the behaviorally-disruptive effects of the drug.

It is important to consider how this activational bias sets the stage for binge drinking and /or other disinhibited behavior in a drinking situation. Although it is understood that alcohol-induced impairments of inhibitory control can increase the propensity to continue drinking, it is likely that the pairing of disrupted inhibitory control with in-tact motor and activational responses amplify the risk for continued consumption during a drinking episode. For instance, drinkers who do not perceive themselves to be significantly intoxicated, due to in-tact motor coordination and reduced, subjective feelings of intoxication, might continue to drink in response to lowered inhibitions as well as an effort to reinstate the initial effects of the drug. We now know that this can occur even at highly elevated BACs, which can result in continued drinking to the point

of gross intoxication, and/or contribute to dangerous decision making, such as operating a motor vehicle.

Understanding the relationship between inhibitory mechanisms and other higher order processes shed light on how such acute changes in the ability to inhibit responses can result in such maladaptive behaviors while drinking. Alcohol-induced impairments of inhibitory mechanisms might actually exert considerable disruptive influence on higher-order executive cognitive functions. Many fundamental cognitive and perceptual processes, such as inhibitory mechanisms, are thought to operate in “bottom-up” manner, exerting increasing influence at each stage of higher-order cognitive functions. Thus, the alcohol-induced disturbances of basic behavioral control mechanisms, such as inhibitory processes, might actually result in pronounced impairments of the higher cognitive operations for which they serve (e.g., decision-making, planning goal maintenance, etc). As such, the impairments we observed in inhibitory mechanisms have far reaching effects on behavior that can lead to serious, negative consequences stemming from a broad, “loss of control” over behavior.

In considering how impairments in inhibitory control can contribute to problematic behavior in “real world” settings, it is necessary to consider the properties of the environmental cues signaling the need to suppress behavior. There is evidence that various characteristics of “no-go” cues can impact the vulnerability of inhibitory mechanisms. Indeed, this dissertation showed that cues presented bimodally, as redundant signals, do not serve to strengthen the signal to stop a response. In fact, following alcohol, impairments on inhibitory control might actually be more robust. Consistent with the activation bias, redundant signals actually reduced alcohol

impairment of behavioral activation. Other studies have also cue-induced disruptions of inhibitory control. For instance, Weafer and Fillmore (2012) examined the degree to which alcohol images can disrupt mechanisms of behavioral control. Sober participants performed a laboratory task that measured response activation and inhibition in response to alcohol-related or neutral images. The study showed that inhibitory failures were more frequent following alcohol images compared to neutral images. By contrast, alcohol-related images had no effect on response times during the task. Thus, altering go and no-go cues by presenting them as alcohol images disrupted response inhibition, but had no such impairing effect on behavioral activation. To date, typical laboratory assessments examine behavioral control in response to arbitrary stimuli. However, given that everyday perception is multisensory, these two studies provide unique models of drinkers' real-world environments by assessing alcohol's effects on inhibitory mechanisms of behavior in response to multisensory stimuli and alcohol-related stimuli. As such, more studies such as these are necessary for understanding behavioral control in ecologically valid environments which reflect settings drinkers might actually encounter. The results of these studies are revealing in terms of how the activational bias of disruption occurs in real-world settings, in the face of meaningful cues that appear to represent high-risk alcohol consumption scenarios.

#### *Disinhibition as a Determinant and Consequence of Alcohol Abuse*

While the results of this dissertation help to explain how alcohol-induced changes in drinkers' inhibitory mechanisms contribute to binge drinking or alcohol abuse, it is also important to consider how individuals with deficits in inhibitory control are at a heightened risk for alcohol and other drug abuse. Longitudinal and cross-sectional studies

have consistently provided support for the idea that impulsive individuals are more likely to initiate drug use and develop drug-related problems and dependence (Barthalow & Wood, 2000; Cloninger 1986; Eysenck 1993; Eysenck & Eysenck 1968). More specifically, this relationship has also been shown for disinhibition, assessed by both trait and behavioral tests. For instance, Tarter et al (2007) showed that disinhibited traits in childhood predicted substance use disorders at age 22, using both questionnaires and neuropsychological tests. In another study, Habeych et al (2006) used an oculomotor response inhibition task to show that children who displayed difficulty in withholding visual responses were at increased risk for alcohol-use disorders.

The aforementioned studies show that measures of impulsive behaviors, and more specifically, disinhibited behaviors, predict early onset and higher likelihood of alcohol and substance use, and studies comparing drug users and non-users on measures of impulsivity also suggest this relationship. A great deal of research has provided evidence that drug users score higher on self-report indices of impulsivity (i.e., Moeller et al., 2001; Sher & Trull, 1994). Similar relationships have been demonstrated for behavioral measures of impulsivity, such as delayed discounting and go/no-go tasks (Fillmore & Rush, 2002; Madden et al., 1997; Monerosso et al., 2005).

One group that has been of particular interest in studies of the relationship between trait impulsivity and substance use are individuals characterized by deficits in inhibitory control and impulsivity (i.e., those with attention deficit hyperactivity disorder, or ADHD). A wealth of research has shown that those with ADHD are at an increased risk for substance abuse and addiction (Goodwin et al., 1975; Tarter et al., 1977). With regard to alcohol abuse, longitudinal studies have shown an increase incidence of alcohol abuse

in adults with ADHD compared with controls (Krause et al, 2002; Ohlmeier et al., 2008; Rasmussen & Gilberg, 2000). Moreover, the pattern of consumption and drug use in adults with ADHD is marked by early experimentation, which is indicative of problematic use reflecting dependence (Carroll & Rounsaville, 1993; Levin & Kleber 1995; Wilens et al., 1997). Explanations for the high comorbidity of ADHD and substance use and dependence point to the marked impulsive nature of these individuals. Deficits across the range of impulsivity appear to play an important role in the development of substance use problems in ADHD individuals. The tendency to engage in rash action, risky decision making, need for stimulation, and an inability to suppress maladaptive behaviors have all been used to explain the heightened incidence of substance use problems in this group (i.e., Ohlmeier et al., 2008).

Another important issue related to the association between disinhibition and substance abuse concerns individual differences in the sensitivity to alcohol's disinhibiting effects. As mentioned above, individuals with chronic deficits in inhibitory control (i.e., those with ADHD) have higher rates of substance abuse compared with their healthy peers. Those with ADHD perform worse on laboratory tasks of inhibitory control compared with healthy controls (i.e., Alderson et al., 2007; Barkley 1997; Oosterlaan et al., 1998; Tannock 1998). Moreover, recent findings indicate that this population also shows a heightened sensitivity to the disinhibiting effects of alcohol compared with controls. For instance, Weafer et al (2009) showed that adults with ADHD made significantly more inhibitory failures on the cued go/no-go task compared with controls, and were impaired at BACs that did not disrupt the performance of controls. Similar results have been shown for other "at-risk" groups, including high sensation seekers and

binge drinkers. Adults who obtained elevated scores on a clinical measure of sensation seeking showed greater disinhibition following an acute dose of alcohol compared with low sensation seekers (Fillmore et al., 2008).

