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TOLERANCE TO THE IMPAIRING EFFECTS OF ALCOHOL ON THE INHIBITION AND ACTIVATION OF BEHAVIOR

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ABSTRACT OF THESIS

TOLERANCE TO THE IMPAIRING EFFECTS OF ALCOHOL ON THE INHIBITION AND ACTIVATION OF BEHAVIOR

Moderate doses of alcohol impair response inhibition activation. Recent work has shown that, during a single dose, response inhibition recovers from the impairing effects of alcohol more slowly than response activation. Evidence for a lag in tolerance development to inhibitory versus activational mechanisms suggests that, as blood alcohol declines, drinkers' response inhibition might continue to be impaired, despite the recovery of response activation. However, this has not been studied across repeated doses. This study examined how cross-session tolerance to alcohol develops differentially between response activation and inhibition. Thirty-two healthy adults performed a cued go/no-go task that measured response activation and inhibition. The study tested the degree to which response activation and inhibition developed acute and cross-session tolerance to a moderate dose of alcohol (0.65 g/kg) administered twice. Alcohol impaired response activation and inhibition during both administrations. Response activation displayed acute tolerance to alcohol during both administrations and cross-session tolerance from the first to second administration. Response inhibition was impaired by each alcohol administration but showed no acute or cross-session tolerance. Evidence of biased recovery of response activation over inhibition during a single dose and as doses are repeated could contribute to some of the impulsive behavior commonly observed under alcohol.

KEYWORDS: Alcohol, Inhibition, Activation, Tolerance, Conflict

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THESIS

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The Graduate School

University of Kentucky

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THESIS

A thesis submitted in partial fulfillment of the
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Chapter 1: Introduction

Alcohol is widely known for its disruptive effects on behavior. Acute alcohol intoxication is considered to play a role in the association of alcohol use with aggression, violence and impulsive or inappropriate behaviors (Bushman & Cooper, 1990). For example, behaviors such as vandalism, physical assaults, sexual assaults, date rape, risky driving, and riding with a drunk driver have all been linked to alcohol intoxication (Hingson, Heeren, Zakocs, Kopstein, & Wechsler, 2002; Wechsler, Moeykens, Davenport, Castillo, & Hansen, 1995). Such "disinhibition" is thought to represent an acute impairment of the ability to intentionally control one's behavior, particularly, the ability to inhibit or suppress inappropriate actions (Bates, Bowden & Barry, 2002; Eckardt, Stapleton, Rawlings, Davis, et al., 1995; Marczinski & Fillmore, 2003; Mulvihill, Skilling, & Vogel-Sprott, 1997).

In addition to the link between poor inhibitory control and drug abuse it has been suggested that extended periods of drug abuse further damage inhibitory control. There is growing evidence that prolonged alcohol abuse can produce permanent neurological adaptations that lead to lasting states of under-controlled and disinhibited behavior (e.g., Bates et al., 2002; Jentsch & Taylor, 1999; Lyvers, 2000). These permanent changes may impair an alcohol abuser in such a way that terminating a drinking session becomes more difficult upon repeated administrations. However, much remains to be discovered about the mechanisms at work in the maintenance of alcohol abuse/dependence and the effects that alcohol use has on these mechanisms.

Behavioral control theory

According to some cognitive theories of behavioral control, behavior is controlled by two opposing mechanisms which can be reduced to a potential for activation or inhibition of an action (Logan, 1994; Logan & Cowan, 1984). These two systems are essentially the behavioral activation system and the behavioral inhibition system. Behavioral control is assumed to arise from the relative strength of either response activation or response inhibition. Therefore, if the potential for response activation is relatively stronger than that of response inhibition (in theory) the response will occur. Furthermore, this theory attempts to explain disinhibited or impulsive behavior as either a weakened inhibitory system or an overactive activation system (Logan, 1994; Logan & Cowan, 1984).

Stop-signal and cued go/no-go models evaluate control of behavior as the ability to activate and to inhibit prepotent (i.e., instigated) responses (Logan, 1994; Logan & Cowan, 1984**;** Miller, Schaffer, & Hackley, 1991). The tasks model behavioral control using a reaction time scenario that measures the countervailing influences of inhibitory and activational mechanisms. Individuals are required to quickly activate a response to a go-signal and to inhibit a response when a stop-signal occasionally occurs. Activation is typically measured as the speed of responding to go-signals and inhibition to stop-signals is assessed by the probability of suppressing the response or by the time needed to suppress the response. In these models, inhibition of a response is usually required in a context in which there is a strong tendency to respond to a stimulus (i.e., a pre-potency), thus making inhibition difficult.

Research has used these laboratory models of behavioral control to study the acute effects of alcohol and found that alcohol has pronounced disruptive effects on the ability to inhibit action (Fillmore & Vogel-Sprott, 1999; Mulvihill et al., 1997). Moreover, there is growing evidence that acute alcohol administration can contribute to alcohol abuse. This may be via cue-induced craving or from acute impairment in the ability to terminate ongoing drinking during an episode (de Wit & Chutuape, 1993; Fillmore, 2001; Ludwig, Wikler & Stark, 1974). Given the potential involvement of acute impairments of inhibitory control in alcohol abuse, it is important to understand how this drug effect might change over time as drinking continues. Therefore, the purpose of this thesis was to examine the development of tolerance to the acute impairing effects of alcohol on inhibitory mechanisms of behavioral control.

Acute effects of alcohol on inhibitory control

Several studies have used the cued go/no-go model to examine the acute disruptive effects of alcohol in inhibitory control (Abroms, Fillmore & Marczinski, 2003; Fillmore, 2004; Fillmore, Marczinski & Bowman, 2005). The task presents go and no-go target stimuli that require a response to be either executed (go) or inhibited (no-go). The task includes a manipulation of response prepotency by presenting a preliminary go or no-go cue before the actual go or no-go target is displayed. The cues provide information concerning the probability that a go or no-go target will be presented. The cue-target relationship is manipulated so that cues have a high probability of correctly signaling a go or no-go target. Go cues generate response prepotency which speeds response time to go targets. However, subjects must overcome this response prepotency in order to inhibit the response if a no-go target is subsequently displayed. Failures to inhibit responses to no-go

targets are more frequent following go cues compared with no-go cues, indicating that it is more difficult to inhibit prepotent responses (Miller et al., 1991).

Studies using this task have found that moderate doses of alcohol impair inhibitory control and response activation (e.g., Abroms et al., 2003; Fillmore, 2004; Fillmore et al., 2005; Schweizer & Vogel-Sprott, 2008). For inhibitory control, alcohol-induced impairment was demonstrated by a significant increase in failures to inhibit a response to no-go targets. Similarly, for response activation, alcohol-induced impairment was evidenced by significant increases in response times to go targets. This evidence suggests that both mechanisms may be vulnerable to the impairing effects of alcohol. However, other evidence suggests that inhibitory control may be particularly vulnerable to the disrupting effects. For example, Mulvihill et al. (1997) found that a moderate dose of alcohol (0.62 g/kg) impaired the ability to inhibit a response without affecting reaction time (response activation) on the task. Fillmore and Vogel-Sprott (1999) obtained similar results, wherein response inhibition displayed impairment while response activation remained unaffected.

Other studies also suggest that response inhibition is particularly vulnerable to the disruptive effects of alcohol. For example, one study demonstrated that the ability to inhibit a response was more susceptible to impairment under alcohol than was the ability to execute an alternate response (Abroms et al., 2003). In one condition of this study, subjects performed the cued go/no-go task as described above. This condition provided information on how alcohol impaired the ability to simply inhibit a prepotent response. The experimental condition also performed the cued go/no-go task, however, this group was required to execute an alternate response to the “no-go target” rather than inhibit a

response. The results of this study demonstrated that alcohol impaired the ability to inhibit prepotent responses but did not impair the ability to execute an alternate response.

Similar to studies examining acute alcohol effects, examinations of tolerance development to the impairing effects of alcohol point to the vulnerability of response inhibition as well. The term tolerance refers to the observation that the intensity of a drug response diminishes as a function of repeated administrations of a drug, such that increasing amounts are necessary to reinstate the initial effect (Kalant, Leblanc & Gibbins, 1971). This effect can also be observed under a single administration of a dose of alcohol. Tolerance can develop in a matter of hours during a single exposure to alcohol and is intuitively referred to as acute tolerance. As alcohol is consumed, the blood alcohol concentration (BAC) initially rises rapidly and begins to gradually decline. The rising phase is referred to as the ascending limb of the BAC curve and the declining phase is referred to as the descending limb of the BAC curve. Acute tolerance can be observed by comparing performance or impairment during equivalent BACs on the ascending and descending limbs of the BAC curve (Kalant et al., 1971; Portans, White & Staiger, 1989). Acute tolerance refers to the observation that the degree of impairment at equivalent BACs is typically greater on the ascending rather than descending limb.

