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Acute Tolerance to Alcohol in At-risk Binge Drinkers

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Abstract

Studies of the impairing effects of alcohol on behavior often show greater tolerance in heavy drinkers compared to light drinkers, suggesting a causal link between heavy consumption and tolerance. Tolerance also develops during the time-course of a single drinking episode, and this “acute tolerance” might play an important role in the escalation to heavy drinking. The present study examined the development of acute tolerance to the impairing effects of alcohol on motor coordination and inhibitory control in a group of at-risk, binge drinkers ($N = 20$) and a group of non-risk, moderate drinkers ($N = 20$). Participants performed the testing battery in response to placebo and a moderate dose of alcohol (0.65 g/kg) twice at comparable blood alcohol concentrations (BACs): once on the ascending limb and once on the descending limb of the blood alcohol curve. Results showed marked acute tolerance to the impairing effects of alcohol on motor coordination in the at-risk drinkers. By contrast, no recovery of motor skill was observed in the non-risk drinkers. Regarding inhibitory control, both groups remained impaired on both the ascending and descending limbs, indicating no acute tolerance in either group. The findings suggest that at-risk, binge drinkers display a faster recovery in their ability to execute versus inhibit action under alcohol. Such an “activation bias” of behavior could account for their continued alcohol consumption and impulsive behaviors while intoxicated, especially as BAC begins to decline.

Keywords

Alcohol; acute tolerance; binge; inhibitory control; motor coordination

The intensity of a behavioral response to a dose of alcohol often diminishes with repeated administrations of the drug. The reduced response is referred to as tolerance. As tolerance develops, higher doses of alcohol might be needed to reinstate the initial effect. Thus, tolerance to alcohol has become recognized as a factor that may contribute to alcohol abuse and dependence by encouraging the use of escalating doses (American Psychiatric Association, 1994). One general assumption concerning alcohol tolerance is that it should be affected by the drinker’s history of alcohol consumption, with heavier drinkers, such as binge drinkers displaying more tolerance compared with light or moderate drinkers. Beginning with Goldberg’s (1943) early systematic analysis of acute reactions to alcohol in “normal” and “habituated” drinkers, the research literature shows a long history of comparing heavy and light drinkers in terms of their responses to a dose of alcohol. Much of this research has examined alcohol effects on measures such as motor skill, reaction time,

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sensory perception, and subjective intoxication (e.g., Brumback, Cao, & King, 2007; Fillmore & Vogel-Sprott, 1995; Holdstock, King, & de Wit, 2000; Townshend & Duka, 2005). Although the evidence is not entirely consistent, the general finding is that heavy drinkers tend to display less impairment (i.e., greater tolerance) to alcohol compared with light drinkers.

Although such findings are commonly interpreted as evidence for a causal link between alcohol consumption and tolerance, less attention has been paid to the specific behavioral mechanisms by which such tolerance might operate to maintain heavy drinking and possibly lead to alcohol dependence in some drinkers. One dynamic aspect of tolerance that could directly contribute to risk but that is often ignored in these group comparisons is acute tolerance. Acute tolerance refers to the diminished response to alcohol during the time-course of a single dose. Early last century, Mellanby (1919) compared the intensity of alcohol impairment at a given BAC during ascending versus descending limbs of the blood alcohol curve (Mellanby, 1919). 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. This reduced impairment during the descending limb is commonly referred to as acute tolerance, suggesting that the reduction might be due to some adaptive process occurring during physiological exposure to the drug over time. In humans, acute tolerance to the effects of alcohol has been examined in several behaviors, including motor coordination, reaction time, and subjective intoxication (Beirness & Vogel-Sprott, 1984; Fillmore, Marczinski, & Bowman, 2005; Fillmore & Vogel-Sprott, 1996; Marczinski & Fillmore, 2009; Schweizer, Jolicoeur, Vogel-Sprott, & Dixon, 2004).

