Examining the Development of Acute Tolerance to Subjective Response to Alcohol in an Alcohol Administration Study

by

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ABSTRACT

Both subjective response to alcohol and acute tolerance possess unique biphasic relations with the blood alcohol concentration curve. However, prior work has generally failed to examine shared relations between the two constructs and has yet to consider the full valence by arousal affective space of subjective response, nor individual differences in metabolism or peak levels of subjective intoxication. As such, the present study sought to characterize acute tolerance to subjective response in addition to examining relations between acute tolerance, subjective response, and related outcomes. Participants (N=258) were randomly assigned to receive alcohol (target blood alcohol concentration = .08 g%) as part of a large placebo-controlled alcohol administration study. Participant family history of alcohol use problems and personal history of alcohol use were collected at baseline. Subjective response to alcohol was assessed across the full valence by arousal affective space at equivalent points on the ascending and descending limbs of the blood alcohol concentration curve. Latent change scores were calculated to characterize the development of acute tolerance, and path analyses tested relations between acute tolerance to subjective response, concurrent patterns of alcohol use, and negative alcohol-related consequences. Age, sex, race/ethnicity, and drinking context were included as covariates. Acute tolerance to low arousal positive (i.e., relaxed, mellow) effects were found to be inversely related to negative consequences such that a maintenance of low arousal positive effects was associated with more negative consequences. The amount of time elapsed between measurements was found to be significantly related to the development of acute tolerance to high arousal positive (i.e., talkative, stimulated) effects, such that more time between measurements was related to a greater decrease in

high arousal positive effects. Peak high arousal positive effects were found to be related to increased drinking and indirectly related to more negative consequences via drinking, whereas high arousal negative was protective against increased drinking and negative consequences. Results suggest that a maintenance of negatively reinforcing effects across the blood alcohol concentration curve may confer risk for negative consequences. Results also suggest that considering individual differences in alcohol metabolism may be useful in understanding alcohol's rewarding, stimulating effects.

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CHAPTER 1

INTRODUCTION

Excessive alcohol consumption represents a pressing national and global public health concern. Past-year prevalence of heavy and excessive drinking has risen to 12.6% of the U.S. population, (Grant et al., 2017) and recent estimates suggest a global prevalence of 18.2% (WHO, 2018). The impact of excessive alcohol use is widespread, accounting for billions of dollars in lost revenue both in the U.S. ($249 Billion; Sacks et al., 2015) and worldwide ($210-$665 billion; Baumberg, 2006). Heavy and excessive drinking has also been linked with a litany of deleterious public-health problems including, but not limited to, altered cerebellar development in adolescents, reduced global cognitive functioning, risky sexual behavior, drunk driving, cancer, and premature death (e.g., Wechsler et al., 1995; Davis et al., 2009; Naimi et al., 2009; Rehm, 2011; Stahre, et al., 2014; Squeglia & Gray, 2016; Kekkonen et al., 2021). Of all age cohorts, young adults (i.e., those aged 18-29) have been shown to engage in the highest rates of excessive drinking (Linden-Carmichael et al., 2017; Kanny et al., 2018) conferring the highest risk for Alcohol Use Disorders (AUD; 37%, Grant et al., 2017).

Such patterns only serve to highlight the need to identify factors that contribute to risky alcohol consumption and the experience of related consequences in young adults. Of note, individual differences in alcohol metabolism across a single drinking episode (i.e., *acute tolerance*) alongside the relative valence and intensity alcohol intoxication (i.e., *subjective response to alcohol)* may represent particularly salient contributors to such outcomes. As such, developing a more detailed understanding of how individual differences of alcohol metabolism and subjective effects of intoxication interact to confer

increased risk signifies a vital topic of research and potential target of intervention to prevent problematic alcohol use.

Acute Tolerance to Alcohol

After consuming an acute dose of alcohol, an individual's blood-alcohol concentration (BAC) reliably and rapidly increases to a peak level, and then more slowly declines as the body metabolizes the alcohol consumed (Wilkinson et al., 1977). This pattern of absorption and metabolism results in individuals reaching the same elevated BAC, and presumed level of impairment, at two separate time points – once on the ascending (rising) BAC limb and once on the descending (declining) BAC limb. However, there is evidence that even at similar ascending and descending BACs, measures of subjective intoxication, behavioral impairment, and willingness to engage in risky behavior differ depending on the BAC limb on which they are measured. This phenomenon, referred to as *acute tolerance* (Martin & Moss, 1993), has become the target of increased empirical interest.

Although there are several experimental models that allow for the assessment of acute tolerance, the most frequently employed experimental paradigm is the Mellanby paradigm (1919) which prescribes assessing relevant constructs at identical, or nearly identical, BAC levels on the ascending and descending limbs. While examining the physical effects of alcohol intoxication in dogs, Mellanby (1919) observed markedly less impairment when their behavior was being monitored on the descending limb, representing some of the first evidence that dose-dependent effects of alcohol may differ depending on the limb upon which measurement occurred. Thus, since Mellanby's (1919) initial observations, acute tolerance has been the subject of research across many

domains, though a unified picture regarding which aspects of alcohol response are susceptible to acute tolerance has yet to emerge (Schweizer & Vogel-Sprott, 2008; Holland & Ferner, 2017; Comley & Dry, 2020).

Subjective intoxication (SI) is the most frequently assessed construct demonstrating reliable differences by limb of the BAC curve. Most often, SI is measured in some form of a visual analog scale, where participants rate their perceived level of intoxication relative to a line of a set distance (e.g., Martin & Moss, 1993; Hiltunen, 1997a; Morzorati et al., 2002; Cromer et al., 2010; Fillmore & Weafer, 2012; Hendershot et al., 2015). Other studies (Marczinski & Fillmore, 2009) have used measures such as the Subjective Intoxication Scale (Fillmore & Vogel-Sprott, 2000), which asks participants to rate how intoxicated they feel in terms of the number of bottles of 5% alcohol beer they think they consumed, and others have utilized a 10-point Likert scale (Amlung et al., 2014) or simply asked participants to rate the total number of standard drinks they believe they have consumed (Fillmore et al., 2005). Regardless of the exact measurement approach, assessments of SI appear to be quite sensitive to acute tolerance. Comley & Dry (2020) found that, of 23 studies that assessed SI, all but four found evidence of acute tolerance, with lower SI reported on the descending limb compared to the ascending limb at identical BACs. Across constructs, results appear to vary as a function of both measurement tool and the construct of interest. For example, Miller and Fillmore (2014) found evidence of acute tolerance on a simple two-choice reaction time task, whereas Hiltunen et al. (2000) found no such evidence on a more complex reaction time measure. Additionally, although reaction times appear to consistently return to pre-intoxication levels, performance accuracy typically remains impaired (e.g., Fillmore et

al., 2005; Fillmore & Weafer, 2012). These findings lend support to the hypothesis that, as behaviors become more complex or require more cognitive effort, acute tolerance is less likely to be observed. In further support, a study designed to eliminate the impact of practice effects on repeated measurements, Cromer et al (2010) found that, while completing a spatial maze task, speed of completion and task acquisition exhibited statistically significant regression to pre-alcohol levels, whereas overall performance accuracy remained impaired across both limbs. Of note, Starkey et al. (2014) failed to find any evidence of acute tolerance across any domain when analyzing performance on the same maze learning task.