To date, only one study has examined acute tolerance to alcohol-induced impairment of inhibitory and activational mechanisms (Fillmore et al., 2005). In this study, twenty adult social drinkers underwent two experimental sessions in which they received either a moderate dose of alcohol (0.65 g/kg) or placebo. Dose order was counterbalanced and each subject received both the active dose and the placebo during the experiment. Within each session, each participant underwent two tests on the cued

go/no-go task. One of these two tests was administered during the ascending limb (30 minutes post-alcohol administration) and the other was administered during the descending limb (90 minutes post-alcohol administration). Both tests occurred at comparable BACs (approximately 65 mg/100ml)**.** Alcohol was found to impair response inhibition and response activation during the ascending limb. Impairment of response activation was evident by significant increases in reaction time under alcohol. Impairment of inhibitory control was evident by a significant increase in the proportion of inhibitory failures under alcohol. Response activation showed acute tolerance to the impairing effect of alcohol as speed of reaction time during the descending limb increased to baseline (i.e., sober) levels. Unlike response activation, response inhibition showed no acute tolerance to the impairing effects of alcohol and remained equally impaired on both limbs of the BAC curve. Taken together, these findings indicate that, during a single dose, inhibitory control recovers from the impairing effects of alcohol more slowly than response activation. The results also demonstrate the necessity to consider the phase of intoxication when interpreting data.

Perhaps equally important to limb consideration is the development of tolerance to alcohol's impairing effects over repeated administrations. Evidence for a lag in acute tolerance development to inhibitory versus activational mechanisms suggests that response activation and response inhibition might also differ in tolerance development as alcohol doses are repeated. Specifically, as doses are repeated, inhibitory control may develop tolerance to a lesser degree than response activation. With heavy continuous drinking, inhibitory control may become more and more impaired during the descending limb, compared to response activation, and this could lead to an "activational-bias" in the

control of behavior. Evidence of such an activational-bias of behavior could provide better understanding of some of the behaviorally-disruptive effects of the drug. An activational-bias in a drinking situation could increase the likelihood of disinhibited behavior under the drug, especially in the presence of environmental cues that instigate responses that are normally suppressed. Thus, an activational-bias could increase the likelihood of aggressive actions or continued, "binge" drinking. However, few studies have examined tolerance development in regards to behavioral control and it remains unclear how tolerance may alter behavioral control under alcohol.

Tolerance has long been considered to contribute to alcohol abuse and dependence largely because it is assumed that drinkers who become tolerant increase their consumption to achieve the effects initially experienced. In addition, any development of an activational-bias in behavior could also contribute to abuse by making it more difficult for the drinker to suppress or terminate ongoing behavior in the drinking situation, such as taking the next drink, and therefore increasing the risk of under controlled, binge drinking. Given that impaired inhibitory control and tolerance have both been implicated in alcohol abuse and dependence it is important to understand how inhibitory control is altered as alcohol tolerance develops. To my knowledge, there are currently no studies that examine the differential development of tolerance in inhibitory and activational mechanisms across repeated doses.

Therefore, the purpose of this thesis was to use the cued go/no-go model to examine the degree of tolerance observed for activational and inhibitory mechanisms across two administrations of a dose of alcohol.

Inhibitory control and response conflict

The findings reviewed in this study show the utility of the cued go/no-go model for distinguishing alcohol effects on inhibitory and activational mechanisms implicated in the control of behavior. The cued go/no-go task is essentially a model of response conflict. Response conflict occurs when both activational and inhibitory mechanisms are aroused simultaneously (i.e., arousal of competing response tendencies) (Steele & Southwick, 1985). The demand to execute fast responses to go targets conflicts with the need to suddenly inhibit these responses when no-go targets are presented. It has long been known that the impairing effects of alcohol on inhibitory control are most evident in these types of conflict (e.g., Fillmore & Vogel-Sprott, 2000; Steele & Southwick, 1985). Alcohol-induced impairment of inhibitory control can be further increased when the conflicting responses are motivated by external reinforcement, such as when there is monetary incentive provided for making fast responses, but also for being able to inhibit responses when necessary (Fillmore et al., 2005; Fillmore, Blackburn & Harrison, 2008). Indeed, Fillmore et al. (2008) studied alcohol effects on inhibitory control using the cued go/no-go task and found that alcohol induced disinhibition was greatest when equal monetary incentives were provided for quick responses and for correctly inhibiting a response when necessary. A meta-analysis of studies of alcohol effects on a variety of social and interpersonal measures (e.g., aggression, risk-taking, sexual behaviors) also found that the disinhibiting effect of the drug was most pronounced when there was some conflicting motivational consequence (e.g., money) for inhibiting and for displaying the response (Steele & Southwick, 1985).

In sum, there appears to be a consistent body of laboratory evidence to suggest that the risk of disinhibited, impulsive behavior under alcohol is greater under motivated conflict situations in which displaying a response is as equally motivating as inhibiting the response. The importance of external reinforcement in conflict models also is well recognized for its ecological relevance to behavior outside the laboratory. Outside the lab, environmental cues that signal conflicting responses are often primary or secondary reinforcers that provide expectations of reward or threats of punishment for particular actions. Given the relevance of conflict to behavioral control under alcohol, this thesis examined the development of tolerance to alcohol impairment of inhibitory and activational mechanisms of behavioral control under conditions of motivated conflict.

Study overview and hypotheses

To date, tolerance in mechanisms of behavioral control has only been observed over the time course of a single dose. Furthermore, nothing is known about how tolerance might develop to inhibition in the presence of a heightened motivational conflict. The current study aimed to investigate the development of tolerance in mechanisms of behavioral control to a dose of alcohol (0.65 g/kg) administered on two separate test sessions. The cued go/no-go task assessed response inhibition and activation twice during each dose administration: once as BAC ascended and again at a comparable BAC on the descending limb. The two tests within each session provided a measure of acute tolerance while the second administration of the dose provided a measure of the development of tolerance across repeated administrations. Participants were tested under a motivational conflict situation as they were monetarily rewarded for fast responding to go targets and punished by an equal monetary loss for failures to inhibit responses to no-go targets. The

equal monetary incentive for inhibition and activation produces a heightened motivational conflict situation that has been shown to disinhibit behavior more so than a non-motivated conflict situation (Fillmore et al., 2008; Fillmore, Rush & Hays, 2005). As such, this thesis tested alcohol tolerance in a "high-risk" situation for disinhibited behavior.

Based on the evidence previously discussed, it was hypothesized that response activation would develop acute tolerance more quickly and to a greater degree than inhibitory control and that this effect would be present during both administrations of the dose. More specifically, alcohol was expected to impair both response activation and inhibition during the ascending limb. Impairment of response activation would be evident by a slowing of reaction time on the cued go/no-go task while impairment of inhibition would be evident by an increase in failures to inhibit responses to no-go targets. If response activation were to develop acute tolerance more quickly than inhibitory control, the slowing effect of alcohol on reaction time should diminish while the increase in failures to inhibit shows little recovery during the declining limb. Acute tolerance was hypothesized to be present within each dose administration.

Previous literature has raised the possibility that tolerance across repeated administrations and acute tolerance share a common mechanism of action (Kalant et al., 1971). However, the nature of the relationship between the degree of acute tolerance observed and the degree of tolerance across sessions has been debated. Specifically, some investigators have raised the possibility that tolerance across repeated administrations is actually just an increase in the development of acute tolerance. Indeed, Beirness and Vogel-Sprott (1984) found that the degree of acute tolerance observed under a single

administration significantly predicted the rate at which tolerance developed across four administrations of the same dose. Therefore, it is possible that tolerance development across the two sessions in the proposed study is due to an increased magnitude of acute tolerance on the second administration compared with the first administration. If so, the magnitude of impairment might be similar on the ascending limb across administrations but differ considerably on the descending limb as acute tolerance strengthens from the first to second administration. This thesis also examined this possibility.

Chapter 2: Methods

Participants

Thirty-two healthy adult volunteers were recruited through advertisements placed on the University of Kentucky campus and in the local community. Half of this sample was male and half was female. Potential volunteers with: histories of serious physical disease, current physical disease, impaired cardiovascular functioning, chronic obstructive pulmonary disease, seizure, head trauma, CNS tumors, past histories of psychiatric disorder, (i.e., Axis I, DSM IV), substance abuse disorder, medical contraindications to alcohol, abstinence from alcohol, use of prescription medications, and current pregnancy or breast-feeding were excluded from participation. Additionally, those reporting a potential risk for alcohol dependence, as determined by a score of 5 or higher on the Short-Michigan Alcoholism Screening Test (S-MAST) (Seltzer, Vinokur & Van Rooijen, 1975) were excluded from participation. Volunteers were required to have: a minimum of grade 8 education, demonstrate reading ability and no uncorrected vision or auditory problems.

The study was reviewed and approved by the University of Kentucky Medical Institutional Review Board, and all subjects provided written informed consent. Subjects earned a minimum of $70 (and a maximum of $95) for participating in the study.