In the past, acute tolerance has been thought of as a general adaptation to a dose of alcohol, and as such it was expected to develop uniformly to all types of alcohol effects. However, recent studies show that this is not the case. For example acute tolerance to alcohol-induced impairment has not been observed on measures of working memory, error monitoring, and choice-response accuracy (Cromer, Cromer, Maruff, & Snyder, 2010; Ostling & Fillmore, 2010; Schweizer & Vogel-Sprott, 2008). Studies in our laboratory have used cued go/no-go and motor skill tasks to compare the degree to which acute tolerance develops to the impairing effects of alcohol on the ability to inhibit versus execute controlled actions (Fillmore et al., 2005; Ostling & Fillmore, 2010; Weafer & Fillmore, 2011). In these studies, subjects typically receive a moderate dose of alcohol (e.g., 0.65 g/kg) and perform the tasks at the same BAC during the ascending and descending limb. During the ascending limb, impairing effects of alcohol are evident on the drinkers' ability to inhibit action and in their ability execute coordinated action. With regard to acute tolerance, the studies find rapid recovery of function with regard to the ability to execute behaviors, but no recovery in their ability to inhibit such action. Evidence for slower recovery of the ability to inhibit versus execute action is important for understanding some of the impulsive behavior commonly observed under alcohol. Generally speaking, impulsivity reflects a biased tendency for action over inaction. Accordingly, the biased rate of recovery that restores the ability to execute action before restoring the ability to inhibit action could contribute to the prolonged display of impulsive behavior even while BAC falls.

A lag in acute recovery of inhibitory control could also play an important role in the abuse potential of alcohol. Reduced inhibitory control has been linked to the abuse potential of the drug. Indeed some studies suggest that acute impairments of inhibition might contribute to excessive, binge drinking (e.g., Marczinski, Combs, & Fillmore, 2007; Weafer & Fillmore, 2008). For example, research shows that drinkers who display greater impairment of inhibitory control from a dose of alcohol also consume more alcohol when given ad lib access (Weafer & Fillmore, 2008). It has been argued that alcohol-induced impairment of inhibitory control might reduce the ability to terminate drinking behavior in the situation

once drinking has begun, thus resulting in excessive, binge drinking (Fillmore, 2003; 2007). The risk for excessive drinking is likely compounded by the fact that the ability to initiate action (e.g., taking the next drink) recovers more quickly from impairment than the ability to inhibit such action. Taken together, binge drinking might be most evident among individuals who display rapid and robust acute tolerance to alcohol with regard to its impairing effects on the ability to execute behavior, but little or no acute tolerance to its impairing effects on the ability to inhibit action.

To date no research has examined how a bias in recovery of the ability to execute versus inhibit action under a dose might be particularly pronounced and especially characteristic of heavy, at-risk binge drinkers. The present study sought to examine acute tolerance to the impairing effects of alcohol on indicators of behavioral execution, such as motor coordination and reaction time, and to the impairing effects on inhibitory control in two groups of drinkers. One group was characterized as “at-risk” binge drinkers who reported a history of binge drinking and who also scored in the at-risk range on the Alcohol Use Disorders Identification Test (AUDIT). These individuals were compared to a group of moderate, social drinkers with no history of binge drinking and who did not meet at-risk criteria on the AUDIT. Participants attended a session during which they received a moderate dose of alcohol (0.65 g/kg) and a session during which they received a placebo. Drinkers’ inhibitory control, reaction time, motor coordination and their subjective intoxication were measured. To assess the degree of acute tolerance, each measure was assessed twice following the dose: once as BAC ascended and again at a comparable BAC on the descending limb of the blood alcohol curve. In accord with previous research (Fillmore et al., 2005; Ostling & Fillmore, 2010), it was hypothesized that the execution of behavior (i.e., the speed and coordination of responses) would display greater acute tolerance to the impairing effects of alcohol than would the inhibition of behavior. With regard to differences between groups, it was hypothesized that, compared with moderate social drinkers, at-risk binge drinkers would display a greater bias in the recovery of their ability to execute behavior versus inhibit behavior under a dose. Specifically, binge drinkers were expected to display greater acute tolerance to impairing effects of alcohol on their speed and coordination of behavior. By contrast, neither group was expected to display any appreciable acute tolerance to the impairing effects of alcohol on their inhibitory control of behavior.

Methods

Participants

Forty adult drinkers (20 women and 20 men) between the ages of 21 and 31 (mean age = 23.1, $SD = 2.9$) were recruited to participate in this study. The sample was comprised of 5 African-American and 35 Caucasian participants. Screening measures were conducted to determine medical history and current and past drug and alcohol use. Any volunteers who self-reported head trauma, psychiatric disorder, or 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; Selzer, Vinokur, & van Rooijen, 1975), were also excluded. Volunteers were recruited via notices placed on community bulletin boards and by university newspaper advertisements. The University of Kentucky Medical Institutional Review Board approved the study, and participants received \$85 for their participation.