There is also evidence that acute tolerance has implications for alcohol-related risk-taking behavior and negative consequences. For example, Weafer & Fillmore (2012) found that, although motor coordination and reports of subjective intoxication improved on the descending limb, driving performance and impulse control remained impaired. In fact, across studies, impulse control, or behavioral inhibition, appears to be resistant to the development of acute tolerance (Fillmore et al., 2005; Ostling, 2010; Fillmore & Weafer, 2012; Miller & Fillmore, 2014). Further, recent evidence has shown that individuals' perceptions of risk (Amlung et al., 2014; Morris et al., 2014), willingness to drive (Starkey et al., 2014), and distance they are prepared to drive when intoxicated (Motschman et al., 2020) are all susceptible to acute tolerance. As a consequence, individuals feel less impaired and less at risk, and are more willing to drive, despite ongoing impairment in behavioral inhibition.

Taken together, these findings suggest that acute tolerance plays a vital role in decisions to engage in risky behavior such as driving while intoxicated. Feeling less

intoxicated while one's ability to control impulses and higher-order cognitive processes remain impaired may well lead to a greater discounting of risk for negative consequences, leading to an increase in risky behaviors. Such actions cost the government upwards of $13.5 billion annually (Sacks et al., 2015), emphasizing the critical need to further understand the role of acute tolerance in both cognitive and behavioral processes related to decision making and risky alcohol-related behaviors.

Although research on acute tolerance has highlighted its importance in understanding alcohol-related risk behavior and consequences, there are significant limitations of prior work. Results are often inconsistent, with studies arriving at different conclusions despite nearly identical measures and study procedures (Comely & Dry, 2020). Additionally, most acute tolerance investigations have focused on single-item measurements, and the most reliable source of evidence for acute tolerance, subjective intoxication, represents a simplistic evaluation of the biological and cognitive impact of alcohol consumption. Thus, more sophisticated evaluation of acute tolerance to subjective alcohol effects is badly needed.

Subjective Response to Alcohol

Subjective response to alcohol (SR) encompasses the combination of pharmacological and expectancy effects of alcohol on both mood and physiology and thus represents a more nuanced evaluation of alcohol intoxication (Morean & Corbin, 2010). SR represents both alcohol's rewarding effects (e.g., sociability, relaxation) which promote continued use, and its punishing effects (e.g., dizziness, anxiety) that inhibit use. Schuckit and colleagues were among the first to investigate SR in the context of an alcohol administration paradigm using the Subjective High Assessment Scale (SHAS;

Schuckit, 1980). The SHAS is comprised of 38 adjectives which describe positive and negative effects of alcohol and has contributed to the development of the *low level of response* model of alcohol use, which posits that those with lower overall SR are more at risk for developing AUD. In support of this theory, low levels of SR have been used to differentiate between men who have a family history of AUD and those who do not (Schuckit, 1984), show that those with dampened responses to alcohol are at significantly greater risk for developing AUD symptoms, regardless of family history (Schuckit, 1994), and show that SR mediates the link between family history and AUD development (Schuckit & Smith, 2000). Although the low-level of response model has garnered considerable support, studies examining the low level of response model have primarily assessed low arousal negative effects of alcohol (e.g., clumsy, confused, dizzy; Schuckit et al., 2000), and do not fully capture unique facets of SR that may confer unique risk for the development of alcohol-related problems (e.g., Morean & Corbin, 2010).

The *Differentiator Model* (Newlin & Thomson, 1990) provides an alternative to the low-level of response model, incorporating a broader range of subjective alcohol effects that occur at different points on the BAC curve. In alcohol administration studies, SR has been shown to follow a reliable parabolic curve that closely mirrors an individual's BAC, where alcohol's more stimulating and rewarding effects are typically experienced at higher levels on the ascending limb and alcohol's sedating effects are typically higher on the descending limb (e.g., Earleywine & Martin, 1993; King et al., 2002; Erblich et al., 2003). The Differentiator Model posits that those who receive more stimulating effects on the ascending limb and less sedative effects on the descending limb of the BAC curve are more susceptible to the development of AUD. Since its initial

conceptualization, the Differentiator Model has received considerable empirical support. Several studies have found that increased sensitivity to alcohol's rewarding effects along with lower sensitivity to alcohol's sedative effects predict increases in binge drinking (King et al., 2011), increases in AUD symptoms and higher rates of binge drinking over a 6-year period (King et al., 2014), and a consistently riskier trajectory for the development of AUD over a 5- and 10-year follow-up period among heavy drinking individuals (King et al., 2016, 2021). These findings were largely corroborated in a meta-analysis conducted by Quinn and Fromme (2011), in which it was found that heavier drinkers responded more strongly to measures of stimulation than their lighter drinking peers, particularly on the ascending limb of the BAC curve.

To better capture the biphasic pattern of SR and allow researchers to assess consequent risk, Martin and colleagues (1993) created and validated the Biphasic Alcohol Effects Scale (BAES). The BAES is a 14-item questionnaire that assesses both stimulating (e.g., stimulated, energized, talkative) and sedative (e.g., slow thoughts, sluggish) effects of alcohol consumption. Martin et al. (1993) observed significant differences in responses across limbs of the BAC curve and found no differences between men and women. Both subscales of the BAES were found to have high internal consistency ($\alpha = 0.85$ to 0.94; Martin et al., 1993), and have since been shown to be closely related to physiological (i.e., heart rate; Ray et al., 2006) and cognitive (i.e., craving; Bujarski & Ray, 2014) indicators of alcohol intoxication. Other studies that have utilized the BAES have found that SR serves as a robust predictor of unique alcohol-related consequences including blacking out and the experience of next-day hangovers (Wetherill & Fromme, 2009), increased rates of binge drinking (King et al., 2011, 2014),

and likelihood of engaging in drinking and driving (Motschman et al., 2020). Taken as a whole, these findings suggest that SR has a unique biphasic relationship with the BAC curve and provide support for the validity of the Differentiator Model.

Despite the generally consistent pattern of findings in support of the differentiator model, critics have pointed out that the BAES, the most widely used tool to assess SR, doesn't account for important aspects of SR. Specifically, the BAES does not differentiate between positive and negative valence across stimulating and sedating alcohol effects. To help address this concern, the Subjective Effects of Alcohol Scale (SEAS) was developed and validated by Morean, Corbin, & Treat (2013). The SEAS includes measures of low arousal positive (LAP) and high arousal negative (HAN) subjective effects which are not captured by other measures. The incorporation of LAP effects is critical for capturing subjective alcohol effects that are relevant to the tension reduction model of alcohol use (Levenson et al., 1980), and drinking to cope, a behavior that has been strongly linked to the experience of alcohol-related consequences (Kunstche et al., 2005; Cooper et al., 2016). The addition of HAN effects aids in understanding the link between alcohol use and alcohol-related consequences resulting from risky behaviors such as physical altercations and sexual aggression. Morean et al. (2013) found that alcohol-related problems were related to stronger experiences of both HAP and HAN effects. Quinn and Fromme (2016) also found that a latent stimulation factor, onto which HAP effects positively loaded, predicted heavier levels of alcohol consumption. HAN effects have also been shown to confer unique risk in adolescent drinkers, contributing to earlier binge drinking age and a shorter time to first intoxication from alcohol initiation (Morean et al., 2019). Research that considers the unique effects of all four aspects of SR is still nascent,

but the growing body of literature suggests that more nuanced evaluations of SR's affective domains have utility.

Acute Tolerance to Subjective Response

Despite both constructs sharing unique associations with the BAC curve, apart from studies focused solely on simple reports of subjective intoxication, only a few studies have examined how alcohol's self-reported subjective effects differ across BAC limbs. Early studies conducted by Earleywine (1995) and Earleywine & Erblich (1996) found evidence of acute tolerance in that participant reports of stimulation were significantly lower on the descending limb when compared to reports at near-identical BAC levels on the ascending limb. In a larger study of alcohol's impact on physical aggression, Giancola and Zeichner (1997) also found that stimulation was higher on the ascending limb compared to the descending limb, whereas no limb dependent effect was observed for sedation. Finally, Fillmore, Marczinski, & Bowman (2005) replicated these findings in a sample of moderate drinkers, finding that only alcohol's stimulant effects were subject to the development of acute tolerance.