Consumption rates also appear to have an effect on the degree to which alcohol impairs inhibitory mechanisms. For instance, heavy drinkers also show more pronounced deficits in inhibitory control in response to alcohol compared with lighter drinkers. A study by Marczinski et al (2007) examined sensitivity to alcohol impairment of inhibitory control in binge drinkers who regularly consumed alcohol to a BAC of at least 0.08%. The study showed revealed no difference in inhibitory failures between binge drinkers and non-binge drinkers following placebo. However, after a moderate dose of alcohol, binge drinkers committed significantly more inhibitory errors compared to non-binge drinkers. These results are somewhat counterintuitive given the principles of alcohol tolerance. That is, we might expect that those who regularly consume alcohol in great amounts (i.e., binge drinkers) to display less sensitivity to alcohol impairment compared with lighter drinkers. However, as presented in the second study of this dissertation, inhibitory mechanisms do not readily develop tolerance to alcohol, even in those who consume alcohol frequently and in great amounts (Miller et al., 2012). Such a heightened sensitivity in at-risk groups characterized by increased impulsivity suggest that they are more likely to engage in other risky behaviors while drinking, including aggressive acts, unprotected sexual activity, and driving while intoxicated (i.e., Jonah 1997; Wechsler et al., 2000). The increased sensitivity to the disinhibiting effects of the alcohol coupled with the activation bias in tolerance for other behaviors (as discussed previously) can



perpetuate the use and misuse of alcohol in increasing amounts, resulting in the escalation to alcohol dependence.

The accumulation of these findings suggest the following: a) impulsive, disinhibited individuals are at an increased risk of engaging in problematic alcohol and substance abuse; b) individuals who are regular, heavy drinkers display greater deficits in inhibitory control on laboratory tasks compared with lighter drinkers; and c) heightened consumption reflecting binge drinking is associated with a greater sensitivity to alcohol's disinhibiting effects. Therefore, although it is clear that impulsivity, and more specifically, inhibitory control is associated with drug use, the relationship is complex. Indeed, disinhibition appears to function as both a determinant and a consequence of alcohol use. What is noteworthy is that inhibitory mechanisms are amenable to long-term and short-term changes. That is, as shown by the studies in this dissertation, several factors can affect inhibitory control, both related to the acute effects of drugs as well as to non-drug related factors (i.e., redundant stimuli). There is some evidence that inhibitory mechanisms can be altered as a consequence of extended drug use on inhibitory mechanisms. It is suggested that prolonged drug use might actually result in fundamental changes in inhibitory capacity over time, possibly indicating a cumulative effect of impairment across drinking sessions (Jentsch & Taylor, 1999). Acute, non-drug factors have also been shown to result in short-term changes in impulsive behaviors. Both physiological and emotional factors, such as sleep deprivation and emotional distress, increase risky decision-making and reduce inhibitory control (Brown et al., 1970; Sicard et al., 20001; Tice et al., 2011), and some of these acute changes have been posited to increase the propensity engage in substance use (Sinha 2001). For example, stress and

negative emotional states result in increased sympathetic arousal, which are suggested to have reciprocal effects on other aspects of behavioral control, such as inhibitory mechanisms (Tice et al., 2001). Thus, both acute and chronic pharmacological and environmental changes thus appear to affect impulsive behavior and inhibitory control.

Evidence that inhibitory mechanisms can be altered quite readily also suggests that there may be factors that can improve inhibitory control, and thus reduce the risk for maladaptive behaviors. As such, research aiming to identify effective interventions for substance abuse and other disorders resulting from impulse control problems can benefit from focusing on methods for improving inhibitory mechanisms of behavioral control.

#### *Considerations for Drug Abuse Relapse Prevention*

Traditional models of drug abuse emphasize the drug's rewarding effects as reinforcing drug use to the point of dependence and addiction. However, this dissertation highlights the potential benefits of focusing on the role of the acute cognitive responses to drugs in abuse and dependence. Treatments for alcohol use disorders typically show poor outcomes, with some outcome studies estimating that 90% of those treated relapse to drinking within the year following treatment (e.g., Miller 1996). In response to high rates of treatment failure, intervention strategies for alcohol and other drug abuse might begin to consider the risks related to poor inhibitory control as a target of treatment.

Cognitive-behavioral therapies (CBTs) are frequently utilized treatments for alcohol and other substance use disorders. The focus of these treatments concerns the development problem-solving skills and enhancing self-awareness of triggers associated with relapse. Often times, the trigger for relapse are reported as a negative emotional state or the presence of drug-related cues. As noted above, both of these factors can disrupt

inhibitory capacities, thus instigating drinking or drug taking behavior. Thus, impaired inhibitory control might be the “endpoint mechanism” by which certain states result in relapse. Understanding the factors that can result in temporary reduction of inhibitory control (i.e., pharmacological, environmental, emotional), are important to provide a link between triggers and relapse risk.

Some recent efforts have been made to address the relationship between compromised inhibitory control and relapse. An important question that researchers have begun to ask is whether inhibitory mechanisms can be strengthened and in turn, can result in reduced substance use. Laboratory evidence has begun to emerge indicating that not only can inhibitory control be improved, but that these improvements can actually result in significant decreases in alcohol consumption. For instance, Houben et al. (2011) developed a protocol to train response inhibition specifically for alcohol-related stimuli. Young adults who were identified as binge drinkers completed a go/no-go task in which alcohol-related cues were consistently associated with the “no-go” condition. As a result, participants consistently had to engage in a stopping response in the presence of alcohol-related stimuli. The study showed that in the week following training, participants reported a significant decrease in their drinking habits compared to controls, suggesting that training participants to inhibit responses to alcohol-related cues on a go/no-go task can have an effect on actual drinking behavior.

In the aforementioned study, inhibition training was specifically focused on the need to inhibit in response to alcohol-related cues in a laboratory setting. Researchers have also been interested in more general modes of improving behavioral control. Mindfulness practice, which is already a frequently utilized therapeutic modality, has

increasingly been cited as a method to improve self-regulation. Originating from Buddhist meditation techniques, the term “mindfulness” refers to self-regulatory skills which involve observing one’s own thoughts and behaviors without judgment (Brown & Ryan, 2003; Kumar 2002). Broadly, mindfulness skills are used as a therapeutic tool to reduce stress and promote general mental well-being (e.g., Baer, 2003; Greenson, 2009). An increasing number of studies have begun to report on the effect of mindfulness training on improving types of attention and inhibition (Zylowska et al., 2008). Because the emphasis of mindfulness is increasing awareness of reactions and reducing behavioral reactivity, possible that by strengthening these skills, individuals can become aware of their tendencies to engage in rash behaviors, such as drinking, which are so often cited as being of the drinker’s control. Indeed, there have been a number of studies demonstrating that mindfulness practice over time can improve improved inhibitory control on a range of behavioral tasks (i.e., Oberle et al., 2012).