Materials and Measures

Grooved Pegboard Task—The grooved pegboard task (Lafayette Instruments) was used to measure motor coordination. 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. Each peg is 3 mm in diameter and 2.5 cm long. Each peg also has a rounded side and a grooved side (with the groove running down the peg vertically). Pegs fit into the holes of the board as a key would fit into a lock. Participants were required to pick up the pegs one at a time and place them in the holes, filling in one row at a time (from left to right) before moving to the next row. A trial on the grooved pegboard was completed once all 25 holes had been filled. The time to complete a trial (in seconds) was the measure of interest. A test consisted of four trials, and these four trials were averaged to calculate the dependent measure.

Cued Go/No-go Task—A cued go/no-go reaction time task used in other research measured participants’ response inhibition to no-go targets and their reaction time to go targets (e.g., (Fillmore et al., 2005; Marczinski & Fillmore, 2003). E-Prime experiment generation software (Schneider, Eschman, & Zuccolotto, 2002) was used to operate the task, which was performed on a PC. The task requires finger presses on a keyboard, and measures the ability to inhibit the prepotent behavioral response of executing the key press. 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 a high probability of signaling the correct 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. 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 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.

Subjective Intoxication—Degree of subjective intoxication was measured on a visual analogue scale that has been used in previous research on acute alcohol tolerance (e.g., Ostling & Fillmore, 2010). Participants rated 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.”

Blood Alcohol Concentrations (BACs) were determined from breath samples measured by an Intoxilyzer, Model 400 (CMI, Inc., Owensboro, KY, USA).

Alcohol Use Disorders Identification Test (AUDIT; Babor, Kranzler, & Lauerma, 1989)—The AUDIT is a screening instrument that was used to classify subjects as at-risk, problem drinkers or non-risk drinkers based on the occurrence and severity of alcohol-related problems. The 10-item, self-report questionnaire covers patterns of drinking, dependence, and other negative consequences of drinking over the past year and has a total score range from zero (no alcohol-related problems) to 40 (most severe alcohol-related problems). A score of 8 or greater was used to classify male subjects as at-risk drinkers with alcohol-related problems. A score of 6 or greater classified female subjects as at-risk, problem drinkers. Psychometric studies have reported that the 6+/8+ cut-scores provide the greatest degree of correct classification in most populations, including college-aged drinkers (Bernier, Kriston, Bentele, & Harter, 2007; Kokotailo et al., 2004; Selin, 2003).

Personal Drinking Habits Questionnaire (PDHQ; Vogel-Sprott, 1992)—This questionnaire provided information regarding participants' alcohol consumption and was used to determine binge drinker status. Participants recorded both history of alcohol use (number of months of regular drinking), as well as information regarding current, typical drinking habits, including: (a) frequency (the typical number of drinking occasions per week); (b) quantity (the number of standard alcoholic drinks (e.g., 1.5 oz of liquor) typically consumed per occasion); and (c) duration (time span in hours of a typical drinking occasion). This information, along with gender and body weight, was used to estimate the resultant BAC typically achieved during a drinking episode for each participant. 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 (McKim, 2007; Watson, Watson, & Batt, 1981). These formulae have been used in previous studies and have been shown to yield high correlations with actual resultant BACs obtained under laboratory conditions (Fillmore, 2001). Participants met binge drinker status if their estimated resultant BAC was 0.08% (80 mg/100 ml) or higher and they met non-binge drinker status if their resultant BAC was below 0.08% (NIAAA, 2004).

Timeline Follow-back (TLFB; Sobell & Sobell, 1992)—The TLFB assesses daily patterns of alcohol consumption over the past 3 months, including the number of drinks consumed each day. The measure uses “anchor points” to structure and facilitate participants' recall of past drinking episodes to provide a more accurate retrospective account of alcohol use during that time period. As a supplement to the PDHQ, the TLFB provided three additional measures of the participants' drinking habits: total number of drinking days in the past 3 months, total number of drinks consumed in the past 3 months, and how many days they felt drunk in the past three months.