Apparatus and materials

Cued go/no-go task The cued go/no-go reaction time task provided the measure of inhibitory control and response activation (Marczinski & Fillmore, 2003; Marczinski & Fillmore, 2005). Cues provide preliminary information regarding the type of imperative target stimulus (i.e., go or no-go) that is likely to follow. The cues have a high probability

of signaling the correct target. Inhibitory and activational tendencies show rapid development of cue-dependence as the cues come to elicit preparatory processes for the inhibition or execution of behavior (e.g., Miller et al., 1991; Posner, 1980). The orientation of the cue (horizontal or vertical) signals the probability that a go or no-go target will be displayed. Cues presented horizontally precede the go target on 80% of the trials and precede the no-go target on 20% of the trials. Cues presented vertically precede the no-go target on 80% of the trials and precede the go target on 20% of the trials. Previous research has demonstrated that this level of cue validity produces prepotent responding (Abroms et al., 2003; Marczinski & Fillmore, 2003; Marczinski & Fillmore, 2005).

The go cue conditions are of particular interest regarding response inhibition. Go cues generate response prepotency which speeds response time to go targets. However, subjects must overcome this response prepotency in order to inhibit the response if a no-go target is subsequently displayed. Failures to inhibit responses to no-go targets are more frequent following go cues compared with no-go cues, indicating that it is more difficult to inhibit prepotent responses (Miller et al., 1991). Moreover, inhibitory control in this prepotent, go cue condition appears to be highly sensitive to the effects of alcohol and other psychoactive drugs (for a review see Fillmore, 2003). Similarly, the no-go cue conditions will be of particular interest regarding response activation because alcohol's slowing effect is most evident in this condition. Just as the go cue condition speeds responses to go targets, no-go cues slow responses to go targets as subjects are not prepared to respond.

Subjects must overcome the lack of response prepotency created by the no-go cue in this situation in order to respond quickly.

The task was operated using E-Prime software (Schneider, Eschman & Zuccolotto, 2002) and performed on a PC. A trial involved the following sequence of events: (a) presentation of a fixation point (+) for 800 ms; (b) a blank, white screen for 500 ms; (c) a cue displayed for one of five stimulus onset asynchronies (SOAs: 100, 200, 300, 400, and 500 ms); (d) a go or no-go target that remained visible until the participant made a response or 1000 ms had elapsed; and (e) an inter-trial interval of 700 ms.

The cue was a white rectangle (7.5 cm x 2.5 cm) framed in a 0.8 mm black outline presented in the center of the computer monitor against a white background. The cue is presented in either a horizontal (height = 2.5 cm, width = 7.5 cm) or vertical (height = 7.5 cm, width = 2.5) orientation. The go and no-go targets are green and blue, respectively. They were displayed on the monitor as a solid hue that filled the interior of the rectangular cue after the duration of the SOA. The different SOAs between cues and targets encourage participants in both conditions to pay attention to the cues, and the variability and randomness of the SOAs prevented the participants from anticipating the exact onset of the targets. 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 appeared. Key presses were made with the index finger of the preferred hand.

A test consisted of 250 trials that present four possible cue-target combinations. An equal number of vertical (125) and horizontal (125) cues were presented before an equal number of go (125) and no-go (125) target stimuli. Each cue-target combination

was presented at each of the five SOAs, and an equal number of SOAs will separate each cue-target combination. The presentation of cue-target combinations and SOAs was random. For each trial, the computer recorded whether or not a response occurred and, if one occurred, the RT was measured in milliseconds from the onset of the target until the key was pressed. To encourage fast and accurate responding, feedback was presented to the participant after each test was completed. Feedback will be discussed in detail below. A test required approximately 15 minutes to complete.

Grooved pegboard task A standard Lafayette Instruments grooved pegboard (Lafayette Instruments # 32025) was used to measure subjects' motor coordination. Participants were required to pick up pegs one at a time to fill in each of the 25 holes on the board one row at a time from left to right and time to complete the trial was measured in seconds. A test consisted of four trials and the average completion time was the measure of motor coordination. Motor coordination is impaired by alcohol at this dose and typically shows acute tolerance (Beirness & Vogel-Sprott, 1984). The pegboard task was included to verify acute tolerance to motor coordination in the present study.

Subjective effect Subjective "intoxication" and subjective "ability to drive" were also measured. Participants rated their subjective intoxication and ability to drive under alcohol on a 100 mm Visual Analogue Scale (VAS) with the left-side (0 mm) indicating "not at all", and the right-side (100 mm) indicating "very much". Subjective intoxication is important to study because self-reported intoxication often displays acute tolerance. However, self-reported intoxication often differs from actual impairment of task performance (Brumback, Cao & King, 2007). Specifically, during the descending limb,

subjective effects ratings are often lower than on the ascending limb at comparable BACs (Portans, White & Staiger, 1989).

Personal drinking habits questionnaire This questionnaire provided three measures of a participant's typical drinking habits: frequency of drinking (the number of occasions per week); dose typically consumed during a single drinking occasion (milliliters of absolute alcohol per kilogram of body weight); and duration of typical drinking occasions (in hours) (Vogel-Sprott, 1992).

Procedure

Subject recruitment Volunteers were recruited via notices posted on community bulletin boards and by word of mouth. All potential volunteers completed a brief telephone interview addressing general medical and legal status. Potential volunteers were between the ages of 21 and 36 and were non-dependent, social drinkers. All respondents were required to be in good health and report occasional alcohol use (e.g., consumed alcohol on at least one occasion per week, and consume at least 3 drinks on one occasion within the past 30 days).

Intake assessment and familiarization The study was conducted at the University of Kentucky. All volunteers were tested individually and were informed that the study examined the effects of alcohol on reaction time and motor skills. Volunteers were excluded if they reported a history of serious medical illness (e.g., cardiovascular disease, neurological or psychiatric disorder). During this initial session all participants provided informed consent and completed a comprehensive medical history questionnaire, alcohol-use questionnaires, and a demographic questionnaire. Following these questionnaires, participants became familiarized with the grooved pegboard task (GPT) and the cued

go/no-go task. Participants underwent 2 tests on the GPT and one test on the cued go no go task. Participants completed two tests (8 trials) on the GPB as this task has been shown to be initially susceptible to practice effects (Bryden & Roy, 2005). However, the GPT has shown fairly high test-retest reliability ($r > 0.80$) and the eight trials during familiarization is sufficient to limit practice effects during subsequent sessions (Lezak, Howieson & Loring, 2004). Previous research has shown that one practice trial on the cued go/no-go task is sufficient in familiarizing participants with the task (Marczinski & Fillmore, 2003).

Design overview Participants were randomly assigned to an alcohol condition (ALC group) or to a control condition (CON group). Each group consisted of 16 subjects of equal gender composition. Table 1 illustrates the general experimental design of the study. First, the initial sober baseline performance level of both groups was assessed by having subjects receive a placebo drink that contained no alcohol and then perform the test battery.

Following baseline assessment, the development of tolerance was examined over two separate dose testing sessions that occurred on different days. During each of these dose sessions, those in the ALC group had their performance measured twice following 0.65g/kg alcohol: once as BAC ascended and again as BAC descended. The CON group was treated identically, but received a placebo instead during these sessions. This group served as a control for any changes in performance owing to repeated testing over the sessions. The following sections describe the procedures in detail.

Table 1. General experimental design and summary of dose administration by session for groups ALC and CON.

Group	Baseline Assessment	Dose Session 1	Dose Session 2
ALC	placebo	alcohol	alcohol
CON	placebo	placebo	placebo

Preliminary checks Subjects were required to fast for 4 h prior to each dose session. At the beginning of each dose session, volunteers completed a pre-session questionnaire that collected information about alcohol consumption, recent medication use, food consumption, and caffeine consumption.

Subjects also performed a standard field sobriety test of motor coordination, and provided a breath sample using a breath-analyzer to verify a zero BAC (Alco-Sensor III, Intoximeters, Inc., St Louis, MO). A urine sample was obtained to test for the presence of cocaine/benzoylecgonine, benzodiazepines, barbiturates, tetrahydrocannabinol (THC), *d*-amphetamine, and opiates (On Trak TesTstiks, Roche Diagnostics Corporation, Indianapolis, IN). Females were also tested for pregnancy via this urine analysis. No smoking was allowed during any session.

Baseline assessment Baseline testing occurred prior to dose session 1. Immediately following preliminary checks, all participants received an alcohol placebo and then completed the test battery. The placebo consisted of carbonated mix with 3 ml of alcohol

floated on the surface and the glass was sprayed with an alcohol mist that resembles condensation and provides a strong alcoholic scent as the beverage is consumed. Participants had 6 minutes to consume the drink. Previous research has shown that individuals report that this beverage contains alcohol (e.g., Fillmore & Blackburn, 2002). Ten minutes after receiving the placebo subjects performed the test battery to measure their sober levels of performance and their subjective states. The test battery consisted of: the cued go/no-go task, the subjective effect questionnaire, and the grooved pegboard test. The battery required approximately 20 minutes to complete. Sober baseline performance was tested after a placebo in order to hold constant the expectancy of alcohol during all test sessions in the experiment.