Each of the aforementioned studies utilized the Mellanby paradigm, with SR reports compared at approximately equal points on the ascending and descending limbs of the BAC curve. An inherent complication of the Mellanby paradigm is that it fails to account for confounding effects related to rising and falling BACs on the ascending and descending limbs. To help offset these complications, several studies have examined the impact of consuming alcohol when BAC is held steady, using a procedure known as an alcohol clamp (e.g., O'Connor et al., 1998). Studies using this approach have demonstrated development of acute tolerance to alcohol's stimulating effects and acute

sensitization to alcohol's sedative effects (Hendershot et al., 2015; Morzorati et al., 2002). These findings support the notion that the development of acute tolerance to subjective response is independent of limb effects associated with rising and falling BACs.

Although the relatively small body of research on acute tolerance begins to present a compelling argument for its importance, the existing research on SR has been limited by the measures used to assess it. All but one of the aforementioned studies utilized simple measures of intoxication or the BAES to assess SR. As stated previously, this means that unique domains of SR including high arousal negative (e.g., aggressive) and low arousal positive (e.g., relaxed) effects, have not been evaluated for their sensitivity to acute tolerance. Development of acute tolerance to alcohol's HAN effects could help explain problematic behaviors such as sexual aggression and domestic violence. Similarly, a better understanding of the experience of limb-dependent LAP effects may prove useful in further elucidating strong links among drinking to cope, drinking for tension reduction, and the experience of alcohol-related consequences.

Proposed Study and Hypotheses

Until now, most acute tolerance investigations have been underpowered with small sample sizes ($\bar{x}$ = 38.5) and relatively homogenous samples with respect to participant sex (67% male; Comely & Dry, 2020). Thus, by using data from a large, placebo-controlled alcohol administration study (N=448, 43% female) in which reports of subjective response were assessed at well matched BACs on the ascending and descending limb ($M_{ascending}$ = .068, $M_{descending}$ = .066) the current study examined how subjective responses to alcohol differ across limbs of the BAC curve. Due to the focus on

changes in subjective responses to alcohol across limbs of the BAC curve, participants who received a placebo beverage were excluded from analyses. Even with only those in the alcohol condition (*N*=258), the current study is the largest investigation of acute tolerance to date.

Hypothesis 1. It was anticipated that acute tolerance to both HAP and LAN effects would be related to concurrent alcohol use and alcohol-related consequences. Individuals who experience a diminished level of alcohol's stimulating, rewarding effects may continue to drink to achieve levels similar to what they experienced on the ascending limb. It is also possible that, as time passes, individuals may perceive that they are no longer as intoxicated as they were before and therefore feel that they are okay to engage in risky behaviors such as driving a vehicle. Further, although not a primary hypothesis of the current study, it is possible that acute tolerance to HAN effects may serve as a protective factor against specific alcohol consequences. A reduction in perceived levels of aggression may reduce the likelihood of someone getting into a physical altercation or engaging in sexually aggressive behavior.

As such it was hypothesized that acute tolerance to SR would be associated with concurrent alcohol-related consequences and drinking quantity. Overall higher levels of acute tolerance were expected to be associated with more alcohol consequences, while higher levels of acute tolerance to HAP effects are expected to be associated with greater drinking. We predicted that acute tolerance in the HAP and HAN domains will most closely related to alcohol-related consequences, with higher overall levels of both HAP and HAN effects being directly related to more alcohol-related consequences.

Hypothesis 2. In addition to developing a better understanding of acute tolerance to the full range of SR, there is a need for research to better understand the antecedents of acute tolerance. The exact biophysiological mechanisms behind the development of acute tolerance are still relatively unknown, but preliminary evidence suggests that acute tolerance operates via epigenetic modulation of potassium channels in response to alcohol consumption, thus moderating alcohol-induced neuronal activation (e.g., Hewitt et al., 2013). However, these mechanisms are unlikely to fully account for individual differences in acute tolerance. Outside of potential physiological explanations, the strong link between biphasic experiences of subjective response and the limb-dependent principles that underly acute tolerance suggest that established risk factors associated with SR, such as family history of alcohol use disorders (FH) and drinking history, may also be linked to acute tolerance.

An extensive body of work has established a strong link between FH and SR which shows that those with a positive FH experience weaker sedative effects after drinking alcohol (Schuckit, 1984; Schuckit & Smith, 1996; Schuckit & Smith, 2000; Trim, Schuckit, & Smith, 2009; Quinn & Fromme, 2011). Other studies, however, present a more complicated picture finding little to no evidence supporting the impact of FH on subjective response (King et al., 2011; Roche, Palmeri, & King, 2014; Kerfoot et al., 2013). Previous investigations into the impact of family history on the development of acute tolerance have yielded similarly mixed results. Using an alcohol-clamp paradigm wherein participants BACs are held constant via IV administration, Morzorati et al. (2002) found that only those with a positive FH experienced a decrease in subjective

intoxication over time whereas Martin, Rose, & Obremski (1991) did not find a significant effect of FH on the development of acute tolerance to subjective intoxication.

Differences in acute tolerance based on family history could be attributable to individual differences in absorption and metabolism that are a result of genetic predispositions. Previous studies have shown that polymorphisms of the ALDH2 gene are among the strongest contributors to the development of AUD (Edenberg & Foroud, 2013). As alcohol is metabolized, it is first broken down to acetaldehyde, an enzyme responsible for many of the negative physical effects of alcohol consumption including dizziness and tachycardia (Hurley & Edenberg, 2012). Acetaldehyde is primarily broken down by aldehyde dehydrogenase 2 (ALDH2) meaning that variants of ALDH2, such as ALDH2*504K that limit its function and cause acetaldehyde to buildup in the system, function as a strong deterrent to drinking alcohol and represent a protective factor against AUD development (Edenberg & Foroud, 2013). Those with a family history of AUD possess a more efficient version of ALDH2, thus limiting their exposure to acetaldehyde's noxious effects, promoting continued use. This more efficient alcohol metabolism may play a vital role in the development of acute tolerance by limiting the overall time that alcohol is in one's system. A shorter time to metabolize alcohol would lead to shorter periods of time between matched-BAC measurements, which may lead to less acute tolerance among those with a positive family history. The failure to account for the time elapsed between ascending and descending limb assessments in prior studies of acute tolerance is a significant limitation. Consequently, little is known about the role of metabolism in acute tolerance or the extent to which metabolism may mediate effects of family history on acute tolerance. Thus, accounting for time elapsed between ascending

and descending limb assessments of SR may improve our understanding of links between family history and acute tolerance.

The link between SR and another well-established risk factor (i.e., heavy drinking) appears to be more consistent. Although King et al. (2011) did not find effects of FH on SR, they did find that heavy drinkers were more sensitive to the stimulating effects and less sensitive to the sedative effects of alcohol when compared to lighter drinkers. Similarly, Holdstock, King, & de Wit (2000) found that moderate and heavy drinkers experienced more stimulation and less sedation and aversive effects than lighter drinkers with no other differences between groups. This pattern of findings has also been shown to exist across cultures, including samples of Chinese men (Rueger et al., 2015). In contrast to findings for overall SR, prior studies on the impact of drinking history on acute tolerance have yielded mixed findings. Both Marczinski et al (2009) and Fillmore et al. (2012) found significantly more acute tolerance in binge drinkers compared to lighter-drinking peers. Specifically, Marczinski et al. (2009) found that only binge drinkers developed acute tolerance to subjective intoxication and driving-related cognitions after consuming a moderate dose of alcohol, and Fillmore et al. (2012) found that only binge drinkers exhibited a return to pre-intoxication performance across measures of motor coordination and response activation on the descending limb of the BAC curve. However, several studies have found evidence to the contrary, showing that acute tolerance can be observed in both light and moderate drinkers (Hiltunen, 1997a), and the experience of acute tolerance in heavier drinkers may be dependent on the size of the alcohol dose (Hiltunen, 1997b).