There are also studies assessing the efficacy of mindfulness on minimizing the risk of relapse in substance users. Mindfulness-based relapse prevention is a form of treatment aimed at increasing awareness of thoughts and feelings through practicing mindfulness, and utilizing mindfulness skills as a coping strategy in high-risk situations (i.e., Kabat-Zinn, 1990; Segal et al., 2002; Witkiewitz et al., 2005). This treatment encourages acceptance of craving without reacting (through initiating substance use). Although this treatment is not explicitly targeted toward improving self-regulatory mechanisms, the focus on accepting discomfort associated with craving without responding requires the ability to withhold a pre-potent response, which requires inhibitory control. The data regarding the efficacy of such mindfulness-based treatments

is promising, with some recent studies reporting a reduction in the frequency and quantity of consumption in groups trained in mindfulness practice (Fernandez et al., 2010; Gallagher et al., 2010; Witkiewitz et al., 2005). Therefore further study into mindfulness as a method of improving inhibitory control or as an adjunct to more traditional forms of treatment (for example, cognitive behavioral methods), is warranted. Although this work is promising for improving self-regulation in dependent individuals who are aiming to remain abstinent, as shown in this dissertation, much of the risk for binge drinking occurs once drinking has begun. Far less work has been devoted to designing approaches for improving inhibitory mechanisms that are impaired following a few drinks, but could be beneficial for reducing the incidence of dangerous binge drinking, particularly in non-dependent drinkers whose drinking might escalate to reflect more serious problems.

In sum, the findings of this dissertation contribute to a wealth of knowledge that implicates inhibitory control as a major contributor to problem drinking. By increasing our understanding of the circumstances that make it difficult for drinkers to discontinue drinking once they begin, this dissertation advances what is known about how alcohol-induced impairments of behavioral mechanisms may contribute to alcohol and substance use disorders. It will be important for future studies to examine the degree to which alcohol tolerance develops for other impulsive behaviors, such as attentional inhibition and risky decision making. Additionally, future research will benefit from extending the current findings to clinical populations identified as highly sensitive to the disinhibiting effects of alcohol (i.e., those with ADHD, binge drinkers).

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## References

- Abroms B.D., & Fillmore, M.T. (2004). Alcohol-induced impairment of inhibitory mechanisms involved in visual search. *Experimental and Clinical Psychopharmacology*, *12*, 243-250.
- Alderson, R.M., Rapport, M.D., & Kofler, M.J. (2007). Attention-deficit/hyperactivity disorder and behavioral inhibition: a meta-analytic review of the stop-signal paradigm. *Journal of Abnormal Child Psychology*, *35*, 745 – 758.
- American Psychiatric Association (1994) *Diagnostic and statistical manual of mental disorders* (4<sup>th</sup> ed). Washington, DC.
- American Psychiatric Association (2000). *Diagnostic and statistical manual of mental disorders* (4<sup>th</sup> ed., text rev). Washington, DC.
- August, G.J., Winters, J.C., Realmuto, G.M., Fahnhorst, T., Botzet, A., & Lee, S. (2006). Prospective study of adolescent drug use among community samples of ADHD and non ADHD participants. *Journal of the American Academy of Child and Adolescent Psychiatry*, *45*, 824 – 832.
- Babor, T.F., Hofmann, M., Del Boca, F.K., Hesselbrock, V.M., Meyer, R.E., Dolinsky, Z.S., & Rounsaville, B. (1992). Types of alcoholics: I. Evidence for an empirically derived typology based on indicators of vulnerability and severity. *Archives of General Psychiatry*, *49*, 599 – 608.
- Baer, R.A. (2003). Mindfulness training as a clinical intervention: A conceptual and empirical review. *Clinical Psychology: Science and Practice*, *10*, 125 – 143.
- Barkley, R.A. (1997). Behavioral inhibition, sustained attention, and executive functions: constructing a unifying theory of ADHD. *Psychological Bulletin*, *121*, 65 – 94.
- Barkley, R.A. (2006). Attention-deficit hyperactivity disorder, 3<sup>rd</sup> ed.: A handbook for diagnosis and treatment. New York, NY: Guilford Press.
- Bartholow, B.D., Pearson, M., Sher, K.J., Wieman, L.C., Fabianai, M., & Gratton, G. (2003). Effects of alcohol consumption and alcohol susceptibility on cognition: A psychophysiological examination. *Biological Psychology*, *64*, 167 – 190.
- Bauer, L.O., & Hesselbrock, V.M. (1999). P300 decrements in teenagers with conduct problems: Implications for substance abuse risk and brain development. *Biological Psychiatry*, *46*, 263 – 272.
- Beirness, D., & Vogel-Sprott, M. (1984). The development of alcohol tolerance: acute recovery as a predictor. *Psychopharmacology (Berl)*, *84*, 398 – 401.
- Blume, A.W., Schmalting, K.B., & Marlatt, G.A. (2005). Memory, executive cognitive function, and readiness to change drinking behavior. *Journal of Addictive Behaviors*, *30*, 301-314.
- Bokura, H., Yamaguchi, S., & Kobayashi, S. (2001). Electrophysiological correlates for response inhibition in a Go/No-Go task. *Clinical Neurophysiology*, *112*, 2224 – 2232.
- Brown, I.D., Tickner, A.H., Simmonds, D.C. (1970). Effect of prolonged driving on overtaking criteria. *Ergonomics*, *13*, 239 – 242.
- Brown, K.W., & Ryan, R.M. (2003). The benefits of being present: Mindfulness and its role in psychological well-being. *Journal of Personality and Social Psychology*, *84*, 822 – 848.