Dose sessions Following completion of the baseline testing, the ALC group was tested in response to 0.65 g/kg of alcohol administered twice (over two sessions). Doses were calculated based on body weight and administered as absolute alcohol mixed with three parts carbonated soda. Participants had 6 minutes to consume the drink. The 0.65 g/kg dose produces an average peak BAC of 80 mg/100ml at approximately 60 minutes following the beverage administration and begins to decline at about 70 minutes post-administration (Fillmore & Blackburn, 2002; Fillmore, Marczinski & Bowman, 2005).

The 0.65 g/kg was chosen based on prior research that has shown that this dose reliability impairs the ability to quickly activate and inhibit responses as measured by the cued go/no-go task (Fillmore & Weafer, 2004; Marczinski & Fillmore, 2003). Participants performed the test battery once while BAC ascended (40 minutes post-administration) and once while it descended (100 minutes post-administration). Based on previous studies of this dose, these testing times were expected to occur at comparable BACs on

each limb (approximately 70 mg/100ml) (Fillmore, Marczinski & Bowman, 2005). Subjects' BACs were measured just prior to and after completing the test battery (at 40, 60, 100 and 120 minutes post-administration). Subjects relaxed and read magazines during the periods between testing. Subjects were at the laboratory only for scheduled sessions and returned home after each session was completed. Once the descending limb test battery was completed, subjects were allowed to watch television and relax until BACs fell below 20 mg/100ml. Once this BAC was reached, participants were released following a field sobriety test. Each dose session required approximately 7 hours to complete. The two dose sessions were conducted on different days, with a minimum inter-session interval of 24 h and a maximum interval of 2 weeks. Participants were debriefed following the completion of dose session 2. The CON group was treated identically to the ALC group, however, CON was tested in response to a placebo (0.0 g/kg). The placebo was identical to the placebo used in the baseline test.

Motivated conflict During the two dose sessions, all participants were monetarily rewarded for performance on the cued go/no-go task. These rewards provided equal incentive to both quickly execute responses and to inhibit responses when necessary. Participants received five cents for each fast response to go targets (255 ms or less). Participants also lost five cents for each failure to inhibit a response to a no-go target (incorrect response). During dose sessions, the cued go/no-go task no longer displayed the reaction time to make a response nor did it inform participants of an incorrect response. Participants were instead informed of how much money was earned on a trial immediately following completion of that trial.

The money earned for performance on the cued go/no-go task was in addition to participation payment. Within each test, the maximum number of possible rewards was 125. Therefore, participants could earn up to $6.25 per test on the cued go/no-go task. With two tests per session and two testing sessions, participants could earn up to $25.00 for performance on this task.

Criterion measures of performance and data analyses

Cued go/no-go performance The cued go/no-go task measured subjects' failures to inhibit a response to a no-go target (failures of inhibition) and speed of responding to go targets (response activation). Response activation was measured by the reaction time (RT) to go targets in the no-go cue condition. Responses with RTs less than 100 ms and greater than 1000 ms were excluded. Reaction times during baseline testing were compared for groups ALC and CON. The two groups were expected to be comparable at baseline due to random assignment. Change from baseline during dose session days was used in order to analyze specific responses to the drug regardless of individual skill level. Baseline performance differences can be controlled for by subtracting baseline performance scores from performance on each test during the dose sessions. Thus, longer RT change scores indicated impaired response activation during a test compared to baseline. These RT change scores were analyzed by a 2 Group (ALC vs. CON) x 2 Test (ascending vs. descending limb) x 2 Session (first vs. second) mixed-design analysis of variance (ANOVA). A main effect of group was expected such that the ALC group has slower reaction times than the CON group. This main effect would indicate the impairing effects of alcohol on reaction time. A Group x Limb interaction was also expected such that the ALC group has quicker reaction times (i.e., less impairment) during descending

rather than ascending tests while the CON group should display no systematic change over these two test periods. This interaction would indicate acute tolerance in the ALC group. Additionally, any evidence of tolerance over repeated doses would be observed by a Group x Session interaction. This interaction was also expected such that the ALC group should have less slowing of their reaction times during dose session 2 compared to dose session 1.

Failure of response inhibition was measured as the proportion of no-go targets in the pre-potent, go cue condition which a subject fails to inhibit a response. The p-inhibition failure scores obtained during baseline testing were compared for groups ALC and CON. The two groups were expected to be comparable at baseline due to random assignment. Change from baseline during dose session days were used in order to analyze specific responses to the drug regardless of individual skill level. Thus, larger p-inhibition failure change scores indicated impaired response inhibition during a test compared to baseline. The p-inhibition failure change scores (from baseline) were analyzed by a 2 Group (ALC vs. CON) x 2 Test (ascending vs. descending limb) x 2 Session (first vs. second) mixed-design analysis of variance (ANOVA). A main effect of group was expected such that the ALC group should have a higher proportion of inhibitory failures than the CON group. This main effect would be evidence of the impairing effects of alcohol on inhibitory control. No evidence of acute tolerance or tolerance over repeated doses was expected. Therefore, no other main effects or interactions were expected for response inhibition.

Grooved pegboard performance Subjects' motor skills impairment was measured by a subject's mean time (sec) to complete the grooved pegboard test. Their mean time

during the baseline testing was subtracted from their mean times during dose sessions. Slower mean change scores from baseline indicated greater motor skills impairment under alcohol. The change scores on the tests during the dose sessions were analyzed by a 2 Group (ALC vs. CON) x 2 Test (ascending vs. descending limb) x 2 Session (first vs. second) mixed-design analysis of variance (ANOVA). A main effect of group was expected such that the ALC group should have slower completion times than the CON group. This main effect would indicate the impairing effects of alcohol on the GPT. Evidence of acute tolerance on the GPT should be observed as a Group x Limb interaction such that the ALC group should have quicker completion times (i.e., less impairment) during descending rather than ascending tests while the CON group should display no systematic change over these two test periods. Additionally, any evidence of tolerance over repeated doses would be observed by a Group x Session interaction such that the ALC group would have less slowing of their completion times during dose session 2 compared to dose session 1. Again, no systematic changes were expected from the CON group.

Subjective measures Participants' subjective ratings from the VAS were each analyzed separately by a 2 Group (ALC vs. CON) x 2 Test (ascending vs. descending limb) x 2 Session (first vs. second) mixed-design analysis of variance (ANOVA). Higher ratings for "intoxication" indicated greater subjective intoxication while lower ratings for "able to drive" were indicative of perceived impairment in driving ability. A main effect of group was expected such that the ALC group should have higher subjective intoxication ratings than the CON group and lower subjective able to drive ratings. Evidence of acute tolerance for subjective effects should be observed as a Group x Limb interaction such

that the ALC group had lower subjective ratings during descending rather than ascending tests (or higher ratings for ability to drive). Additionally, any evidence of tolerance over repeated doses would be observed by a Group x Session interaction such that the ALC group would have lower subjective ratings of intoxication during dose session 2 compared to dose session 1 (and higher ratings of ability to drive). No systematic changes were expected from the CON group.

BAC Subjects' blood alcohol concentration were analyzed by a 2 Group (ALC vs. CON) x 2 Test (ascending vs. descending limb) x 2 Session (first vs. second) mixed-design analysis of variance (ANOVA).

Gender differences Outcome measures were initially analyzed by 2 (Group) x 2 (Gender) x 2 (Test) x 2 (Session) ANOVAs. Men and women did not differ in their response to alcohol on any measure in the test battery, as evident by the lack of significant Group x Gender interactions (*ps* > .18). Men and women also did not differ in their rate of recovery from ascending to descending limb tests as evident by a lack of Group x Gender x Limb interactions (*ps* > .20). Therefore, analyses of the test battery are reported with the gender factor removed.

Chapter 3: Results

Sample characteristics

No significant difference between ALC and CON groups was obtained with respect to age or weight (*ps* > .68). The average age of the sample was 22.9 years (SD = 2.4) and the average weight of the sample was 68.9 kg (SD = 11.7). The groups also did not differ in respect to drinking habits as measured by weekly frequency of alcohol use, number of drinks typically consumed, and duration of typical drinking episode (*ps* > .27). The entire sample reported an average weekly frequency of 2.8 (SD = 1.9) drinking occasions, with a typical consumption of 4.7 (SD = 2.2) drinks per occasion over an average duration of 3.8 hours (SD = 1.6). The groups also did not differ in respect to the intersession interval between dose session 1 and dose session 2 (*p* > .41). The average intersession interval for the sample was 5.4 days (SD = 3.6).