Procedure

Interested volunteers responded to study advertisements by calling the laboratory to participate in an intake-screening interview conducted by a research assistant. At that time, they were informed that the purpose of the study was to examine the effects of alcohol on cognitive and behavioral tasks. All sessions were conducted in the Behavioral Pharmacology Laboratory of the Department of Psychology and testing began between 10 a.m. and 6 p.m. All participants were tested individually. Sessions were scheduled at least 24 hours apart and were completed within three weeks. Participants were instructed to fast for four hours prior to each alcohol session, as well as to refrain from consuming alcohol or any psychoactive drugs or medications for 24 hours before all sessions. Prior to each session, participants provided urine samples that 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, HCG, in order to verify that they were not pregnant (Mainline Confirms HGL, Mainline Technology, Ann Arbor, MI, USA). Breath samples were also provided at the beginning of each session to verify a zero BAC.

Intake Session—All participants completed an intake session in order to become acquainted with laboratory procedures. During this session, informed consent for participation was provided. Participants' heights and weights were measured, and the questionnaire measures were completed. Participants also performed practice tests to become familiar with the cued go/no-go and grooved pegboard 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 on a separate test session, and dose order was randomized with equal numbers of participants in each group assigned to each

dose order. Sessions were separated by a minimum of one day and a maximum of one week. Participants were told that they would receive alcohol on each session, and that the dose would not necessarily be the same each session. Alcohol doses were calculated on the basis of body weight and administered as absolute alcohol mixed with three parts carbonated soda. The 0.65 g/kg alcohol dose produces an average peak BAC of 80 mg/100 ml at approximately 65 min and begins to decline at about 75 min (Fillmore et al., 2005; Ostling & Fillmore, 2010). 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 & Vogel-Sprott, 1998). In within-subjects studies of alcohol tolerance the placebo condition has advantages over a “no beverage” condition as an experimental control. Some studies of alcohol tolerance show that tolerance might be mediated, in part, by compensatory reactions to the alcohol administration cues (i.e., smell and taste of the beverage). Studies find that subjects who display greater compensatory reactions to placebo also display the same compensatory reaction to alcohol, as evident by reduced impairment to the drug (e.g., Beirness & Vogel-Sprott, 1984; Marcinksi & Fillmore, 2005). As such, the placebo is a useful comparison because it holds compensatory reaction constant across conditions so that observed differences between alcohol and control conditions can be better attributed to pharmacological effects.

All drinks were consumed in six minutes. Participants performed the 20 min test battery (cued go/no-go task, pegboard task, and subjective intoxication scale) twice after each dose. The first test occurred 30–50 minutes post-drinking while BAC ascended in the active dose condition, and the second test occurred 90–110 min post-drinking when BAC was descending. Based on previous studies, these testing times were expected to occur at comparable BACs on each limb (approximately 60 mg/100 ml) (Fillmore et al., 2005; Ostling & Fillmore, 2010).

Participants' BACs were measured at 30, 50, 65, 90, 110, 130, and 150 min after drinking began. Breath samples were also obtained at these times during the placebo session, ostensibly to measure participants' BACs. Once the testing was finished, participants remained at leisure in the lounge area until their BACs, which were monitored at 20-minute intervals, reached 20 mg/100 ml or below. Participants were provided a meal during this leisure time and were allowed to watch movies and read magazines. Transportation home was provided as needed. Upon completing the final session, participants were paid and debriefed.

At-risk Binge Drinker Classification

Group classification (at-risk binge drinker vs. non-risk moderate drinker) was based on both AUDIT scores and binge drinking status. Participants were classified as at-risk binge drinkers if they met the following criteria: 1) scored in the at-risk range on the AUDIT (i.e., a score of 8+ for men and 6+ for women) and 2) met binge drinker status based on typical drinking habits reported on the PDHQ (i.e., estimated resultant BAC of .08% or higher). In order to be classified as non-risk moderate drinkers, participants were required to: 1) score below at-risk criteria on the AUDIT and 2) report typical drinking patterns that produce an estimated resultant BAC of less than .08%. Based on this classification scheme 20 at-risk binge drinkers (10 men and 10 women) and 20 non-risk, moderate drinkers (10 men and 10 women) were recruited. Volunteers who did not meet criteria for either group were excluded from participation.

Criterion Measures and Data Analyses

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

Reaction Time—The cued go/no-go task measured participants' reaction time by the mean RT to go targets in the go cue condition. Shorter RTs indicated greater facilitation of response execution. Responses with RTs 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).

Response Inhibition—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).