- Brumback, T., Cao, D., & King, A. (2007). Effects of alcohol on psychomotor performance and perceived impairment in heavy binge social drinkers. *Drug and Alcohol Dependence, 91*, 10-17
- Carroll, K.M., & Rounsaville, B.J. (1993). History and significance of childhood attention deficit disorder in treatment-seeking cocaine abusers. *Comprehensive Psychiatry, 34*, 75 – 82.
- Cavina-Pratesi, C., Bricolo, E., Prior, M. & Marzi, C.A. (2001). Redundancy gain in the stop-signal paradigm: Implications for the locus of coactivation in simple reaction time. *Journal of Experimental Psychology: Human Perception and Performance, 27*, 932-941.
- Chait, L.D., & Perry, J.L. (1994). Acute and residual effects of alcohol and marijuana, alone and in combination on mood and performance. *Psychopharmacology, 115*, 340 – 349.
- Cheng, S., Lee, H., Lee, J., Tsai, S. (2010). Comparing the effects of light alcohol consumption on human response to auditory and visual stimuli. *Perceptual and Motor Skills, 111*, 589 – 560.
- Chung, T., & Martin, C.S. (2009). Subjective stimulant and sedative effects of alcohol during early drinking experiences predict alcohol involvement in treated adolescents. *Journal of Studies on Alcohol and Drugs, 70*, 660 – 667.
- Cloninger, C.R. (1986). A unified biosocial theory of personality and its role in the development of anxiety states. *Psychiatry Development, 4*, 167 – 226.
- Collins, R.L. (1993) Drinking restraint and risk for alcohol abuse. *Experimental and Clinical Psychopharmacology, 1*, 44-54.
- Degenhardt, L., Hall, W., Lynskey, M. (2001). Alcohol, cannabis and tobacco use among Australians: A comparison of their associations with other drug use disorders, affective and anxiety disorders and psychosis. *Addiction, 96*, 1603 – 1614.
- de Wit, H. (2008). Impulsivity as a determinant and consequence of drug use: a review of underlying processes. *Addiction Biology, 14*, 22 – 31.
- de Wit, H., Crean, J., & Richards, J.B. (2000). Effects of d-amphetamine and ethanol on a measure of behavioral inhibition in humans. *Behavioral Neuroscience, 114*, 830-837.
- Easdon, C., Izenberg, A., Armilio, M.L., Yu, H., & Alain, C. (2005). Alcohol consumption impairs stimulus- and error-related processing during a go/no-go task. *Cognitive Brain Research, 25*, 873 – 883.
- Eng, M.Y., Schuckit, M.A., & Smith, T.L. (2005). The level of response to alcohol in daughters of alcoholics and controls. *Drug and Alcohol Dependence, 79*, 830 – 837.
- Eysenck, H.J. (1993). The nature of impulsivity. In: *The Impulsive Client: Theory, Research, and Treatment*. Johnson, J.L., Sure, M.B. (eds). Washington, DC: American Psychological Association. Pp. 57 – 70.
- Eysenck, H.J., & Eysenck, S.B.G. (1968). *Eysenck Personality Inventory*. San Diego, CA: Education and Industrial Testing Service.
- Falkenstein, M., Hoormann, J., & Hohnsbein, J. (1999). ERP components in Go/Nogo tasks and their relationship to inhibition. *Acta Psychologica, 101*, 267 – 291.

- Fernandez, A.C., Wood, M.D., Stein, L.A.R., & Rossi, J.S. (2010). Measuring mindfulness and examining its relationship with alcohol use and negative consequences. *Psychology of Addictive Behaviors*, 24, 608 – 616.
- Fillmore, M.T. (2001). Cognitive preoccupation with alcohol and binge drinking in college students: alcohol-induced priming of the motivation to drink. *Psychology of Addictive Behaviors*, 21, 346-354.
- Fillmore, M.T. (2003). Drug abuse as a problem of impaired control: current approaches and findings. *Behavioral and Cognitive Neuroscience Review*, 2, 179-197.
- Fillmore, M.T. (2007). Acute alcohol-induced impairment of cognitive functions; past and present findings. *International Journal on Disability and Human Development*, 6, 115- 125.
- Fillmore, M.T. (2010). Processing bimodal stimulus information under alcohol: Is there a risk to being redundant? *Experimental and Clinical Psychopharmacology*, 18, 429-435.
- Fillmore, M.T., Dixon, M.J., & Schweizer, T.A. (2000). Alcohol affects processing of ignored stimuli in a negative priming paradigm. *Journal of Studies on Alcohol*, 61, 571 – 578.
- Fillmore, M.T., Marcziński, C.A., & Bowman, A.M. (2005). Acute tolerance to alcohol effects on inhibitory and activational mechanisms of behavioral control. *Journal of Studies on Alcohol*, 33, 663-672.
- Fillmore, M.T., & Rush, C.R. (2002). Impaired inhibitory control of behavior in chronic cocaine users. *Drug and Alcohol Dependence*, 66, 265 – 273.
- Fillmore, M.T., & Van Selst, M. (2002). Constraints on information processing under alcohol in the context of response execution and response suppression. *Experimental and Clinical Psychopharmacology*, 10, 417 – 424.
- Fillmore, M.T., & Vogel-Sprott, M. (1995). Behavioral effects of alcohol in novice and experienced drinkers: alcohol expectancies and impairment. *Psychopharmacology*, 122, 175-181
- Fillmore, M.T., & Vogel-Sprott, M. (1996). Social drinking history, behavioral tolerance and the expectation of alcohol. *Psychopharmacology (Berl)* 127, 359-364.
- Fillmore, M.T. & Vogel-Sprott, M. (1997). Resistance to cognitive impairment under alcohol: The role of environmental consequences. *Experimental and Clinical Psychopharmacology*, 5, 251-255.
- Fillmore, M.T., & Vogel-Sprott, M. (1998). Behavioral impairment under alcohol: cognitive and pharmacokinetic factors. *Alcoholism: Clinical and Experimental Research*, 22, 1476- 1482.
- Fillmore, M.T., & Vogel-Sprott, M. (1999) An alcohol model of impaired inhibitory control and its treatment in humans. *Experimental and Clinical Psychopharmacology*, 7, 49-55.
- Fillmore, M.T., & Weafer, J. (2004). Alcohol impairment of behavior in men and women. *Addiction*, 99, 1237 – 1246.
- Fillmore, M.T., & Weafer, J. (2012). Acute tolerance to alcohol in at-risk binge drinkers. *Psychology of Addictive Behaviors*, 20, 693 – 702.
- Fillmore, M.T., & Weafer J. (2013). Behavioral inhibition and addiction. In J. MacKillop and H. de Wit (eds.), *The Wiley-Blackwell Handbook of Addiction*



- Psychopharmacology*. West Sussex UK: John Wiley and Sons Limited, pp. 135 – 164.
- Finnigan, F., Hammersley, R., & Cooper, T. (1998). An examination of next-day hangover effects after a 100 mg/100 ml dose of alcohol in heavy social drinkers. *Addiction*, *93*, 1829 – 1838.
- Finnigan, F., Schulze, D., Smallwood, J., & Helander, A. (2005). The effects of self-administered alcohol-induced “hangover” in a naturalistic setting on psychomotor and cognitive performance and subjective scale. *Addiction*, *100*, 1680 – 1689.
- Gallagher, K., Hudepohl, A., & Parrott, D. (2010). Power of being present: The role of mindfulness on the relation between men’s alcohol use and sexual aggression toward intimate partners. *Aggressive Behavior*, *36*, 405 – 413.
- Goldberg, L. (1943). Quantitative studies on alcohol tolerance in man: the influence of ethyl alcohol on sensory, motor, and psychological functions referred to blood alcohol in normal and habituated individuals. *Acta Physiologica Scandanavia*, *5*, 1-128.
- Gondon, M., Lange, K., Rosler, F., & Roder, B. (2004). The redundant target effect is affected by modality switch costs. *Psychonomic Bulletin and Review*, *11*, 307-313.
- Gondon, M., Niederhaus, B., Rosler, F., & Roder, B. (2005). Multi-sensory processing in the redundant –target effect: A behavioral and event-related potential study. *Perception and Psychophysics*, *67*, 713-726.
- Goodwin, D.W., Schulsinger, F., Hermansen, L. et al. (1975). Alcoholism and the hyperactive child syndrome. *Journal of Nervous and Mental Disease*, *160*, 349 – 353.
- Gourdriaan, A.E., Grekin, E.R., & Sher, K.J. (2007). Decision making and binge drinking: A longitudinal study. *Alcoholism: Clinical and Experimental Research*, *31*, 928 – 938.
- Greeson, J.M. (2009). Mindfulness research update: 2008. *Complementary Health Research Practice Review*, *14*, 10 – 18.
- Grice, G.R., Canham, L., & Boroughs, J.M. (1984). Combination rule for redundant information in reaction time tasks with divided attention. *Perception and Psychophysics*, *35*, 451-463.
- Habeych, M.E., Folan, M.M., Luna, B., & Tarter, R.E. (2006). Impaired oculomotor response inhibition in children of alcoholics: The role of attention deficit hyperactivity disorder. *Drug and Alcohol Dependence*, *82*, 11 – 17.
- Holdstock, L., King, A.C., & de Wit, H. (2000). Subjective and objective responses to ethanol in moderate/heavy and light social drinkers. *Alcoholism: Clinical and Experimental Research*, *24*, 789-794.
- Holloway, F.A. (1995). Low-dose alcohol effects on human behavior and performance. *Alcohol, Drugs, and Driving*, *11*, 39 – 56.
- Houben, K., Nederkoorn, C., Wiers, R.W., & Jansen, A. (2011). Resisting temptation: Decreasing alcohol-related affect and drinking behavior by training response inhibition. *Drug and Alcohol Dependence*, *116*, 132 – 136.
- Houghton, G., & Tipper, S.P. (1994). A model of inhibitory mechanisms of selective attention. In Dagbach D, Carr TH (eds). *Inhibitory processes in attention, memory, and language*. Academic Press, San Diego CA, pp 53-112.