In summary, absolute levels of SR and acute tolerance both play integral roles in understanding alcohol use and related risk behavior and may have shared risk factors. Several studies have found that a positive family history leads to development of acute tolerance to subjective intoxication, and a compelling body of literature supports the impact of FH on sedative alcohol effects. Further, SR and acute tolerance have both been shown to be impacted by heavy drinking patterns, suggesting that previous alcohol exposure contributes to the experience of both. Coupled with SR's unique biphasic relationship with the BAC curve, studies of acute tolerance to the full range of subjective responses are warranted. Accounting for absolute levels of SR and time elapsed between ascending and descending limb assessments may also refine our understanding of acute tolerance and the extent to which it is impacted by family history and drinking history.

Thus, we hypothesized that greater density of positive family history for AUD and greater frequency and quantity of prior alcohol consumption would lead to a shorter time elapsed between corresponding BACs on the ascending and descending limbs. Greater family history density was expected to predict lower levels of overall sedation whereas earlier alcohol consumption was expected to predict higher overall levels of stimulation. We also hypothesized that those with higher average levels of SR will experience greater acute tolerance, irrespective of the SR domain. Finally, we hypothesized that time elapsed between assessments and higher SR levels will positively mediate relations between FH, drinking history, and acute tolerance.

CHAPTER 2

METHODS

Original Study

Data for the current study comes from a previous investigation designed to better understand how social and physical context influence subjective response to alcohol. Participants completed a battery of questionnaires including demographic variables and information regarding family and personal alcohol-history. Participants then returned to the lab for an alcohol challenge. Participants completed four subsequent follow-up web-based assessments over a two-year period though only the baseline survey and lab data are used in the current study.

Participants

Participants (*N*=448) were recruited from a large southwestern university and the surrounding community as part of a large lab-based alcohol administration study designed to investigate subjective responses to alcohol. Eligible participants were aged 21-25 and endorsed at least one past-month heavy drinking episode (4+ drinks on one occasion for women, 5+ for men). Individuals who reported medical conditions that contraindicated alcohol use, use of psychotropic or pain medications, averse physical reactions to alcohol consumption, use of illicit drugs other than marijuana, daily or near daily marijuana use, pregnancy or nursing, current or previous treatment seeking for alcohol-related problems, or past-month Alcohol Use Disorder, mood or anxiety disorder were excluded. Due to the nature of the proposed study, analyses were restricted to those assigned to the alcohol condition (N=258). Twelve other participants failed to reach a peak BAC of at least .06, and as such were excluded from the analyses, resulting in a

final sample of 258 participants. Participants (42.6% female) ranged in age from 21-25, and closely matched community demographics (66.1% White, 26.1% Hispanic/LatinX). For more descriptive statistics, refer to Table 1.

Procedure

All study procedures were approved by Arizona State University's Institutional Review Board (Protocol #1210008481). Participants were first screened by phone and were scheduled to complete a baseline assessment. During this session, participants were screened for past-month Alcohol Use Disorder symptomology using the Alcohol Use Disorders and Associated Disabilities Interview Schedule (AUDADIS-IV; Grant et al., 2003), along with a battery of additional questionnaires that included assessment of age of alcohol initiation and the Timeline Follow-Back (TLFB; Sobell & Sobell, 1992) interview. If participants did not meet criteria for past-month AUD, mood, or anxiety disorder, and did not report any physical or medical concerns that would contraindicate consumption of alcohol, they were scheduled to attend an alcohol challenge session. They were asked to not consume alcohol for 24 hours before the session, and not to consume food or caffeine for 4 hours before coming into the lab.

At the time of their scheduled session, participants were randomly assigned to one of four contexts in which alcohol would be consumed. Physical (simulated bar vs. traditional lab) and social (solitary vs. group) contexts were crossed to create the four contexts. Assignments to drinking contexts were as follows: 68 (26.4%) were assigned to the group bar, 62 (24%) to the group lab, 65 (25.2%) to the solitary bar, and 63 (24.4%) to the solitary lab condition. The simulated bar represents a unique, custom-built space designed to emulate a more traditional drinking setting, complete with bar stools, neon

lights, popular music, and alcohol bottles and empty glassware behind the bar top. The lab setting represents a much more sterile environment, containing several computer screens, and filing cabinets but not much other decoration. For each session, participants were randomized to alcohol or placebo conditions at a ratio of 3 alcohol participants to every 2 placebo participants.

When participants arrived for the alcohol challenge, research assistants verified they were of eligible age, and reviewed consent forms. Before participating, breathalyzers were administered to ensure a BAC of .00 g/kg BAC, and female participants provided a urine sample to confirm a negative result for pregnancy. Trained research assistants then prepared alcoholic beverages comprising 100 proof vodka, cranberry juice, lemon-lime soda, and lime juice which were based on participant height, weight, and sex (Curtin & Fairchild, 2003) targeting a BAC of .08 g/kg BAC. Each dose was divided into three drinks and was then served to participants with instructions to consume one beverage in six minutes, with one minute in between beverages. After all three beverages were consumed, BAC readings were taken every 10 minutes until participants reached .06 g/kg, at which time measurements of SR on the ascending limb were taken. Descending SR measurements were given at a BAC as close as possible to the ascending BAC ($M_{ascending}$ = .068 g/kg, $M_{descending}$ = .066 g/kg). After completing all study tasks, participants were held in the lab until their BAC fell below .03 g/kg, at which time they were debriefed, compensated, and provided transportation home.

Measures

Measures were administered either at baseline (e.g., demographics, family history, TLFB), during the alcohol challenge (e.g., BAC), or both (e.g., SR).

Demographics. Demographic information including age, sex, race, and ethnicity were collected via a self-report questionnaire administered during the initial baseline session.

Family History. Family history of alcohol related problems was assessed at baseline using the Family Tree Questionnaire (Mann et al., 1985). Participants were asked to classify parents, grandparents, and siblings as non-drinkers, social drinkers, possible problem drinkers, or definite problem drinkers. In total, eight categories of family members were assessed (paternal grandfather/grandmother, maternal grandfather/grandmother, father, mother, brother(s) and/or sister(s)). Due to the possibility that siblings were not of drinking age at the time of assessment, family history density was calculated using only grandparents and parents. Test-retest reliability has been shown to be excellent for first degree relatives with AUD (κ = .92) and acceptable for second degree relatives with AUD (κ = .78; Vogel-Sprott, Chipperfield, & Hart, 1985). Ratings of a family member as a non-drinker or social drinker were scored as a 0, whereas possible problem drinking or definite problem drinking among grandparents and parents were scored as a 1 or 2, respectively. Due to family history of AUD being a zero-inflated variable in the current sample, FH was dichotomized for analyses.

Drinking History. Age of alcohol initiation was assessed using the Comprehensive Early Drinking History Form (CEDHF; Hartman et al., 2019). The CEDHF aggregates data about participant's age of first use, age of first intoxication, age when drinking at least once a month began, and quantity and frequency data for each year from when the individual started drinking at least monthly. The proposed analyses utilized questions about the age at which participants consumed their first standard drink, the age at which

they first became intoxicated, and the age at which they first became regular drinkers (i.e., at least once a month).