There was no detectable BAC in the placebo condition. BACs of the ALC group were analyzed by a 2 Gender x 2 Test (ascending vs. descending limb) x 2 Session (first vs. second) ANOVA that revealed no significant main effects or interactions (*ps* > .13). The BACs were comparable between men and women across limbs and across the sessions. During dose session 1, the mean BACs for the ascending and descending limbs were 75 mg/100 ml (SD = 19) and 84 mg/100 ml (SD = 18), respectively. During dose session 2, the mean BACs for the ascending and descending limbs were 81 mg/100 ml (SD = 21) and 80 mg/100 ml (SD = 16), respectively.

Cued go/no-go performance

Response activation The baseline RT of the two groups did not differ significantly during sober baseline assessment (*p* > .47). The mean baseline RT of the sample was

301.8 ms (SD = 22.8). The 2 (Group) x 2 (Test) x 2 (Session) ANOVA of change in RT showed a significant main effect of Group, $F(1, 30) = 10.43$, $p < .01$, and a significant Group x Test interaction, $F(1, 30) = 6.19$, $p = .02$. Figure 1 plots the mean change in RT for each group during the ascending and descending limbs on each dose session. The figure shows that the group effect was due to a slowing of RT in the ALC group compared with little change from baseline displayed in the CON group. Thus, as expected, alcohol impaired response activation by slowing RT. Figure 1 also shows that the interaction was due to reduced impairment over limbs in the ALC group (i.e., acute tolerance) coupled with little change in RT across limbs in the CON group. For the ALC group, planned comparison *t* tests confirmed significantly less impairment on tests during the descending versus the ascending limbs (*ps* < .03) and less impairment during the second versus first dose administration (*ps* < .04). By contrast, no significant changes in RT were observed in the CON group (ps > .05).

Figure 1

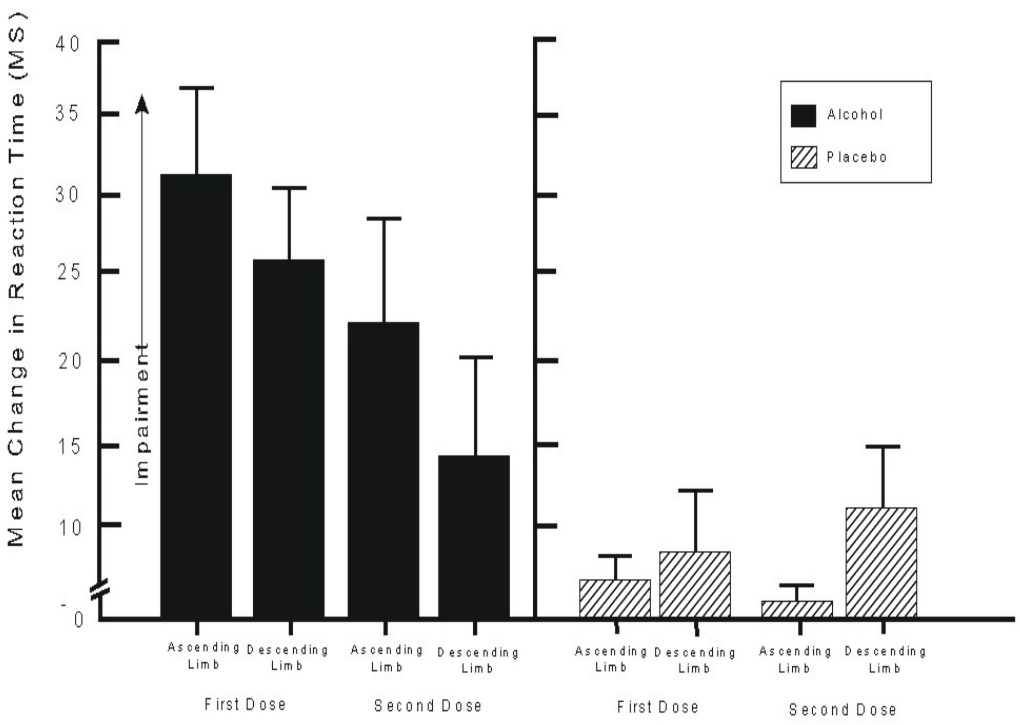

Figure 1. Mean change from baseline in reaction time on the cued go/no-go task for both groups in response to either the placebo or active dose of alcohol (0.65 g/kg). Each dose session includes both ascending and descending limb performance for the two groups. Capped vertical lines show the standard error of the mean.

Response inhibition The baseline p-failure scores of the two groups did not significantly differ during baseline ($p > .94$). The mean p-failure score of the sample during baseline was 0.07 (SD = 0.1). The 2 (Group) x 2 (Test) x 2 (Session) ANOVA showed a significant main effect of Group, $F(1, 30) = 2.99$, $p = .05$. No other main effects or interactions were observed. Figure 2 plots the mean change in p-failures for each group during the ascending and descending limbs during each dose session. The figure shows that the group main effect was due to increased inhibitory failures of the ALC group compared with the CON group during both sessions.

Motor skill performance and subjective intoxication

The baseline pegboard scores of the two groups did not differ significantly during baseline ($p > .58$). The mean baseline completion time of the sample was 54.0 seconds (SD = 5.7). The 2 (Group) x 2 (Test) x 2 (Session) ANOVA of change from baseline showed a significant main effect of Session, $F(1, 30) = 8.41$, $p = .01$, and a Group x Test interaction, $F(1, 30) = 7.27$, $p = .01$. Table 2 and Figure 3 present the pegboard change scores. Positive change scores represent slower completion times compared with baseline (i.e., impairment). The table and figure show a slowing in the ALC group that was not observed in the CON group. Moreover, there was little evidence of impairment on descending limb tests for the ALC group during both sessions. Planned comparisons confirmed significantly less impairment in the ALC group during the descending versus ascending limbs ($p < .01$), but no difference in impairment from first to second dose session ($p > .51$).

Figure 2

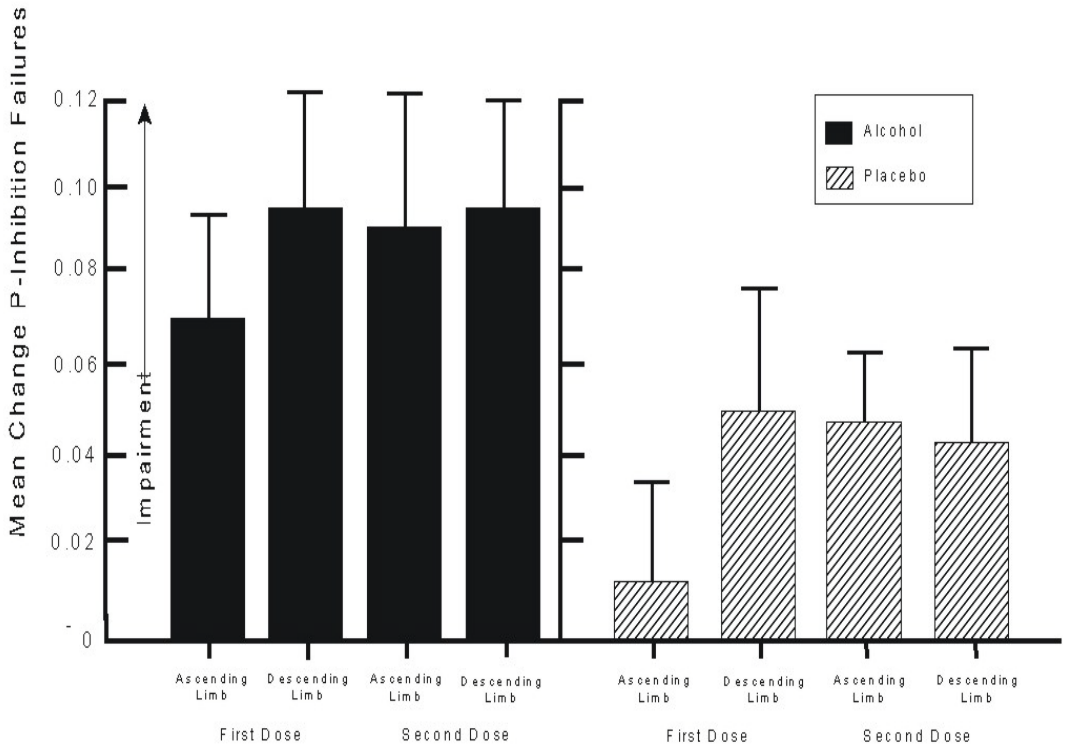

Figure 2. Mean change from baseline in inhibitory failures for both groups in response to either the placebo or active dose of alcohol (0.65 g/kg). Each dose session includes both ascending and descending limb performance for the two groups. Capped vertical lines show the standard error of the mean.