All dependent measures were analyzed by a 2 group (at-risk vs. non-risk) $\times$ 2 dose (0.0 g/kg vs. 0.65 g/kg) $\times$ 2 test (test 1 - ascending limb vs. test 2 - descending limb) mixed-design analysis of variance (ANOVA) in which group was the between-subjects factor and dose and test were within-subjects factors. Acute tolerance to alcohol was tested by *a priori* simple effect comparisons of test 1 and test 2 using pair-wise *t* tests. Effect sizes for these contrasts are reported using Cohen's *d*. Initially, all analyses were conducted with gender (male vs. female) and dose order (placebo first vs. alcohol first) as between-subjects factors. There were no significant main effects or significant interactions involving gender and dose order for any of the dependent measures of interest. Therefore, all subsequent analyses presented are collapsed across gender and dose order.

Results

Drinking Habits and Demographics

Table 1 presents the questionnaire data on drinking habits, impulsivity, and demographic information for the at-risk and non-risk drinker groups. The PDHQ showed that compared with non-risk drinkers, at-risk drinkers reported more drinks consumed per occasion, $t(38) = 6.9$, $p < .001$, a longer duration of drinking episode, $t(38) = 2.4$, $p = .023$, and a higher estimated BAC per episode, $t(38) = 10.0$, $p < .001$. The TLFB assessment of the past three months showed that, compared with non-risk drinkers, at-risk drinkers drank alcohol on more days, $t(38) = 2.8$, $p = .007$, were drunk on more days, $t(38) = 4.9$, $p < .001$, and consumed a larger total number of drinks over the period, $t(38) = 4.9$, $p < .001$. No group differences were observed in age, height, or body weight ($ps > .67$).

Blood Alcohol Concentrations

No detectable BACs were observed under the placebo condition. Group differences in BAC under the active dose condition were examined by a 2 (group) $\times$ 7 time (30, 50, 65, 90, 110, 130, 150 min) mixed design ANOVA. No main effects or interactions involving group were observed, $ps > .761$. There was a main effect of time owing to the rise and fall of BAC over the course of the session, $F(6, 228) = 370.6$, $p < .001$. Table 2 presents the mean BACs at each time point for each group and for the sample as a whole. The table shows that the groups' mean BACs were similar at each time point over the time-course of the dose. Moreover, the mean BAC at the completion of the test battery was similar during the ascending limb and the descending limb. For the sample as a whole, mean BACs at the completion of the testing during ascending and descending limbs were 54.9 ($SD = 9.4$) mg/100 ml and 57.8 ($SD = 11.0$), mg/100 ml, respectively, and this difference is within the

measurement error of the breathalyzer. Thus any reduction in alcohol effect on the descending versus ascending limb cannot be explained by BAC.

Group Differences in Alcohol Effects and Acute Tolerance

Motor Coordination—Pegboard completion times were analyzed by a 2 (group) $\times$ 2 (dose) $\times$ 2 (test) ANOVA and significant interactions were obtained between group and dose, $F(1, 38) = 6.7$, $p = .013$, and between dose and limb, $F(1, 38) = 5.9$, $p = .020$. Figure 1 plots the mean completion times for each group at each test following alcohol and placebo. The figure shows that completion time was slowed (i.e., impaired) following alcohol compared with placebo in both groups, and that at-risk drinkers displayed less impairment compared with non-risk drinkers. With respect to acute tolerance, the figure shows non-risk drinkers displayed no appreciable change in their completion times between the ascending (test 1) and descending (test 2) limb following alcohol, and a simple effect comparison revealed no significant difference in performance between these tests ($p > .10$). By contrast, Figure 1 shows that at-risk drinkers displayed marked recovery from alcohol impairment from the ascending to descending limb. This acute tolerance was confirmed by a simple effect comparison that revealed significantly faster completion time during the descending versus ascending limb under the active dose, $t(19) = 3.6$, $p = .002$, $d = 0.81$. Moreover, their motor coordination during descending limb appeared fully recovered to placebo levels. Indeed, their completion time during test 2 under alcohol did not differ significantly from their completion times during either test 1 or test 2 following placebo ($ps > .624$).