Subjective Response. Subjective response to alcohol was measured using the Subjective Effects of Alcohol Scale (SEAS; Morean et al., 2013). Participants rated the extent to which they felt the effects of alcohol across four affective domains "right now". The four domains cross valence and arousal and include high arousal positive (HAP), low arousal positive (LAP), high arousal negative (HAN) and low arousal negative (LAN) effects. Importantly, participants completed the SEAS at matched BACs on the ascending and descending limbs of the blood alcohol curve. SEAS was also assessed at peak BAC. Scores for each time point were calculated by averaging items within each of the four subscales. Internal reliability was good across all assessments (α = .79 - .94). For assessments of acute tolerance, SEAS scores collected at matched BACs on the ascending and descending limbs were considered.

Alcohol Use. Alcohol use was assessed via the Timeline Follow Back (TLFB; Sobell & Sobell, 1992). Participants provided frequency, quantity, and time spent drinking for the 30 days prior to their baseline session. Trained research assistants oversaw the administration of the TLFB, and participants were provided with a standard drinks chart to ensure consistent definitions of a standard drink. The TLFB demonstrates strong validity across younger adult (r = .86-.97) and alcohol dependent populations (r = .73-1.0) and is positively correlated with other assessments of alcohol use (Sobell & Sobell, 1992). For each participant, an average drinks per drinking day variable was calculated and used in subsequent analyses.

Alcohol Consequences. Alcohol consequences were assessed using the Young Adult Alcohol Consequences Questionnaire (YAACQ; Read et al., 2006). The YAACQ is a 48-item questionnaire that assesses potential consequences of drinking alcohol across 8 domains. Participants were asked to indicate how many of the consequences they had experienced in the past 30 days using a dichotomous yes/no response format. Read et al. (2006) found that internal consistencies for each of the subscales were .70 or greater. The current study used the total summed score, and internal consistency was good in our sample ($\alpha = .89$).

Data Analytic Plan

Preliminary Analyses. Before conducting the primary analyses, all variable distributions were evaluated for outliers. Outliers were windsorized by replacing any values more than 3 standard deviations away from the mean with a value one higher than the highest value within the distribution (Tabachnick, Fidell, & Ullman, 2007). Any further non-normality was accounted for by using the Maximum Likelihood Estimator with Robust Standard Errors (MLR) and Full Information Maximum Likelihood (FIML) was used to estimate missing data.

Primary Analyses. Path analyses were conducted via MPlus Version 8.4 (Muthen & Muthen, 2020). Separate models were be tested for each of the four domains of SR (i.e., high arousal positive, high arousal negative, low arousal positive, low arousal negative). For each model, model fit was assessed based on guidelines originally described by Hu & Bentler (1999) (i.e., CFI & TLI $\geq$.95, RMSEA $\leq$ .06, & SRMR $\leq$ .08).

In all models, participant age, sex, and race & ethnicity (i.e., a binary White/Non-Hispanic vs. all other racial/ethnic minorities identifier) were included as covariates.

Because the study from which the data were collected administered beverages in four contexts (group bar, solitary bar, group lab, and solitary lab), both physical (i.e., bar or lab) and social (i.e., solitary or group) contexts were also included as covariates. Acute tolerance was modeled by calculating latent change scores (LCS) for each participant. LCS represent a preferred alternative to raw difference scores, which have been shown to be unreliable in the measurement of alcohol's acute effects due to their dependence on the range of scores being calculated and the high correlation between ascending and descending limb measurements (Earleywine, 1995). In contrast, LCS take changes over time and decomposes them into "linear slices" (King et al., 2006), and LCS models have been shown to be more accurate and powerful than difference score models (Castro-Schilo & Grimm, 2017). To test whether acute tolerance was accurately captured, a one-sample t-test was run comparing LCS for each SR domain against zero. A significant t-test in the positive direction would signify that acute tolerance was reliably observed. Factor scores for each latent change score model were saved out and included in further analyses.

In each model, LCS for a given SR domain was regressed onto the family history density and drinking history variables, as well as time-elapsed and absolute levels of SR to test the potential mediated pathways between FH, drinking history variables, and acute tolerance to SR. Time elapsed and average SR were regressed onto the FH and drinking history variables to examine relations between hypothesized proximal antecedents of acute tolerance and distal risk factors. Acute tolerance (LCS) was regressed onto time elapsed and average SR, and both alcohol use (TLFB) and alcohol-related consequences

(YAACQ scores) were regressed onto acute tolerance LCS and absolute SR to test for potential direct and indirect effects.

CHAPTER 3

RESULTS

Descriptive Statistics: The distributions of all study variables fell within acceptable guidelines for normality (i.e., skewness between -2 and 2; Hair et al., 2010; Kline, 2011), apart from peak high arousal negative effects (skewness=2.34). A total of 8 cases for high arousal negative effects were winsorized to equal a value three standard deviations above the mean (Tabachnick et al., 2007). After censoring these cases, peak high arousal negative effects fell within an acceptable range (skewness=1.92). Descriptive statistics can be found in Table 2 and bivariate correlations among antecedent variables are reported in Table 3.

Drinking History Latent Variable: Prior to running primary analyses, a measurement model was developed to create a latent variable designed to capture participant drinking history. Indicators included the age participants first reported having a standard drink of alcohol, the age they first recalled becoming intoxicated, and how long (in years) they have been a regular drinker. All indicators were scaled to be measured in months. The measurement model was fully saturated, and thus model fit statistics were not available. All indicators loaded positively and significantly onto the latent factor (all $\beta > .84$, see Figure 1), and factor scores were saved and included as measured variables in subsequent models.

Calculation of Latent Change Scores: Latent change scores for each SR domain were calculated within the same model. For each SR domain, latent change was defined as a function of ascending and descending values. The latent change factor for each domain was calculated by loading the descending measurement of SR at a fixed value.

Descending measurements were regressed onto ascending measurements with the variance of ascending measurements being fixed. The intercepts of descending measurements were set to zero. Correlations between latent change scores and baseline SR measurements and between ascending and baseline SR measurements were also estimated. The latent change model showed adequate fit to the data ($\chi^2(30)=83.28$, $p<.01$, RMSEA=.083, CFI=.92, SRMR=.10). Latent change factor scores were saved and used as measured variables in subsequent models.

To test the ability of latent change scores to capture the development of acute tolerance, a series of one-sample t-tests were conducted using the calculated latent change scores. Latent change scores for high arousal positive [$t(257)=11.21$, $p<.001$], low arousal positive [$t(257)=2.53$, $p=.012$], and low arousal negative effects [$t(257)=9.85$, $p<.001$] all significantly differed from zero whereas latent change scores for high arousal negative effects were not significant [$t(257)=1.72$, $p=.087$]. All mean differences were in the positive direction, indicating that the calculation of latent change scores reliably captured acute tolerance across three of the four SR domains. Although results for high arousal negative effects were non-significant, results were in the expected direction.

Subjective Response Models: For clarity, the effects of covariates (age, sex, race & ethnicity, physical and social context) from each model are reported in Table 4.

High Arousal Positive Model: Results from the high arousal positive model are reported in Figure 2. The model showed excellent fit ($\chi^2(8)=5.45$, $p>.05$, RMSEA<.001, CFI=1.00, SRMR=.01). No significant relations were observed between family history of AUD and other study variables, whereas participant drinking history ($\beta=.24$, S.E.=.08, $p<.01$) was positively associated with concurrent negative consequences such that an

earlier age of alcohol initiation was associated with more negative consequences. Notably, although no significant predictors of time elapsed were observed, time elapsed emerged as the only variable with a significant association with acute tolerance (β=.15, S.E.=.07, p<.05), such that more time between ascending and descending limb measurements was related to a greater decrease in high arousal positive effects over time. Additionally, although peak high arousal positive SR was not significantly related to acute tolerance, peak high arousal positive SR exhibited the only significant association with heavier drinking (β=.15, S.E.=.05, p<.01). Heavier drinking was also positively associated with negative consequences (β=.19, S.E.=.06, p<.01). Further, peak high arousal positive SR was indirectly linked with negative consequences through drinking (95%CI=[.01, .06]). No other indirect effects were observed.