Figure 3

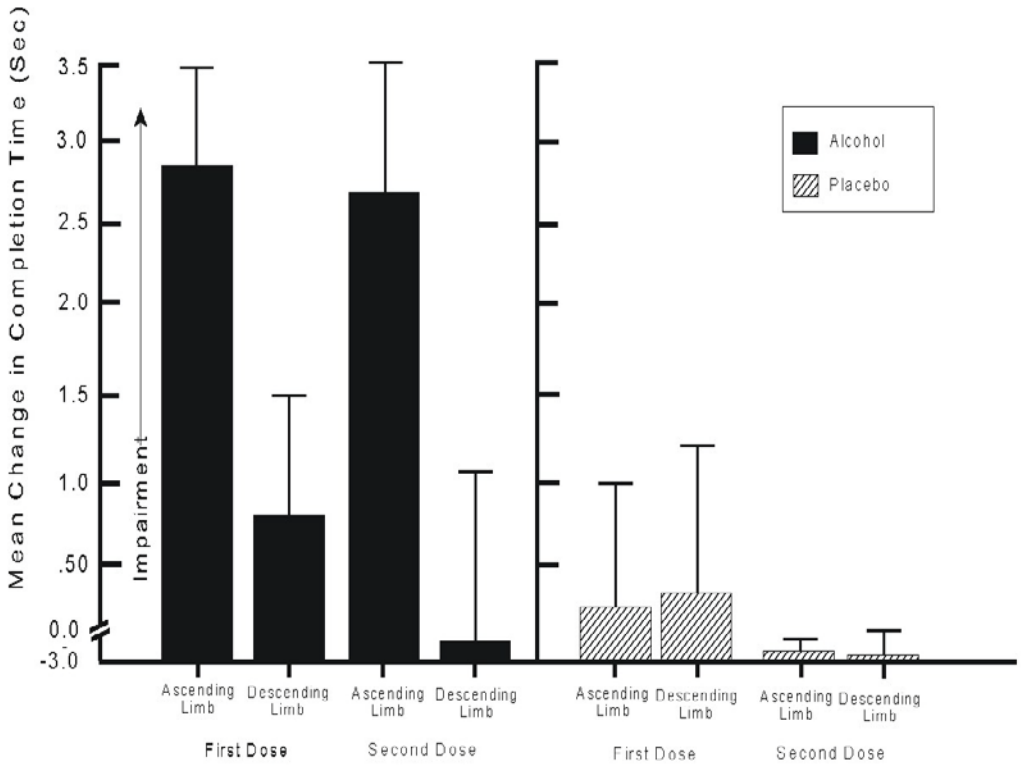

Figure 3. Mean change from baseline in grooved pegboard completion times for both groups in response to either the placebo or active dose of alcohol (0.65 g/kg). Each dose session includes both ascending and descending limb performance for the two groups. Capped vertical lines show the standard error of the mean.

The CON group showed similar levels of performance on ascending versus descending limbs during both sessions. The figure shows that the main effect of session was due to a slight speeding effect for both groups during the second versus first dose session. The groups did not differ significantly in baseline ratings of intoxication (*ps* > .62). The mean rating of the sample during baseline assessment was 13.2 (SD = 12.5). Change from baseline for subjective effect ratings are presented in Table 2. Positive scores for ratings of intoxication indicate a perceived increase in subjective intoxication and negative scores for ratings of able to drive indicate a perceived decrease in ability to drive. For intoxication ratings, the (Group) x 2 (Test) x 2 (Session) ANOVA showed a significant main effect of Group, $F(1, 30) = 63.11$, $p < .01$, and a Group x Test x Session interaction, $F(1, 30) = 6.86$, $p = .01$. Figure 4 shows that ALC group reported increased subjective intoxication that diminished on descending versus ascending limb tests (i.e., acute tolerance). Simple effects comparisons confirmed that subjective intoxication decreased significantly from ascending to descending limbs in both sessions ($p < .01$). Figure 4 also shows that ALC group's subjective intoxication ratings were significantly lower during the second versus first dose session ($p < .01$).

The groups did not differ significantly in baseline ratings of able to drive (*ps* > .64). The mean rating of the sample during baseline assessment was 75.2 (SD = 26.4). Change from baseline for subjective effect ratings are presented in Table 2. The ANOVA revealed a significant main effect of Group, $F(1, 30) = 41.01$, $p = .000$, such that the ALC group had decreased ratings of ability to drive compared with the CON group. The analysis also showed a main effect of Test, $F(1, 30) = 13.90$, $p = .001$, and a main effect of Session, $F(1, 30) = 4.83$, $p = .036$, such that ratings were higher on

descending limb tests and during dose session two. The analysis also showed a significant Group x Test x Session interaction, $F(1, 30) = 5.08$, $p = .032$, such that the CON and ALC groups both displayed increased ratings from the ascending to descending limb of dose session one but only the ALC group displayed an increase from ascending to descending limb of dose session two. Figure 5 shows that, during dose session two, the CON group displayed ratings very comparable to the descending limb of dose session one. Simple effects comparisons for the ALC group confirmed that perceived ability to drive significantly increased from ascending to descending limbs during both sessions ($p < .05$). Figure 5 also shows, however, that ALC group's able to drive ratings were not significantly lower during the second versus first dose session ($p > .10$).

Figure 4

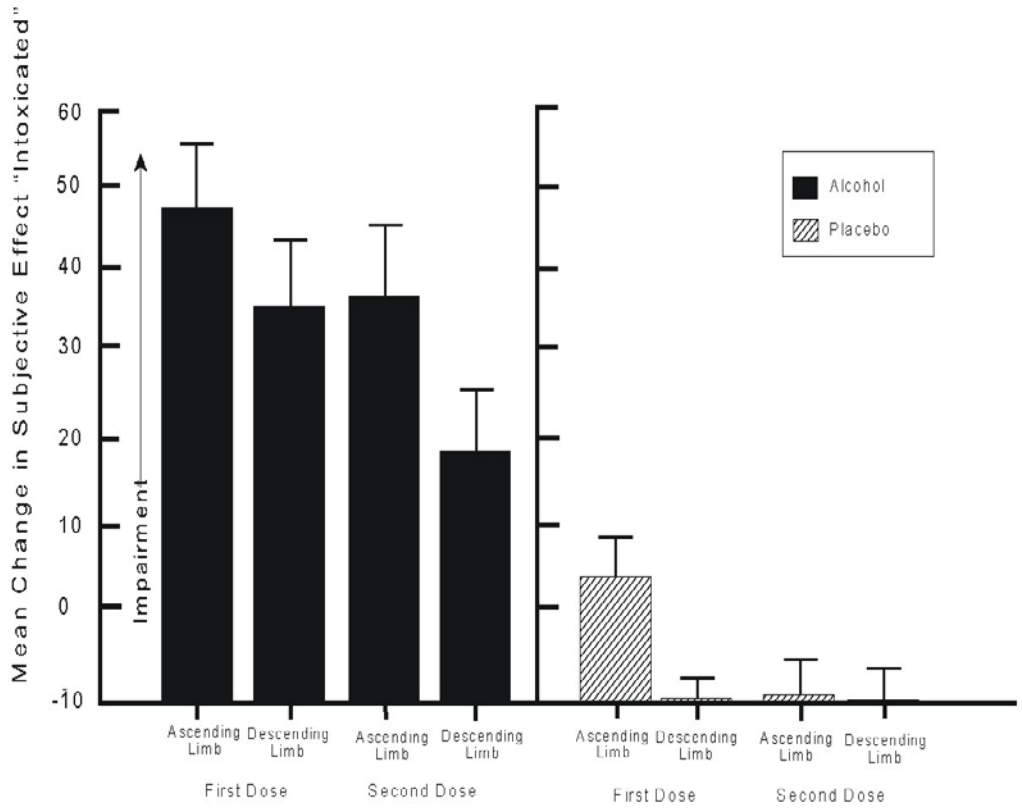

Figure 4. Mean change from baseline in ratings of intoxicated for both groups in response to either the placebo or active dose of alcohol (0.65 g/kg). Each dose session includes both ascending and descending limb performance for the two groups. Capped vertical lines show the standard error of the mean.