- Iacono, W.G., Malone, S.M., & McGue, M. (2003). Substance use disorders, externalizing psychopathology, and P300 event-related potential amplitude. *International Journal of Psychophysiology*, 28, 147 – 178.
- Jentsch, J.D., & Taylor, J.R. (1999). Impulsivity resulting from frontostriatal dysfunction in drug abuse: Implications for the control of behavior by reward-related stimuli. *Psychopharmacology*, 146, 373 – 390.
- Johnston, L.D., O'Malley, P.M., Bachman, J.G., & Schulenberg, J.E. (2010). Monitoring the Future National Survey Results on Drug Use, 1975 – 2009. Volume II: College Students and Adults Ages 19 – 50. National Institute on Drug Abuse, Bethesda, MD, NIH Publication No. 10 – 7585.
- Jonah, B.A. (1997). Sensation seeking and risky driving: A review and synthesis of the literature. *Accident Analysis and Prevention*, 29, 651 – 665.
- Kabat-Zinn, J. (1990). *Full Catastrophe Living*. New York: Delacorte.
- Kalant, H., Leblanc, A.E., & Gibbons, R.J. (1971). Tolerance to, and dependence on ethanol. In Y. Israel and J. Mardonze (eds.), *Biological basis of alcoholism*. Wiley/Interscience, New York, pp 235-269.
- Kandel, D. & Yamaguchi, K. (2001). From beer to crack: developmental patterns of drug involvement. *American Journal of Public Health*, 83, 851 – 855.
- Kim, R., Peters, M.A.K., & Shams, L. (2012). 0 + 1 > 1: How adding noninformative sound improves performance on a visual task. *Psychological Science*, 23, 6 – 12.
- Kruisselbrink, L.D., Martin, M.L., Megeney, M., Fowles, J.R., & Murphy, R.J. (2004). Physical and psychomotor functioning of females the morning after consuming low to moderate quantities of beer. *Journal of Studies of Alcohol*, 67, 416 – 420.
- Kok, A., Ramautar, J.R., De Ruiter, M.B., Band, G.P., & Ridderinkhof, K.R. (2004). ERP components associated with successful and unsuccessful stopping in a stop-signal task. *Psychophysiology*, 41, 9 – 20.
- Kumar, S.M. (2002). An introduction to Buddhism for the cognitive-behavioral therapist. *Cognitive and Behavioral Practice*, 9, 40 – 43.
- Laberg JC, Loberg T (1989) Expectancy and tolerance: A study of acute alcohol intoxication using the balanced placebo design. *Journal of Studies on Alcohol* 50, 448 – 455.
- Levin, F.R., & Kleber, H.D. (1995). Attention-deficit hyperactivity disorder and substance abuse: Relationships and implications for treatment. *Harvard Review of Psychiatry*, 2, 246 – 258.
- Logan, G.D. (1994). On the ability to inhibit thought and action: A user's guide to the stop signal paradigm. In: Dagenbach D, Carr TH (eds). *Inhibitory processes in attention, memory, and language*. Academic Press: San Diego, CA, pp 189-239.
- Logan, G.D., Cowan, W.B. (1984) On the ability to inhibit thought and action: A theory of an act of control. *Psychological Review*, 91, 295-327.
- Logan, G.D., Schachar, R.J., & Tannock, R. (1997). Impulsivity and inhibitory control. *Psychological Science*, 8, 60 – 64.
- Lyvers, M. (2000). "Loss of control" in alcoholism and drug addiction: a neuroscientific interpretation. *Experimental and Clinical Psychopharmacology*, 8, 225-249.
- Madden, G.J., Petry, N.M., Badger, G.J., & Bickel, W.K. (1997). Impulsive and self control choices in opioid dependent patients and non-drug-using control

- participants: drug and monetary rewards. *Experimental and Clinical Psychopharmacology*, 5, 256 - 262.
- Malloy, P., Bihrlle, A., Duffy, J., & Cimino, C. (1993). The orbitomedial frontal syndrome. *Archives of Clinical Neuropsychology*, 8, 185 – 201.
- Marczinski, C.A., Combs, S.W., Fillmore, M.T. (2007). Increased sensitivity to the disinhibiting effects of alcohol in binge drinkers. *Psychology of Addictive Behaviors*, 21, 346 – 354.
- Marczinski, C.A., & Fillmore, M.T. (2003). Preresponse cues reduce the impairing effects of alcohol on the execution and suppression of responses. *Experimental and Clinical Psychopharmacology*, 11, 110-117.
- Marczinski, C.A., & Fillmore, M.T. (2009). Acute tolerance on subjective intoxication and simulated driving performance in binge drinkers. *Psychology of Addictive Behaviors*, 23, 238 – 247.
- Marzi, C.A., Smania, N., Martini, M.C., Gambina, G., Tomelleri, G., Palamara, A., Alessandrini, F., & Prior, M. (1996). Implicit redundant-target effects in visual extinction. *Neuropsychologia*, 34, 9 – 22.
- Maylor, E.A., Rabbit, P.M., James, G.H., Kerr, S.A. (1992). Effects of alcohol, practice, and task complexity on reaction time distributions. *Quarterly Journal of Experimental Psychology*, 49, 119 – 139.
- McKim, W.A. (2007). *Drugs and Behavior: An Introduction to Behavioral Pharmacology*, 6<sup>th</sup> ed. Prentice Hall, New Jersey.
- Medina, E.L. (1970). The role of the alcoholic in accidents and violence. In Phpham, R.E. (Ed) *Alcohol and Alcoholism*. University of Toronto Press: Toronto, Canada. Pp. 350 – 355.
- Mellanby, E. (1919). *Alcohol: Its absorption into and disappearance from the blood under different conditions (Special Report Series Monograph No. 13)*. London, England: Medical Research Committee.
- Mendelson, J.H., & Mello, N.K. (1966). Experimental analysis of drinking behavior of chronic alcoholics. *Ann NY Acad Sci* 133: 828-845.
- Miller, J. (1982). Divided attention: Evidence for coactivation with redundant signals. *Cognitive Psychology*, 14, 247 – 279.
- Miller, J. (1986). Timecourse of coactivation in bimodal divided attention. *Perceptual Psychophysiology*, 40, 331 – 343.
- Miller, J., Schaffer, R., & Hackley, S.A. (1991). Effects of preliminary information in a go versus no-go task. *Acta Psychological*, 76, 241-292.
- Miller, M.A., Hays, L.R., & Fillmore, M.T. (2012). Lack of tolerance to the disinhibiting effects of alcohol in heavy drinkers. *Psychopharmacology*, 4, 511 – 518.
- Miller, W.R. (1996). What is a relapse? Fifty ways to leave the wagon. *Addiction*, 91, S15 – S27.
- Moeller, F.G., Dougherty, D.M., Barratt, E.S., Schmitz, J.M., Swann, A.C., & Grabowski, J. (2001). The impact of impulsivity on cocaine use and retention in treatment. *Journal of Substance Abuse Treatment*, 21, 193 – 198.
- Monterosso, J.R., Aron, A.R., Cordova, X., Xu, J., & London, E.D. (2005). Deficits in response inhibition associated with chronic methamphetamine abuse. *Drug and Alcohol Dependence*, 79, 273 – 277.