High Arousal Negative Model: The high arousal negative model showed excellent fit to the data ($\chi^2(8)=3.58$, p>.05, RMSEA<.001, CFI=1.00, SRMR=.01). Results are reported in Figure 4. Again, no significant relations were observed between family history and other variables. Drinking history was directly associated with both personal drinking (β=.16, S.E.=.08, p<.05) and negative consequences (β=.24, S.E.=.08, p<.01) such that an earlier age of alcohol initiation was related with higher overall alcohol risk. Higher peak high arousal negative effects (β=.17, S.E.=.07, p<.05) and more drinks per drinking day (β=.19, S.E.=.06, p<.01), were both directly associated with the experience of more negative consequences. Of note, no significant antecedents of acute tolerance were observed, and acute tolerance to high arousal negative effects was not related to either drinking (β=.09, S.E.=.06, p>.05) or negative consequences (β=-.05, S.E.=.07, p>.05). No indirect effects were observed.

Low Arousal Positive Model: Results from the low arousal positive model are shown in Figure 5. The model provided excellent fit to the data ($\chi^2(8)=3.30$, p>.05, RMSEA<.001, CFI=1.00, SRMR=.01). Significant associations between family history and negative consequences (β=.14, S.E.=.07, p<.05) and drinking history and negative consequences (β=.25, S.E.=.08, p<.01) were observed such that both a higher density of familial alcohol-related problems and an earlier age of alcohol initiation were related to more negative consequences. Of note, although no antecedents of acute tolerance were observed, acute tolerance to low arousal positive effects was inversely related with negative consequences (β=-.15, S.E.=.06, p<.01) such that a maintenance of low arousal positive effects across the BAC curve (i.e., less acute tolerance) was associated with more negative consequences. As in previous models, drinks per drinking day remained positively related with negative consequences (β=.20, S.E.=.06, p<.01). No indirect effects were observed.

Low Arousal Negative Model: The low arousal negative model provided excellent fit to the data ($\chi^2(8)=4.19$, p>.05, RMSEA<.001, CFI=1.00, SRMR=.01). Results are shown in Figure 6. Participant drinking history was inversely related with peak low arousal negative effects (β=-.22, S.E.=.08, p<.01) whereas family history was significantly associated with acute tolerance to low arousal negative effects (β=.13, S.E.=.06, p<.05), indicating that a greater family density of alcohol-related problems was related to more acute tolerance (i.e., a greater reduction of low arousal negative effects across the BAC curve). Peak low arousal negative effects were also significantly related to acute tolerance such that higher peak SR was related to a larger reduction in low arousal negative effects on the descending limb (β=.17, S.E.=.08, p<.05). Acute tolerance

to low arousal negative effects were not related to drinking (β= -.09, S.E.=.05, p>.05) or negative consequences (β= -.01, S.E.=.06, p>.05). Participant drinking history (β=.24, S.E.=.08, p<.01) and drinks per drinking day (β=.21, S.E.=.06, p<.01) were positively related to negative consequences, whereas peak low arousal negative effects were directly protective against participant drinking (β=-.16, S.E.=.06, p<.01) and indirectly protective against negative consequences through drinking (95%CI: [-.29, -.03]). No other indirect effects were observed.

CHAPTER 4

DISCUSSION

The current study is the largest and most comprehensive examination of acute tolerance to date and represents the first study to investigate the development of acute tolerance across the full valence by arousal affective space of subjective response. The current study also expands on the somewhat limited literature regarding antecedents of acute tolerance by testing the influence of family history of alcohol use disorder, personal drinking history, and individual differences in alcohol metabolism on the experience of acute tolerance. Results are discussed in turn.

Development of Acute Tolerance

Prior studies that have focused on acute tolerance to subjective response have found that individuals readily develop acute tolerance to alcohol's stimulating effects whereas little evidence exists in favor of acute tolerance to alcohol-induced sedation (Comley & Dry, 2020). The current study builds upon this prior work by examining the development of acute tolerance to subjective response across the full valence by arousal domain. Results from the current study indicated that participants developed acute tolerance to high arousal positive (stimulation), low arousal positive (relaxation), and low arousal negative (sedation) effects whereas no limb-dependent effects were observed for high arousal negative (e.g., reckless, aggressive) effects. These findings align with prior work by demonstrating a reduction in alcohol stimulation when comparing identical BACs on the ascending and descending limbs (e.g., Earleywine, 1995; Earleywine & Erblich, 1996; Filmore et al., 2005) but diverge from prior work by demonstrating that acute tolerance to alcohol's sedating effects, regardless of the valence (i.e., low arousal

positive and negative), can be captured over the course of an acute alcohol administration challenge. It is possible that domains of subjective response captured by the high arousal negative scale (i.e., aggressive, demanding) are more trait like than other domains and therefore remain stable across a drinking episode. Further, recent work has also shown that alcohol increases the likelihood that individuals ruminate about negative emotions (Mollaahmetoglu et al., 2021). Therefore, the lack of acute tolerance to high arousal negative effects may be due to an increased attention to high arousal negative effects which contributes to the perceived maintenance of those effects across the BAC curve. Future work would benefit from attention to antecedents and cognitive reappraisals of high arousal negative effects to better characterize the course of such effects across a drinking episode.

Antecedents of Acute Tolerance

Of the four novel antecedents of acute tolerance considered in the current study (i.e., family history of AUD, drinking history, time elapsed, peak subjective response) time elapsed emerged as a significant contributor to the development of acute tolerance to high arousal positive effects, such that slower metabolism (e.g., longer time elapsed between matched ascending and descending BACs), was associated with greater reduction of high arousal positive effects over time. It is possible that such effects are observed due to individuals with a slower metabolism having a longer exposure to alcohol, resulting in more activation of physiological compensatory mechanisms that reduce the impact of alcohol on the body's homeostasis (e.g., Zakhari, 2006). These findings are largely in line with prior work demonstrating that a faster metabolism was related to a greater maintenance of alcohol-related stimulation on the descending limb of

the BAC curve (Boyd & Corbin, 2018). Further, Boyd & Corbin (2018) found that maintenance of alcohol-related stimulation was positively related to ad-lib beverage consumption and within-session craving. Notably, the current study also found that peak high arousal positive effects were positively related to both alcohol use and negative consequences whereas acute tolerance to high arousal positive effects did not, meaning that those who experience higher levels of rewarding stimulation are more at risk for negative alcohol-related consequences irrespective of whether they maintain those effects or not. Thus, future interventions highlighting protective behavioral strategies focused on pacing alcohol consumption and highlighting awareness of personal, positively valanced alcohol stimulation, may be effective at reducing overall risk.