Reaction Time—A 2 (group) $\times$ 2 (dose) $\times$ 2 (test) ANOVA of reaction time revealed a significant three-way interaction, $F(1, 38) = 9.1$, $p = .005$. Figure 2 plots the mean reaction times. The figure shows that following placebo, reaction time was generally consistent across test 1 and test 2 in both groups. However, the groups differed in their response to alcohol. For non-risk drinkers, the reaction time following alcohol slowed from ascending (test 1) to descending (test 2) limb. A simple effect comparison confirmed this observation, $t(19) = 2.3$, $p = .031$, $d = 0.52$. By contrast, at-risk drinkers displayed a marked speeding of reaction time from the ascending to the descending limb. A simple effect comparison for this group confirmed faster reaction time during test 2 compared with test 1 under alcohol, $t(19) = 2.6$, $p = .016$, $d = 0.59$.

Response Inhibition—A 2 (group) $\times$ 2 (dose) $\times$ 2 (test) ANOVA of p-inhibition failures obtained a significant main effect of dose, $F(1, 38) = 16.9$, $p < .001$. No other main effects or interactions were observed. Figure 3 plots the mean p-inhibition failures for each group at each test following alcohol and placebo. The figure shows that the dose effect was due to increased inhibition failures following alcohol compared with placebo. The figure also shows that the alcohol-induced increase in inhibition failures was evident on both limbs with no evidence of any recovery of inhibitory control during the declining limb on test 2 for either group.

Subjective Intoxication—Intoxication ratings were analyzed by a 2 (group) $\times$ 2 (dose) $\times$ 2 (test) ANOVA that obtained a significant dose $\times$ limb interaction, $F(1, 38) = 13.7$, $p < .001$. Figure 4 plots subjective intoxication for each group. The figure shows increased intoxication in response to alcohol compared with placebo, and this effect was comparable in both groups. With respect to acute tolerance, subjective intoxication under alcohol diminished considerably on the descending limb, and this effect was evident in both groups. Simple effect comparisons confirmed that subjective intoxication decreased significantly from ascending to descending limbs under alcohol in non-risk, $t(19) = 5.8$, $p < .001$, $d = 1.30$, and at-risk drinkers, $t(19) = 5.7$, $p < .001$, $d = 1.29$.

Discussion

The present study sought to examine acute tolerance to the impairing effects of alcohol on indicators of behavioral execution, such as motor coordination, and to the effects of alcohol on inhibitory control, in at-risk drinkers and non-risk drinkers. It was hypothesized that, compared with non-risk drinkers, at-risk drinkers would display greater acute tolerance to the impairing effects of alcohol on their speed and coordination of behavior. By contrast, neither group was expected to display any appreciable acute tolerance to the impairing effects of alcohol on their inhibitory control of behavior.

The findings support the hypotheses. At-risk drinkers displayed less alcohol-induced impairment of their motor coordination compared with non-risk drinkers. Moreover, at-risk drinkers displayed marked acute tolerance to this impairing effect as BAC descended. In fact, when tested during the descending limb, their motor coordination recovered to placebo levels despite the fact that their BAC was still appreciably elevated (i.e., above 50 mg/100 ml). With regard to reaction time, similar effects were observed. At-risk drinkers showed speeding of their reaction time under alcohol as BAC descended, whereas the reaction time of non-risk drinkers slowed during this same time period. The study also demonstrated acute tolerance to drinkers' perceived level of intoxication as measured by self-report. Subjective levels of intoxication increased in response to alcohol compared with placebo, and both groups displayed robust acute tolerance to this effect. It is also important to note that BACs were comparable when testing was completed at each limb of the blood alcohol curve. Therefore, the diminished responses observed during the descending limb cannot be attributed to lower BACs but rather suggest the development of acute tolerance to these alcohol effects.

In contrast to measures of behavioral execution and subjective intoxication, neither group displayed any acute tolerance to the impairing effect of alcohol on their inhibitory control. Alcohol impaired response inhibition on the ascending limb as evident by increased failures to inhibit responses following alcohol compared with placebo. There was no reduction in inhibitory failures during the descending limb in either group, indicating no recovery from impairment as BAC declined.

The findings are consistent with previous research that examined differential development of acute alcohol tolerance between the execution and the inhibition of actions (e.g., Fillmore et al., 2005; Ostling & Fillmore, 2010). Those studies also found that impaired response activation displayed acute tolerance while response inhibition remained impaired from ascending to descending limb tests. The present study builds on this earlier work by demonstrating that such differences in the recovery of specific functions are even more pronounced in at-risk, binge drinkers. Indeed, the at-risk drinkers in the current study demonstrated complete recovery of their ability to execute behavior with regard to its speed and coordination during the descending limb, while their ability to inhibit action remained impaired. As such, a biased recovery of the ability to execute versus inhibit action under a dose might be especially characteristic of at-risk binge drinkers.