- Mordkoff, J.T., & Yantis, S. (1991). An interactive race model of divided attention. *Journal of Human Perception and Performance*, 17, 520 – 538.
- Moskowitz, H., & De Pre, D. (1968). Differential effect of alcohol on auditory vigilance and divided attention task. *Quarterly Journal of Studies on Alcohol*, 29, 54 – 63.
- Moskowitz, H., & Robinson, C. (1988). Effects of low doses of alcohol on driving-related skills: A review of the evidence. U.S. Department of Transportation: Washington, DC.
- Mulvihill, L.E., Skilling, T.A., & Vogel-Sprott, M. (1997). Alcohol and the ability to inhibit behavior in men and women. *Journal of Studies on Alcohol*, 58, 600 – 605.
- Murray, M.M., Foxe, J.J., Higgins, B.A., Javitt, D.C., & Schroeder, C.E. (2001). Visuo-spatial neural response interactions in early cortical processing during a simple reaction time task: A high-density electrical mapping study. *Neuropsychologia*, 39, 828 – 844.
- Nathan, P.E., O'Brien, J.S., Lowenstein, L.M. (1971). Operant studies of chronic alcoholism: interaction of alcohol and alcoholics. In: McIsaac, W., Creaven, P. (Eds). Biological aspects of alcohol. University of Texas Press, Austin, Texas, pp. 341 – 370.
- Nigg, J.T. (2006). What causes ADHD? Understanding what goes wrong and why. New York: Guilford Press.
- Oberle, E., Schonert-Reichl, K.A., Lawlor, M.S., & Thomson, K.C. (2012). Mindfulness and inhibitory control in early adolescence. *Journal of Early Adolescence*, 32, 565 – 588.
- Ohlmeier, M.D., Peteres, K., Te Wildt, B.T., Zedler, M., Ziegenbein, M., et al., (2008). Comorbidity of alcohol and substance dependence with attention-deficit/hyperactivity disorder (ADHD). *Alcohol and Alcoholism*, 43, 300 – 304.
- Oosterlaan, J., Logan, G.D., & Sergeant, J.A. (1998). Response inhibition in AD/HD, CD, comorbid AD/HD + CD, anxious, and control children: a meta-analysis of studies with the stop task. *Journal of Child Psychology and Psychiatry*, 39, 411 – 425.
- Ostling, E.W., & Fillmore, M.T. (2010). Tolerance to the impairing effects of alcohol on the inhibition and activation of behavior. *Psychopharmacology*, 212, 465-473.
- Patrick, C.J., Bernat, E., Malone, S.M., Iacono, W.G., Krueger, R.F., & McGue, M.K. (2006). P300 amplitude as an indicator of externalizing in adolescent males. *Psychophysiology*, 43, 84 – 92.
- Pihl, R.O., Paylan, S.S., Gentes-Hawn, A., & Hoaken, P.N.S. (2003). Alcohol affects executive cognitive functioning differentially on the ascending versus descending limb of the blood alcohol concentration curve. *Alcoholism: Clinical and Experimental Research*, 27, 773 - 779.
- Poulos, C.X., Parker, J.L., & Le, D.A. (1998). Increased impulsivity after injected alcohol predicts later alcohol consumption in rats: Evidence for “loss-of-control drinking” and marked individual differences. *Behavioral Neuroscience*, 112, 1247 – 1257.
- Prat, G., Adan, A., Perez-Pamies, M., & Sanchez-Turet, M. (2008). Neurocognitive effects of alcohol hangover. *Addictive Behaviors*, 33, 15 – 23.
- Rasmussen, P., & Gilberg, C. (2000). Natural outcome of ADHD with developmental coordination disorder at age 22 years: A controlled, longitudinal, community-