The Low Level of Response Model (LLR; Schuckit, 1984) posits that those who experience less subjective response, and in particular, less sedating, are at higher risk for the development of AUDs. Assessment of such effects typically occurs on the descending limb of the BAC curve (Earleywine & Martin, 1993; Erblich et al., 2003; King et al., 2002). Results from the current study partially support the LLR in that peak levels of low arousal negative subjective response were also found to be positively related to acute tolerance such that higher peak low arousal negative effects (e.g., woozy, wobbly) was associated with a greater decrease in subjective effects on the descending limb when compared to an identical point on the ascending limb. Most prior work concerning alcohol's sedating effects typically assess them on the descending limb of the BAC curve. Such findings may be interpreted in line with the Low Level of Response Model (LLR; Schuckit, 1984), which posits that those who experience less subjective response, and in particular, less sedating, aversive effects, are at higher risk for the development of

Alcohol Use Disorders. Thus, it may be that, in addition to capturing lower overall levels of subjective response, alcohol-related risk as defined by the LLR may also be capturing greater acute recovery from alcohol's aversive, sedating effects. Therefore, rather than capturing lower levels of response to alcohol-induced sedation, LLR studies may be capturing those who are more reactive to alcohol's low arousal negative effects and recover more efficiently than others. Such recovery may be due to a chronic tolerance to these effects as evidenced by drinking history significantly predicting peak levels of low arousal negative effects.

Acute Tolerance and Alcohol-Related Outcomes

Acute tolerance to each of the four subjective response domains were not related to concurrent alcohol use or negative alcohol consequences. This contrasts with prior work that has established acute tolerance as a robust risk factor for several consequences including drinking and driving (e.g., Motschman et al., 2020). Notably, the only significant relations observed between acute tolerance and negative consequences were found in the low arousal positive model and the results were counter to hypotheses. Results indicated that greater acute tolerance to low arousal positive effects (i.e., a greater reduction in low arousal positive effects across the two limbs) were protective against negative consequences. Put differently, a maintenance of low arousal positive effects across the BAC curve may operate as a mechanism of risk for more negative consequences. Such findings are in line with the tension reduction theory of alcohol use (Cappell & Herman, 1972) which posits that patterns of use are reinforced by alcohol's ability to alleviate negative affect or stress. Low arousal positive effects encompass effects including feeling "calm" or "relaxed" (Morean et al., 2012), allowing for the

findings presented in the current study to align with prior work linking tension reduction expectancies, subjective response, and negative outcomes (e.g., Thompson et al., 2009; Dvorak et al., 2018; Lee et al., 2020). It is important to note that the current study elected to include a summed count of consequences experienced rather than specific domains of consequences as measured by the YAACQ. Due to the physiological and cognitive nature of acute tolerance, it is possible that acute tolerance to different domains of subjective response may be differentially related to unique domains of negative consequences.

The current study also did not find significant relations between acute tolerance and concurrent drinks per drinking day. These findings were also counter to expectations. In general, it was expected that acute tolerance to both high arousal positive and low arousal positive SR would be positively related to higher levels of alcohol use as both domains represent reinforcing effects of alcohol use. Specifically, alcohol-related stimulation is considered the most rewarding of the four SR domains (Morean et al., 2012; Boyd & Corbin, 2018) and it was therefore hypothesized that a reduction in such effects across the BAC curve may drive higher rates of drinking via levels of craving. It is possible that acute tolerance may be more closely related to drinking behavior in the moment as individuals seek to maintain effects of alcohol they receive on the ascending limb and may be more closely related to proximal antecedents to drinking, such as craving, rather than direct alcohol use. Further, it is also possible that acute tolerance may be more closely related to in-the-moment ad lib consumption as opposed to global measures of alcohol use as experiencing a reduction in desired effects may drive continued use. Thus, future studies would benefit from implementing ecological

momentary assessments across a drinking episode to better understand temporal relations between acute tolerance and drinking behavior.

Importantly, most extant literature that examines acute tolerance has found the most robust evidence exists in support of acute tolerance to subjective intoxication and other outcomes (e.g., Comley & Dry, 2022). It is possible that assessments of acute tolerance to subjective response are too fine grained to be able to detect reliable relations between acute tolerance and later behavior as alcohol restricts introspection to the most salient affective cues (alcohol myopia, Steele & Josephs, 1990). Therefore, certain items that are subsumed under different subjective response factors (e.g., drunk) may be more closely related to negative consequences or alcohol use and future studies would benefit from examining acute tolerance to specific subjective response items.

Subjective Response and Alcohol-Related Outcomes

Whereas the current study did not find any significant relations between acute tolerance to subjective response and alcohol outcomes, results regarding subjective response largely present robust evidence in support of leading subjective response theories. Consistent with prior work, peak levels of high arousal positive effects were directly associated with heavier drinking whereas peak levels of low arousal negative effects were protective against drinking (Morean et al., 2012). Further, both domains were indirectly related to negative consequences via drinking. These findings provide support for Newlin & Thompson's (1990) Differentiator Model of alcohol use and are largely in line with prior studies demonstrating that higher levels of alcohol-induced stimulation are related to heavier drinking and more consequences (e.g., King et al., 2011; Corbin et al., 2015; Corbin et al., 2021) whereas higher levels of alcohol's

sedating, aversive effects are associated with less alcohol consumption and negative consequences. The current study also demonstrates that high arousal negative effects are directly related to negative consequences, building on prior work that examines subjective response to alcohol across the full valence by arousal space (Morean et al., 2012). Together these findings contribute to an already rich literature emphasizing the importance of understanding how subjective response to alcohol conveys unique risk for heavy alcohol use and negative consequences.

Limitations

Results must be interpreted in light of several limitations. First, the current study included a sample of social drinkers who were aged 21-25 and primarily college students, endorsed at least monthly binge drinking, and did not meet criteria for a past month Alcohol Use Disorder. Thus, the overall drinking patterns of the sample, while higher risk, were rather homogenous when compared to the larger population and as such may not generalize to other populations. Such homogeneity may have also made it difficult to capture significant variability in alcohol use across study participants. Future studies would benefit from sampling a more diverse population regarding alcohol use. Further, although more diverse than similar alcohol administration studies, the current sample was predominantly white and non-Hispanic/Latinx and lacked diversity within racial/ethnic identities to model specific inter-group differences. Prior work has shown that subjective response may differ across racial and ethnic identities (e.g., Richner et al., 2018) meaning that results from the current study may not generalize across varying racial and ethnic identities.

Second, the current study relied on self-reports of family history of AUD, past and current alcohol use, and subjective response, although recent work has shown that self-reports and objective assessments of intoxication are highly correlated at low-to-moderate breath alcohol concentrations (Cox et al., 2022). Finally, analyses outlined in the present study come from a larger study designed to examine the effects of social and physical context on subjective response. Although the effects of context were controlled for in the current study, it is possible that individuals could differentially develop acute tolerance depending on their drinking context. For instance, social settings replete with stimulating cues are associated with stimulant alcohol effects (Corbin et al., 2015; Fairbairn & Sayette, 2013; Kirkpatrick & De Wit, 2013; Sayette et al., 2012). Therefore, it is possible that stimulation derived from one's immediate context may supplement decreases of alcohol-related stimulation that occur on the descending limb of the BAC curve, and thus drive increased levels of alcohol-related risk. Developing a more nuanced understanding of how context may influence the development of acute tolerance would inform prevention efforts by aiding in the identification of high-risk contextual situations.

Conclusions

Despite these limitations, this is the largest single study to investigate acute tolerance and represents the first study to our knowledge to examine the development of acute tolerance to the full valence by arousal domains of subjective response to alcohol alongside theoretically relevant antecedents to a cute tolerance including peak subjective response, metabolism, and family history of AUD. Findings suggest that individual differences in alcohol metabolism and peak levels of subjective response may play a significant role in the development of acute tolerance and point to the maintenance of

tension reduction effects across the BAC curve as an important mechanism through which risk for negative consequences is conferred. Future ecological momentary research is needed to better understand how acute tolerance develops in real-world drinking settings in the hopes of developing effective prevention programs aimed at reducing risk related to acute tolerance to alcohol, such as reducing the likelihood that individuals will drink and drive or make risky decisions. It is our hope that the current study will aid in the development of such programs and spur continued research into this vital area of interest.