Like all cross-sectional studies that compare heavy drinkers to moderate or light drinkers, this study cannot demonstrate a specific causal-relationship between heavy drinking and tolerance to alcohol. However, it is reasonable to suggest that the history of excessive binge drinking by the at-risk group led to greater acute tolerance to the impairing effects of alcohol on their motor coordination and reaction time. Acute tolerance is considered to represent a physiological adaptation to alcohol exposure and studies of laboratory animals show that acute tolerance can be accelerated by prior exposures to large doses of alcohol (LeBlanc, Gibbins, & Kalant, 1973). The at-risk drinkers in the present study consumed much higher

amounts of alcohol than did the non-risk drinkers. Indeed, in addition to reporting regular, frequent binge drinking, at-risk drinkers consumed nearly three times the amount of alcohol over the past 90 days compared with non-risk drinkers. As such, it is likely that the heavy alcohol use by this group resulted in an increased acute adaptive reaction to the drug which was observed as acute tolerance.

It is also possible that such reduced responses to alcohol might actually precede heavy drinking in at-risk drinkers, and possibly predict the development of their excessive drinking patterns. Differences in the degree of behavioral impairment under alcohol have been considered as possible “behavioral markers” that correspond to other known risk factors for the development of alcohol-related problems, such as family history of alcoholism (e.g., Chung & Martin, 2009; Eng, Schuckit, & Smith, 2005; Tolentino et al., 2011). In particular, there is interest in the possibility that a low-level of response to alcohol can predict later alcohol abuse and dependence (Schuckit, 2009). The findings from the present study are consistent with this general notion, but raise questions about the methodology needed to identify such markers. The current findings suggest that the ability to identify a low-level response as a behavioral marker for abuse risk will depend upon the particular behavioral measures examined. For example, some measures, such as inhibitory control, do not appear to show reduced impairment in at-risk drinkers. The current findings also call importance to the time-course during which the responses to alcohol are assessed. Results of the current study show more pronounced group differences in response to alcohol during the descending limb as compared with the ascending limb. Specifically, the at-risk drinkers’ diminished response to alcohol was most evident during the descending limb, owing to greater acute tolerance in these drinkers. As such, consideration needs to be given to the time-course of the testing under the dose, as acute changes in response to alcohol can affect the ability to identify any specific response as a stable and reliable marker for abuse.

The current findings might also provide some account for how acute tolerance could contribute to excessive, binge drinking. Prolonged impairment of inhibitory control during the descending limb, coupled with a recovering ability to execute action could lead to impulsive actions, including resuming alcohol consumption resulting in excessive binge drinking in the situation. Many drinkers report intentions to limit their alcohol use to one or two drinks only to fail and instead drink excessively (Collins, 1993). Such accounts have fueled the notion that alcohol reduces control over consumption in some individuals. Terminating a drinking episode requires inhibition of ongoing alcohol-consumptive behaviors. Any impairment of normal inhibitory mechanisms resulting from an initial dose of alcohol could compromise the ability to stop additional alcohol administrations in a drinking situation, resulting in a “binge” episode. Indeed, prior research in our laboratory shows that drinkers who display greater impairment of inhibitory control from alcohol also tend to drink more when given ad lib access, suggesting that impaired inhibition can promote excessive drinking (Weafer & Fillmore, 2008). Moreover, when such impairment is accompanied by acute recovery in the ability to execute action, the likelihood for reinitiating drinking behavior in the situation might be increased. As such, the recovery bias could play an important role in the development of alcohol abuse, and possibly in the transition to alcohol dependence in these at-risk drinkers. Although speculative at this point, the account highlights the importance of understanding how individual aspects of behavioral control are affected by alcohol over the time-course of the dose.