- based study. *Journal of the American Academy of Child and Adolescent Psychiatry* 39, 1424 – 1431.
- Roehrs, T., & Roth, T. (2001). Sleep, sleepiness, and alcohol use. *Alcohol Research and Health. The Journal of the National Institute on Alcohol and Alcoholism*, 25, 101 – 109.
- Rohrbaugh, J.W., Stapleton, J.M., Parasuraman, R., Zubovic, E.A., Frowein, H.W., Varner, J.L., Adnioff, B., Lane, E.A., Eckardt, M.J., & Linnoila, M. (1987). Dose-related effects of ethanol on visual sustained attention and event-related potentials. *Alcohol*, 4, 293 – 300.
- Schneider, W., Eschman, A., & Zuccolotto, A. (2002). E-Prime user's guide. Psychology Software Tools, Pittsburgh.
- Schroger, E., & Widmann, A. (1998). Speeded responses to audiovisual signal changes result from bimodal integration. *Psychophysiology*, 35, 755 – 759.
- Schuckit, M.A. (2009). An overview of genetic influences in alcoholism. *Journal of Substance Abuse Treatment*, 36, S5 – 14.
- Schweizer, T.A., Jolicoeur, P., Vogel-Sprott, M., & Dixon, M.J. (2004). Fast, but error-prone, responses during acute alcohol intoxication: effects of stimulus-response mapping complexity. *Alcoholism: Clinical and Experimental Research*, 28, 643 - 649.
- Segal, Z., Williams, J.M.G., & Teasdale, J.D. (2002). *Mindfulness-based cognitive therapy for depression: A new approach to preventing relapse*. New York: Guilford Press.
- Selzer, M.L., Vinokur, A., & Rooijen, L. (1975). A self-administered Short Michigan Alcoholism Screening Test (SMAST). *J Stud Alcohol* 36: 117-126.
- Sher, K.J., Bartholow, B.D., & Wood, M.D. (2000). Personality and substance abuse disorders: A prospective study. *Journal of Consulting and Clinical Psychology*, 68, 818 – 829.
- Sher, K.J., & Trull, T.J. (1994). Personality and disinhibitory psychopathology: alcoholism and antisocial personality disorder. *Journal of Abnormal Psychology*, 103, 92 – 102.
- Sicard, B., Jouve, E., & Blin, O. (2001). Risk propensity assessment in military special operations. *Military Medicine*, 166, 871 – 874.
- Sinha, R. (2001). How does stress increase risk of drug abuse and relapse? *Psychopharmacology (Berl)*, 158, 343 – 359.
- Sobell, L., & Sobell, M. (1992). Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Litten R, Allen J (eds) *Measuring alcohol consumption: Psychosocial and biochemical methods*. Human Press, New Jersey, pp 41-72.
- Steele, C.M., & Josephs, R.A. (1990). Alcohol myopia: Its prized and dangerous effects. *American Psychologist*, 45, 921-933.
- Steele, C.M., & Southwick, L. (1985). Alcohol and social behavior: The psychology of drunken excess. *Journal of Personality and Social Psychology*, 45, 18 – 34.
- Stein, B.E. (1998). Neural mechanisms for synthesizing sensory information and producing adaptive behaviors. *Experimental Brain Research*, 123, 124 – 135.
- Stinson, F.S., Grant, B.F., Dawson, D.A., Ruan, W.J., Huang, B., & Saha, T. (2005). Comorbidity between DSM-IV alcohol and specific drug use disorders in the

- United States: results from the National Epidemiological Survey on Alcohol and Related Conditions. *Drug and Alcohol Dependence*, 80, 105 -116.
- Substance Abuse and Mental Health Services Administration (2012). Results from the 2011 National Survey on Drug Use and Health: Summary of National Findings, Substance Abuse and Mental Health Services Administration. NSDUH Series H-44, HHS Publication No. (SMA) 12 – 4713. Rockville, MD.
- Tannock, R. (1998). Attention deficit hyperactivity disorder: Advances in cognitive, neurobiological, and genetic research. *Journal of Child and Adolescent Psychiatry*, 41, 1231-1238.
- Tarter, R.E., Kirisci, L., Habeych, M., Reynolds, M., & Vanyukov, M. (2004). Neurobehavior disinhibition in childhood predisposes boys to substance use disorder by young adulthood: direct and mediated etiologic pathways. *Drug and Alcohol Dependence*, 73, 121-132.
- Tarter, R.E., Kirisci, L., Feske, U., & Vanyukov, M. (2007). Modeling the pathways linking childhood hyperactivity and substance use disorder in young adulthood. *Psychology of Addictive Behaviors*, 21, 266 – 271.
- Tarter, R.E., McBride, H., Buonpane, N., & Schneider, D. (1977). Differentiation of alcoholics: Childhood history of minimal brain dysfunction, family history, and drinking patterns. *Archives of General Psychiatry*, 34, 761 – 768.
- Tice, D.M., Bratslavsky, E., & Baumeister, R.F. (2001). Emotional distress regulation takes precedence over impulse control: if you feel bad, do it! *Journal of Personality and Social Psychology*, 80, 153 – 167.
- Todd, J.W. (1912). Reaction to multiple stimuli. *Archives of Psychology*, 3, 1 – 65.
- Towshend, J.M., & Duka, T. (2005). Binge drinking, cognitive performance and mood in a population of young social drinkers. *Alcoholism: Clinical and Experimental Research*, 29, 317-325.
- Vogel-Sprott, M. (1992). *Alcohol tolerance and social drinking: Learning the consequences*. New York, NY: Guilford Press.
- Wagner, F.A., & Anthony, J.C. (2002). Into the world of illegal drug use: exposure opportunity and other mechanisms linking the use of alcohol, tobacco, marijuana, cocaine. *American Journal of Epidemiology*, 155, 918 – 925.
- Watson, P.E., Watson, I.D., Batt, R.D. (1981). Prediction of blood alcohol concentrations in human subjects: Updating the Widmark Equation. *Journal of Studies on Alcohol* 42, 547-556.
- Weafer, J., & Fillmore, M.T. (2008). Individual differences in acute alcohol impairment of inhibitory control predict ad libitum alcohol consumption. *Psychopharmacology*, 201, 315-324.
- Weafer, J., & Fillmore, M.T. (2012). Alcohol-related stimuli reduce inhibitory control of behavior in drinkers. *Psychopharmacology*, 222, 489 - 498.
- Weafer, J., Fillmore, M.T., & Milich, R. (2009). Increased sensitivity to the disinhibiting effects of alcohol in adults with ADHD. *Experimental and Clinical Psychopharmacology*, 17, 113 - 121.
- Wechsler, H., Lee, J.E., Kuo, M., & Lee, H. (2000). College binge drinking in the 1990s: A continuing problem: Results of the Harvard School of Public Health 1999 College Alcohol Study. *Journal of American College Health*, 48, 199 – 210.

- Wechsler, H., & Nelson, T.F. (2001). Binge drinking and the American college student: What's five drinks? *Psychology of Addictive Behaviors, 15*, 287 – 291.
- Wilens, T.E., Biederman, J., Mick, E. et al. (1997). Attention deficit hyperactivity disorder (ADHD) is associated with early onset substance disorders. *Journal of Nervous and Mental Disease, 185*, 445 – 448.
- Witkiewitz, K., Marlatt, G.A., & Walker, D. (2005). Mindfulness-based relapse prevention for alcohol and substance use disorders. *Journal of Cognitive Psychotherapy: An International Quarterly, 19*, 211 – 228.
- Zucker, R.A. (1987). The four alcoholisms: A developmental account of the etiologic process. In: Rivers, P.C. (Ed) *Alcohol and Addictive Behavior*. Lincoln NE: University of Nebraska Press, pp 27 – 83.
- Zylowska, L., Ackerman, D.L., Yang, M.H., Futrell, J.L., Horton, N.L. et al. (2008). Mindfulness training in adults and adolescents with ADHD: A feasibility study. *Journal of Attention Disorders, 11*, 737 – 746.

## VITA

**Melissa Angelina Miller**

### **EDUCATION**

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Predoctoral Internship in Clinical Psychology 2012 – 2014

University of Kentucky Medical Center: Department of Pediatrics, Eastern State  
Psychiatric Hospital, Department of Women's Health, Department of Dentistry/Orofacial  
Pain Center.

M.S. University of Kentucky 2010  
Clinical Psychology  
Thesis: "The Acute Effects of Alcohol on Attentional Bias toward Alcohol-Related  
Stimuli in Heavy Drinkers."