Figure 5

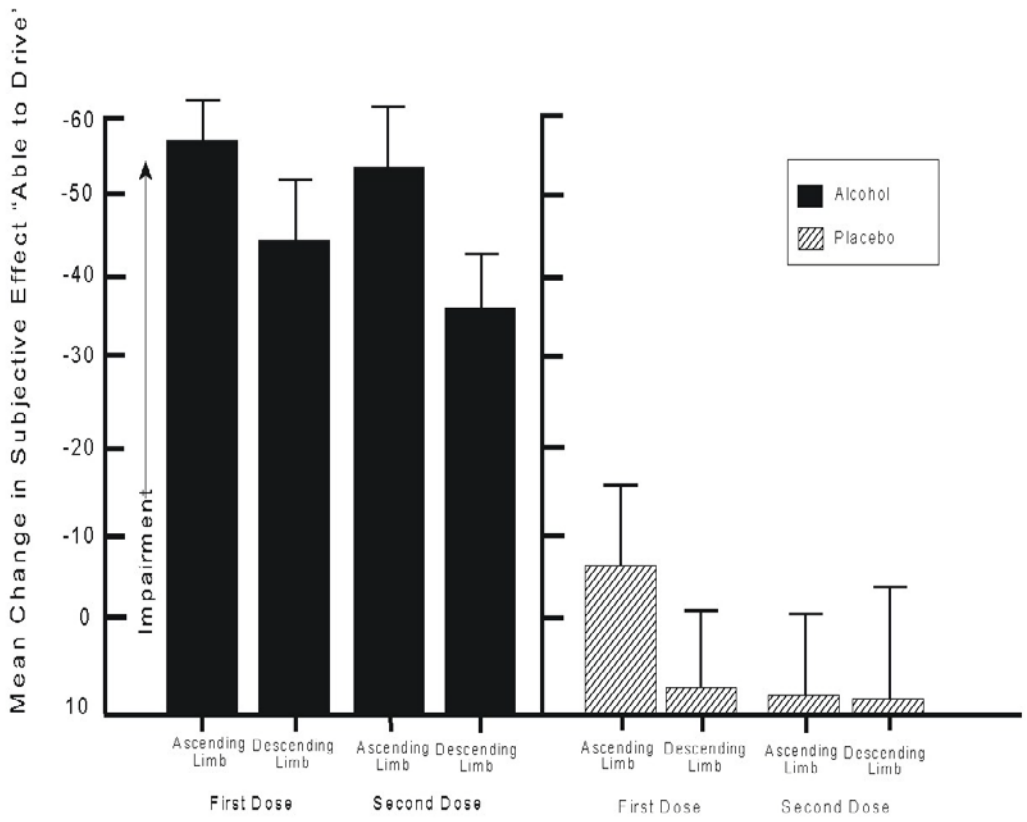

Figure 5. Mean change from baseline in ratings of able to drive for both groups in response to either the placebo or active dose of alcohol (0.65 g/kg). Each dose session includes both ascending and descending limb performance for the two groups. Capped vertical lines show the standard error of the mean.

Table 2

Change scores from baseline for grooved pegboard performance and subjective effect ratings

		Dose Session One				Dose Session Two			
		Test 1		Test 2		Test 1		Test 2	
	Group	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Pegboard	ALC	2.8	3.3	0.8	3.0	2.7	4.2	-0.02	4.9
	CON	0.2	2.9	0.4	3.0	-1.9	2.9	-2.1	2.6
Subjective Effects									
Able to Drive	ALC	-56.6	31.3	-44.3	31.3	-53.0	31.6	-35.7	28.7
	CON	-9.3	23.3	6.25	21.0	7.7	31.2	7.1	36.2
Intoxicated	ALC	48.3	23.7	35.4	27.2	37.4	24.2	19.3	23.0
	CON	4.5	14.1	-10.0	10.3	-8.4	9.9	-11.8	13.6

Note. The numerical values presented are the means and standard deviations of change from baseline for groups ALC and CON. Pegboard scores are presented in seconds and positive scores indicate slowed performance compared to baseline. Negative change scores for “able to drive” indicate a decreased perception in ability to drive and positive change scores of “intoxicated” indicate an increase in perceived level of intoxication.

Chapter 4: Discussion

This study examined the differential development of tolerance to the impairing effects of alcohol on activational and inhibitory mechanisms of behavioral control. The study showed that response activation and inhibition were significantly impaired by the dose of alcohol during both sessions. However, impairment of response activation under alcohol displayed evidence of acute tolerance as impairment was significantly less during the descending versus ascending limbs of both dose sessions. Alcohol-induced impairment of response activation also displayed evidence of cross-session tolerance as impairment was diminished during the second dose session.

Alcohol also impaired response inhibition, and this impairment was evident by increased failures to inhibit responses following both doses of alcohol. In contrast to response activation, response inhibition showed no acute or cross-session tolerance to the impairing effects of alcohol. Indeed, the degree to which alcohol increased inhibitory failures remained fairly similar across limbs within a session and between the sessions. Finally, the study also demonstrated acute tolerance to the perceived effect of alcohol intoxication and ability to drive (as measured by self-report) and to the impairing effect of alcohol on psychomotor function (as measured by the pegboard task).

The evidence was obtained from a within-subjects design, using a single task that provided concurrent assessment of activational and inhibitory aspects of behavioral control. The scheduling of tests was based on considerable prior research on the pharmacokinetic profile of the active dose. The average BACs during the testing periods on each limb of the blood alcohol curve were nearly identical, and thus the reduced impairment observed on the descending limb cannot be attributed to limb-differences in

BAC. Differences in the recovery of impaired activation and inhibition during the dose also cannot be attributed to any speed-versus-accuracy trade-off. In a speed-accuracy trade-off, any alcohol-induced slowing of RT should actually improve response inhibition by allowing more time to inhibit responses when necessary. Instead, the alcohol-induced slowing of response activation in the present research was accompanied by a reduction in the ability to inhibit responses.

This study is the first to examine the differential development of tolerance to impaired response activation and response inhibition across repeated alcohol administrations. The findings are consistent with those investigating the differential development of acute tolerance between response activation and response inhibition during a single dose administration. Such studies have found that during a single alcohol exposure impaired response activation displays acute tolerance while response inhibition remains impaired from ascending to descending limb tests (Fillmore, Marczinski & Bowman, 2005). Previous demonstrations of this "activational-bias" in recovery during the declining limb also did not involve a motivated conflict situation. The present study employed a motivational conflict situation because it has been argued to better represent conflicting response tendencies outside the laboratory. Outside of the laboratory, there are often consequences motivating competing response tendencies. Despite the addition of motivated conflict, the differences in tolerance development between activation and inhibition were remarkably similar to those observed without the motivating consequences (e.g., Fillmore, Marczinski & Bowman, 2005). Moreover, as the current study obtained evidence of acute tolerance for response activation during two separate dose sessions, it provides a repeated demonstration of this effect in the same subjects.

Taken together, these studies provide support for the argument that tolerance develops more rapidly to the impairing effects of alcohol for activational aspects compared with inhibitory aspects of behavioral control, and that this activational-bias in recovery might be a robust effect, evident across a range of environmental circumstances.

Evidence for an activational-bias in recovery of behavioral control during the declining limb might have important implications for understanding some of the impulsive behavior and poor-decision making commonly observed under alcohol. Generally speaking, impulsivity reflects a biased tendency for action over inaction. Accordingly, the biased recovery of response activation over inhibition could contribute to the display of impulsive behavior even while BAC falls during the declining portion of the BAC curve. Moreover, critical decisions are often made by the drinker during the descending portion of the BAC curve, such as the decision to drive. This phase of intoxication is also when perceived impairment from alcohol begins to decrease and when motor coordination begins to recover. The current results revealed that, during the declining limbs of each session, ALC group's subjective ratings of intoxication and able to drive displayed acute tolerance. It is possible that the perceived recovery of impairment combined with recovery of motor coordination serve as a cue for sobriety. However, based on the current results, the drinker may still have significantly impaired inhibitory control for some time. This amount of time remains unknown, however, it is clear that impairment is present even though perceived effects are not. Taken together, a bias towards behavioral activation coupled with a reduced perception of intoxication during the declining limb could jointly contribute to poor decision making and risky behavior for some period of time after drinking has ended. In addition, this effect may be

exacerbated upon repeated administrations due to the development of cross-session tolerance to response activation.

The study also provides some information on the relationship between acute tolerance during a single dose and cross-session tolerance as the dose is repeated. Some theories suggest that acute tolerance contributes to the development of chronic tolerance, because they both share some common underlying adaptive processes (e.g., Kalant et al., 1971). Some investigators have suggested that tolerance over repeated doses might actually occur as a result of greater acute tolerance as doses are repeated (e.g., Beirness & Vogel-Sprott, 1984). That is, tolerance develops over repeated doses because acute recovery during the declining limb increases each time the dose is administered. In the present study, speed of response activation demonstrated acute tolerance during each dose and tolerance across the two doses. However, the increased tolerance observed during the second dose was not confined to the declining limb. Figure 1 shows marked reduction in impairment during the ascending limb of the second dose compared with either test during the first dose. Thus, the tolerance displayed during the second dose appeared on both limbs and was not simply due to greater recovery during the declining limb. In sum, the evidence suggests that cross-session tolerance to impaired response activation might reflect a recovery that is evident during both limbs of the BAC curve. Though acute tolerance was present for motor skills impairment during both sessions, cross-session tolerance was not observed. As was previously mentioned, this task was included as a manipulation check showing that the current methods and dose were sufficient to impair motor coordination. Therefore, participants were not rewarded for their performance on the pegboard task. Due to this difference in procedure concerning

rewards, comparisons cannot be accurately made between cognitive and motor skills tolerance development. The results of the current study are in agreement with previously discussed literature that suggests motor coordination is slower to recover from alcohol impairment than some aspects of cognitive impairment. However, the lack of cross-session tolerance in the current study may be due to the lack of reward (and therefore lack of motivation or feedback). Future research may want to include rewards for performance on the pegboard and compare motor skill tolerance development to that of cognitive impairment under motivated conflict. Regardless of this limitation, the results suggest that motor skill impairment recovers more swiftly than inhibitory control. It is therefore important to consider which cognitive mechanism (or which model) is being compared to motor impairment, as all cognitive impairments do not recover uniformly.