Finally, it is also worthwhile to comment on the methods used to classify drinkers as at-risk in the present study. These individuals had to meet criteria as regular binge drinkers by self-reporting typical quantities that were sufficient to yield BACs of at least 80 mg/100 ml per occasion in accord with the NIAAA (2004) definition of binge drinking. Moreover, these binge drinkers also had to meet risk criteria for problem drinkers based on the occurrence

and severity of alcohol-related problems as measured by the AUDIT. It is recognized that the AUDIT score is, in part, determined by levels of typical quantity of alcohol consumed per occasion (items 2 and 3). Therefore, some differences in AUDIT scores between binge and non-binge drinkers could simply reflect overlapping criteria. However, supplemental analyses of AUDIT scores with the two quantity items removed also confirmed that binge drinkers achieved significantly higher AUDIT scores than non-bingers ($p = .002$). Thus, compared with non-bingers, the binge drinkers in our study reported greater alcohol-related problems on the AUDIT based on symptoms other than those concerning excessive quantity of consumption.

In sum, these findings highlight the importance of examining specific mechanisms of tolerance in relation to abuse potential. It has long been thought that tolerance to the effects of alcohol can encourage consumption of greater amounts, yet the degree to which this effect operates within a single episode has been relatively unexplored. Although the degree to which the current findings reflect a cause or consequence of heavy drinking is unknown, our evidence for a protracted period of impaired inhibitory control coupled with restored ability to quickly execute coordinated action might play an important role in the etiology and escalation of binge drinking and other impulsive behaviors.

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Figure 1.

Mean grooved pegboard completion time (sec) for Tests 1 and 2 for the at-risk and non-risk drinker groups under the 0.0 g/kg (placebo) and 0.65 g/kg alcohol dose conditions. Capped vertical lines show standard errors of the mean.

Figure 2. Mean reaction time on the cued go/no-go task (msec) for Tests 1 and 2 for the at-risk and non-risk drinker groups under the 0.0 g/kg (placebo) and 0.65 g/kg alcohol dose conditions. Capped vertical lines show standard errors of the mean.

Figure 3. Mean p-inhibition failures on the cued go/no-go task for Tests 1 and 2 for the at-risk and non-risk drinker groups under the 0.0 g/kg (placebo) and 0.65 g/kg alcohol dose conditions. Capped vertical lines show standard errors of the mean.

Figure 4.

Mean self-reported subjective intoxication for Tests 1 and 2 for the at-risk and non-risk drinker groups under the 0.0 g/kg (placebo) and 0.65 g/kg alcohol dose conditions. Capped vertical lines show standard errors of the mean.

Table 1

Demographic and Drinking Habit Measures by Group

	Group				Contrasts
	At-risk (<i>n</i> = 20)		Non-risk (<i>n</i> = 20)		
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	
<u>Demographics</u>					
Age	23.1	3.1	23.2	2.8	<i>ns</i>
Gender (male:female)	10:10		10:10		<i>ns</i>
Weight (kg)	71.0	7.5	72.3	11.1	<i>ns</i>
<u>PDHQ</u>					
History	78.7	39.0	59.2	34.7	<i>ns</i>
Frequency	2.5	1.0	1.9	0.9	<i>ns</i>
Quantity	6.4	2.0	3.0	1.0	Sig***
Duration	3.8	1.3	2.9	1.2	Sig*
Estimated resultant BAC(mg/100ml)	110.2	28.5	34.4	17.9	Sig***
<u>AUDIT</u>	9.3	2.6	5.0	1.3	Sig***
<u>TLFB (past 90 days)</u>					
Number of drinking days	30.3	15.4	19.3	8.2	Sig**
Number of 'drunk' days	14.0	7.7	4.8	3.4	Sig***
Total drinks consumed	175.3	97.9	61.6	36.5	Sig***

Note. Group contrasts were tested by one-way between subjects ANOVAs. Sig* indicates a significance value of $p < .05$, Sig** indicates a significance value of $p < .01$, and Sig*** indicates a significance value of $p < .001$.

Table 2

Mean Blood Alcohol Concentrations (mg/100 ml)

	Time after drinking (min)						
	30	50	65	90	110	130	150
At-risk drinkers (<i>M</i>)	33.2	55.4	71.8	63.9	57.5	53.1	44.9
(<i>SD</i>)	5.1	8.6	11.0	9.9	9.1	12.1	10.1
Non-risk drinkers (<i>M</i>)	32.7	54.5	70.7	63.7	58.1	54.6	45.7
(<i>SD</i>)	6.2	10.4	13.5	12.3	11.3	10.5	10.2
Whole sample (<i>M</i>)	32.9	54.9	71.3	63.8	57.8	53.9	45.3
(<i>SD</i>)	5.6	9.4	12.2	11.0	10.1	11.2	10.0