B.A. Indiana University (Summa Cum Laude, Psychology, Sociology, Spanish) 2007  
Honors Thesis: "Disinhibited personality and cognitive ability in alcohol dependence:  
The associated between traits that reflect deficits in self-regulation, working memory  
capacity, executive function, and intelligence."

### **HONORS AND AWARDS**

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Ruth L. Kirschstein National Research Service Award (F31AA021028) 2012 - 2014  
National Institute on Alcohol Abuse and Alcoholism  
Redundant Signal Effect and Alcohol Impairment of Behavioral Inhibition in ADHD  
\$66,292 direct costs  
Role: Principal Investigator

NIDA Pre-Doctoral Research Training Grant in Drug Abuse Behavior 2010 - 2012  
T32 DA07304

Research Society on Alcoholism Enoch Gordis Award Finalist 2009  
Annual meeting of the Research Society on Alcoholism, San Diego, CA



Travel Award International Society for the Research on Impulsivity Scientific Meeting	2009
Student Merit Award Research Society on Alcoholism Annual Meeting	2009 - 2013
Lynam T. Johnson Graduate Student Fellowship University of Kentucky	2007 - 2009

## **PUBLICATIONS**

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- Roberts, W., Miller, M.A., Weafer, J., & Fillmore, M.T. (in press). Heavy drinking and the role of inhibitory control of attention. *Experimental and Clinical Psychopharmacology*.
- Miller, M.A., & Fillmore, M.T. (in press) Protracted impairment of impulse control under an acute dose of alcohol: A time course analysis. *Addictive Behaviors*.
- Miller, M.A., & Fillmore, M.T. (2013). Can the use of multiple stop signals reduce the disinhibiting effects of alcohol? *Alcoholism: Clinical and Experimental Research*
- Miller, M.A., Hays, L.R., & Fillmore, MT. (2012). Lack of tolerance to the disinhibiting effects of alcohol in heavy drinkers. *Psychopharmacology*, 224, 511 -518.
- Miller, M.A. & Fillmore, M.T. (2011). Persistence of attentional bias toward alcohol-related stimuli in intoxicated social drinkers. *Drug and Alcohol Dependence*, 117, 184 – 189.
- Weafer, J., Miller, M.A., & Fillmore, M.T. (2010). Response conflict as an environmental determinant of gender differences in sensitivity to alcohol impairment. *Current Drug Abuse Reviews*, 3, 147-155.
- Miller, M.A., & Fillmore, M.T. (2010). The effect of image complexity on attentional bias toward alcohol-related images in adult drinkers. *Addiction*, 105, 883 – 890.
- Miller, M.A., Weafer, J., & Fillmore, M.T. (2009). Gender differences in alcohol impairment of simulated driving performance and driving related skills. *Alcohol and Alcoholism*, 44, 586-593.
- Finn, P.R., Rickert, M.E., Miller, M.A., Lucas, J., Bogg, T., Bobova, L.,& Cantrell, H. (2009). Reduced cognitive ability in alcohol dependence: Examining the role of covarying externalizing psychopathology. *Journal of Abnormal Psychology*, 118, 100-116.

## **PRESENTATIONS AT SCIENTIFIC MEETINGS**

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Miller, M.A. & Fillmore, M.T. Poor impulse control and heightened attraction to alcohol-related imagery in repeat DUI offenders. Paper presented at the International Council on Alcohol, Drugs and Traffic Safety. Brisbane, Australia. 2013.

Miller, M.A. & Fillmore, M.T. Beyond drinking and driving: Underlying cognitive and behavioral processes in recidivist DUI offenders. Poster presented at the annual meeting of the Research Society on Alcoholism, Orlando, FL, 2013

Miller, M.A. & Fillmore, M.T. Effects of recent drinking habits on tolerance to alcohol impairment in non-dependent drinkers. Poster presented at the annual meeting of the Research Society on Alcoholism, San Francisco, CA, 2012.

Miller, M.A. & Fillmore, M.T. Using sight and sound to stop drinkers: The risks of being redundant. Poster presented at the annual meeting of the Research Society on Alcoholism. Atlanta, GA, 2011.

Miller, M.A. & Fillmore, M.T. Using sight and sound to stop drinkers: The risks of being redundant. Paper presented at the NIDA Training Grant Symposium, University of Kentucky. Lexington, KY 2011.

Miller, M.A., Weafer, J., & Fillmore, M.T. Protracted impairment of inhibitory control under an acute dose of alcohol: A time-course analysis. Poster presented at the bi-annual meeting of the European Behavioural Pharmacology Society. Amsterdam, Netherlands. 2011.

Miller, M.A. & Fillmore, M.T. The acute effects of alcohol on attentional bias toward alcohol-related stimuli in heavy drinkers. Poster presented at the annual meeting of the Research Society on Alcoholism. San Antonio, TX, 2010.

Miller, M.A. & Fillmore, M.T. Levels of impulsivity in drinkers predict the degree of attentional bias toward alcohol. Poster presented at the International Society of Research on Impulsivity. San Diego, CA, 2009.

Miller, M.A., Weafer, J. & Fillmore, M.T. Gender differences in alcohol impairment of simulated driving performance and driving related skills. Paper presented at the Research Society on Alcoholism. San Diego, CA. 2009.\*Enoch Gordis Award Finalist

### **Invited Addresses**

Yozwiak, J.A., Miller, M.A. Substance abuse and dependence among adolescents. Address given at Medical Resident Seminar, Department of Pediatrics, University of Kentucky College of Medicine. Lexington, KY, 2012.

Susman, D.T., Miller, M.A., & Combs, J.L. Teaching and promoting health literacy in the community. Address given at the annual conference of The National Area Health Education Center. Lexington, KY, 2011

## **CLINICAL POSITIONS**

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Clinical Psychology Intern, University of Kentucky Internship Consortium 2012 – 2014

Adolescent Medicine Rotation  
Department of Pediatrics, University of Kentucky

Eastern State Psychiatric Hospital Rotation

Individual Therapist 2008 - 2012  
Jesse G. Harris Psychological Services Center, University of Kentucky

Practicum Therapist  
Federal Medical Center, Atwood Prison Camp 2010 - 2011

Dialectical Behavioral Therapy Skills Group Co-Leader 2010 - 2011  
Jesse G. Harris Psychological Services Center, University of Kentucky

Children's Social Skills Group Therapist 2010  
Jesse G. Harris Psychological Services Center, University of Kentucky

Group Therapy Coordinator 2009 - 2010  
Jesse G. Harris Psychological Services Center, University of Kentucky

Anger Management Parenting Skills Group 2009  
Jesse G. Harris Psychological Services Center, University of Kentucky

Individual Practicum Therapist 2008 – 2009  
Counseling Center, University of Kentucky

Interpersonal Process Group Therapist 2009  
Counseling Center, University of Kentucky

University Guest Lecture Roles  
2010 – 2013: PSY633 Clinical Interviewing  
2012: PSY312 Brain and Behavior

AD HOC JOURNAL REVIEWER  
Biology Addiction

Drug and Alcohol Dependence  
Addictive Behaviors  
The Journal of Adolescent and Pediatric Gynecology