It is also important to recognize that a variety of methods have been used to study acute alcohol tolerance in humans. The present findings were based on comparisons between ascending and descending limbs of a blood alcohol curve following a single administration of alcohol. Although BACs can be matched across limbs, there are usually differences in the rate of change in BAC between limbs. The rate of rise in BAC is usually swifter than the rate of descent. These rate differences could also affect impairment (e.g., Fillmore & Vogel-Sprott, 1999). Acute alcohol tolerance also has been studied using frequent administrations of low doses to achieve a "steady state" BAC over time within a session (Kaplan, Sellers, Hamilton, Naranjo & Dorian, 1985) and more recently by intravenous ethanol infusion techniques designed to "clamp" the infusion rate to maintain a specific BAC (O'Connor, Morzorati, Christian & Li, 1998). The clamping technique appears quite effective in holding BAC stable in an individual, and may be a

useful procedure to further investigate differences in acute tolerance to impaired inhibition and activation of behavior as a function of exposure time as BAC is held constant.

In conclusion, the results highlight the importance of considering behavioral requirements when testing for the development of tolerance under a dose of alcohol. By modeling behavioral control as the net effect of countervailing activational and inhibitory influences, the study suggests that fundamental mechanisms of control might not display uniform tolerance development. Evidence for a lag in tolerance development to inhibitory mechanisms raises important questions about the point at which inhibitory control does recover during the time-course of a single dose, and if impaired inhibitory control might eventually demonstrate cross-session tolerance as a function of more repeated doses.

References

Abroms, B. A., Fillmore, M. T., & Marczinski, C. A., (2003). Alcohol-induced impairment of behavioral control: Effects on the alteration and suppression of prepotent responses. *The Journal of Studies on Alcohol, 64,* 687-695.

Bates, M. E., Bowden, S. C., & Barry, D., (2002). Neurocognitive impairment associated with alcohol use disorders: Implications for treatment. *Experimental and Clinical Psychopharmacology, 10 (3),* 193-212.

Beirness, D., & Vogel-Sprott, M., (1984). The development of alcohol tolerance: Acute recovery as a predictor. *Psychopharmacology, 85,* 398-401.

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 (1),* 10-17.

Bryden, P. J., & Roy, E. A., (2005). A new method of administering the Grooved Pegboard Test: Performance as a function of handedness and sex. *Brain and Cognition, 58 (3),* 258-268.

Bushman, B. J., & Cooper, H. M., (1990). Effects of alcohol on human aggression: An integrative research review. *Psychological Bulletin, 107 (3),* 341-354.

de Wit, H., & Chutuape, M. A., (1993). Increased ethanol choice in social drinkers following ethanol preload. *Behavioral Pharmacology, 4,* 29-36.

Eckardt, M. J., Stapleton, J. M., Rawlings, R. R., Davis, E. Z., et al., (1995). Neuropsychological functioning in detoxified alcoholics between 18 and 35 years of age. *American Journal of Psychiatry, 152 (1),* 45-52.

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, 15,* 325-332.

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., (2004). Environmental dependence of behavioral control mechanisms: Effects of alcohol and information processing demands. *Experimental and Clinical Psychopharmacology, 12 (3),* 216-223.

Fillmore, M. T., & Blackburn, J., (2002). Compensating for alcohol-induced impairment: Alcohol expectancies and behavioral disinhibition. *The Journal of Studies on Alcohol, 63,* 237-246.

Fillmore, M. T., Blackburn, J. S., & Harrison E. L. R., (2008). Acute disinhibiting effects of alcohol as a factor in risky driving behavior. *Drug and Alcohol Dependence, 95 (1-2),* 97-106.

Fillmore, M. T., Marczinski, C. A., & Bowman, A. M., (2005). Acute tolerance to alcohol effects on inhibitory and activational mechanisms of behavioral control. *The Journal of Studies on Alcohol, 33,* 663-672.

Fillmore, M. T., Rush, C. R., & Hays, L., (2005). Cocaine improves inhibitory control in a human model of response conflict. *Experimental and Clinical Psychopharmacology, 13 (4),* 327-335.

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., & Vogel-Sprott, M., (2000). Response inhibition under alcohol: Effects of cognitive and motivational conflict. *Journal of Studies on Alcohol, 61,* 239-246.

Fillmore, M. T., & Weafer, J., (2004). Alcohol impairment of behavior in men and women. *Addiction, 99,* 1237-1246.

Hingson, R. W., Heeren, T., Zakocs, R. C., Kopstein, A., & Wechsler, H., (2002). Magnitude of alcohol-related mortality and morbidity among U.S. college students ages 18-24. *Journal of Studies on Alcohol, 63 (2),* 136-144.

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 (4),* 373-390.

Kalant, H., Leblanc, A. E., & Gibbins, R. J., (1971). Tolerance to, and dependence on, ethanol. In Y. Israel & J. Mardonze (Eds.), Biological Basis of Alcoholism (pp. 235-269). New York: Wiley/Interscience.

Kaplan, H. L., Sellers, E. M., Hamilton, C., Naranjo, C. D., & Dorian, P., (1985). Is there acute tolerance to alcohol at steady state? *Journal of Studies on Alcohol,46,* 253-256.

Lezak, M. D., Howieson, D. B., & Loring, D. W., (2004). *Neuropsychological Assessment.* 4th ed. Oxford, UK: Oxford University Press.

Logan, G. D., (1994). On the ability to inhibit thought and action: A user's guide to stop-signalParadigm. In Dagenbach, D., Carr, T. H. (Eds.), *Inhibitory Processes in Attention, Memory, and Language* (pp. 189-239). San Diego, CA: Academic Press.

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.

Ludwig, A. M., Wikler, A., & Stark, L. H., (1974). The first drink: Psychobiological aspects of craving. *Archives of General Psychiatry, 30,* 539-547.

Lyvers, M., (2000). "Loss of control" in alcoholism and drug addiction: A neuroscientific interpretation. *Experimental and Clinical Psychopharmacology, 8,* 225-249.

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., (2005). Alcohol increases reliance on cues that signal acts of control. *Experimental and Clinical Psychopharmacology, 13,* 15-24.

Miller, J., Schaffer, R., & Hackley, S. A., (1991). Effects of preliminary information in a go versus no-go task. *Acta Psychology, 76,* 241-292.

Mulvihill, L. E., Skilling, T. A., & Vogel-Sprott, M., (1997). Alcohol and the ability to inhibit behavior in men and women. *The Journal of Studies on Alcohol, 58,* 600-605.

O'Connor, S., Morzorati, S., Christian, J., & Li, T. K., (1998) Clamping breath alcohol concentration reduces experimental variance: Application to the study of acute tolerance to alcohol elimination rate. *Alcoholism: Clinical and Experimental Research, 22,* 202-210.

Portans, I., White, J. M., & Staiger, P. K., (1989). Acute tolerance to alcohol: Changes in subjective effects among social drinkers. *Psychopharmacology, 97 (3),* 365-369.

Posner, M. I., (1980). Orienting of attention. *The Journal of Experimental Psychology, 32,* 3-25.

Schneider, W., Eschman, A., & Zuccolotto, A., (2002). E-Prime User's Guide, Pittsburgh, PA: Psychology Software Tools.

Schweizer, T. A., Vogel-Sprott, M., (2008). Alcohol-impaired speed and accuracy of cognitive functions: A review of acute tolerance and recovery of cognitive performance. *Experimental and Clinical Psychopharmacology, 16,* 240-250.

Selzer, M. L., Vinokur, A., & Van Rooijen, L., (1975). A self-administered Short Michigan Alcoholism Screening Test (SMAST). *Journal of Studies on Alcohol, 36,* 117-126.

Steele, C. M., & Southwick, L., (1985). Alcohol and social behavior: The psychology of drunken excess. *Journal of Personality and Social Psychology, 48 (1),* 18-34.

Vogel-Sprott, M., (1992). *Alcohol Tolerance and Social Drinking: Learning the Consequences.* Guilford Press, New York.

Wechsler, H., Moeykens, B., Davenport, A., Castillo, S., & Hansen, J., (1995). The adverse impact of heavy episodic drinking on other college students. *Journal of Studies on Alcohol, 56,* 628-634.

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PROFESSIONAL PUBLICATIONS AND PRESENTATIONS

Publications

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Presentations

University of Kentucky Masters Thesis Defense, *Tolerance to the Impairing Effects of Alcohol on the Inhibition and Activation of Behavior.* 2010.

University of Kentucky Masters Thesis Proposal, *Tolerance to the Impairing Effects of Alcohol on the Inhibition and Activation of Behavior.* 2009.

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