Table 1: Demographics

Variable	N	Mean (SD)
Age	**258**	22.25 (1.23)
Sex	**258**	
Male	148 (57.4%)	
Female	110 (42.6%)	
Race	**258**	
White	170 (65.9%)	
Black/African American	20 (7.8%)	
Asian	28 (10.9%)	
American Indian/Native	4 (1.6%)	
Other	35 (13.6%)	
Missing	1 (.4%)	
Ethnicity	**258**	
Hispanic/Latin-X	65 (25.2%)	
Non-Hispanic/Latin-X	184 (71.3%)	
Missing	9 (3%)	

Table 2: Descriptive Statistics of Study Variables

Variable	N (%)	Range	Mean (SD)	Skewness
Family History				
Positive	57 (22.1%)			
Negative	201 (77.9%)			
Time Elapsed (minutes)	258	(15.00 - 225.00)	97.93 (36.17)	.70
Subjective Response				
High Arousal Positive	256	(0.00 - 10.00)	5.50 (2.22)	-.33
High Arousal Negative	258	(0.00 - 3.80)	.57 (1.01)	1.92
Low Arousal Positive	256	(0.75 -10.00)	6.46 (1.85)	-.15
Low Arousal Negative	256	(0.00 – 7.67)	1.37 (1.69)	1.40
Acute Tolerance (LCS)				
High Arousal Positive	258	(-3.75 – 9.00)	1.40 (1.99)	.92
High Arousal Negative	258	(-4.33 – 6.00)	.11 (1.00)	.67
Low Arousal Positive	258	(-7.50 – 6.50)	.27 (1.74)	-.30
Low Arousal Negative	258	(-6.67 – 6.67)	.87 (1.42)	.25
YAACQ Scores	252	(0.00 – 32.00)	7.88 (7.10)	1.22
Drinks per Drinking Day	257	(0.00 – 14.00)	4.60 (2.22)	1.09

Note: SD: Standard Deviation; LCS: Latent Change Scores; YAACQ: Young Adult Alcohol Consequences Questionnaire

Table 3. Bivariate Correlations Among Study Variables

	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.	15.
1. Age	1														
2. Biological Sex	.08	1													
3. Race/Ethnicity	.03	.22*	1												
4. Family History	.03	-.01	-.08	1											
5. Drinking History	.48*	.07	-.26*	.08	1										
6. Peak HIGH+	.07	.26*	.14*	.06	-.04	1									
7. Peak HIGH-	.15*	.16*	.10	-.03	.08	.14*	1								
8. Peak LOW+	.05	.12	.03	.06	.10	.36*	-.04	1							
9. Peak LOW-	-.08	.11	.24*	.05	-.23*	.23*	.26*	.09	1						
10. HIGH+ Acute Tolerance	-.12	-.09	-.11	-.08	.05	-.14*	-.01	-.03	-.11	1					
11. HIGH- Acute Tolerance	.12*	.13*	-.01	-.09	.05	.02	.09	.08	-.02	.04	1				
12. LOW+ Acute Tolerance	.06	.001	-.01	.07	.02	-.05	-.02	-.09	-.04	.07	-.22*	1			
13. LOW- Acute Tolerance	.19*	.05	.08	.12*	-.03	-.05	.04	.03	.19*	.10	.15*	.01	1		
14. YAACQ Scores	-.001	-.02	-.03	.14*	.19*	.05	.16*	-.003	-.02	.09	-.04	-.14*	-.04	1	
15. DPDD	-.07	.28*	-.03	.01	.10	.17*	.08	.13*	-.16*	.07	.11	-.04	-.13*	.19*	1

Note. HIGH+: High arousal positive; HIGH-: High arousal negative; LOW+: Low arousal positive; LOW-: Low arousal negative; YAACQ: Young Adult Alcohol Consequences Questionnaire.

* $p < .05$

Table 4. Relations Between Covariates and Study Variables Across Four SR Models

Covariate	Family History	Drinking History	Peak SR	Acute tolerance to SR	Time Elapsed	Drinks per Drinking Day	Negative Consequences
High Arousal Positive							
Age	-.01 (.01)	**.47 (.05)**	.07 (.07)	**-.15 (.07)**	-.06 (.09)	**-.16 (.08)**	-.10 (.07)
Sex	.004 (.06)	.08 (.06)	**.24 (.06)**	-.07 (.07)	**.12 (.06)**	**.27 (.06)**	-.11 (.07)
Race/Ethnicity	-.09 (.07)	**-.27 (.06)**	.07 (.06)	-.07 (.07)	.10 (.07)	-.05 (.07)	.08 (.07)
Social Context	.10 (.06)	-.02 (.06)	.09 (.06)	.03 (.06)	.02 (.06)	-.01 (.06)	-.002 (.06)
Physical Context	.10 (.06)	.08 (.06)	-.07 (.06)	.01 (.06)	-.11 (.06)	-.09 (.06)	.06 (.06)
High Arousal Negative							
Age	-.01 (.01)	**.47 (.05)**	.14 (.08)	.11 (.08)	-.06 (.09)	**-.18 (.08)**	-.12 (.07)
Sex	.004 (.06)	.08 (.06)	**.13 (.06)**	**.13 (.06)**	**.12 (.06)**	**.28 (.06)**	-.12 (.07)
Race/Ethnicity	-.09 (.07)	**-.27 (.06)**	.06 (.06)	-.06 (.06)	.10 (.07)	-.04 (.07)	.07 (.07)
Social Context	.10 (.06)	-.02 (.06)	.06 (.06)	**.16 (.06)**	.02 (.06)	-.09 (.06)	-.001 (.06)
Physical Context	.10 (.06)	.08 (.06)	-.05 (.07)	.06 (.06)	-.11 (.06)	.06 (.06)	.003 (.06)
Low Arousal Positive							
Age	-.01 (.01)	**.47 (.05)**	-.003 (.08)	.06 (.07)	-.06 (.09)	**-.16 (.08)**	-.10 (.07)
Sex	.004 (.06)	.08 (.06)	.11 (.06)	.01 (.07)	**.12 (.06)**	**.29 (.05)**	-.10 (.07)
Race/Ethnicity	-.09 (.07)	**-.26 (.06)**	.02 (.07)	.002 (.07)	.10 (.07)	-.05 (.07)	.08 (.07)
Social Context	.10 (.06)	-.02 (.06)	-.04 (.06)	**-.16 (.06)**	.02 (.06)	-.07 (.06)	-.03 (.06)
Physical Context	.10 (.06)	.08 (.06)	**-.15 (.07)**	.02 (.06)	-.11 (.06)	.07 (.06)	-.01 (.06)
Low Arousal Negative							
Age	-.01 (.01)	**.48 (.05)**	.01 (.08)	**.26 (.07)**	-.07 (.09)	-.14 (.08)	-.10 (.07)
Sex	.004 (.06)	.08 (.06)	.09 (.06)	.004 (.06)	**.12 (.06)**	**.32 (.05)**	-.11 (.07)
Race/Ethnicity	-.08 (.07)	**-.27 (.06)**	**.17 (.07)**	-.01 (.07)	.11 (.07)	-.02 (.06)	.07 (.07)
Social Context	.10 (.06)	-.02 (.06)	.07 (.06)	.03 (.06)	.02 (.06)	-.06 (.06)	-.003 (.06)
Physical Context	.10 (.06)	.07 (.06)	-.06 (.06)	-.01 (.06)	-.11 (.06)	.04 (.06)	-.003 (.06)

Note: Results reported are standardized and listed as β (S.E.). Bolded results indicate significant path estimates (p<.05).

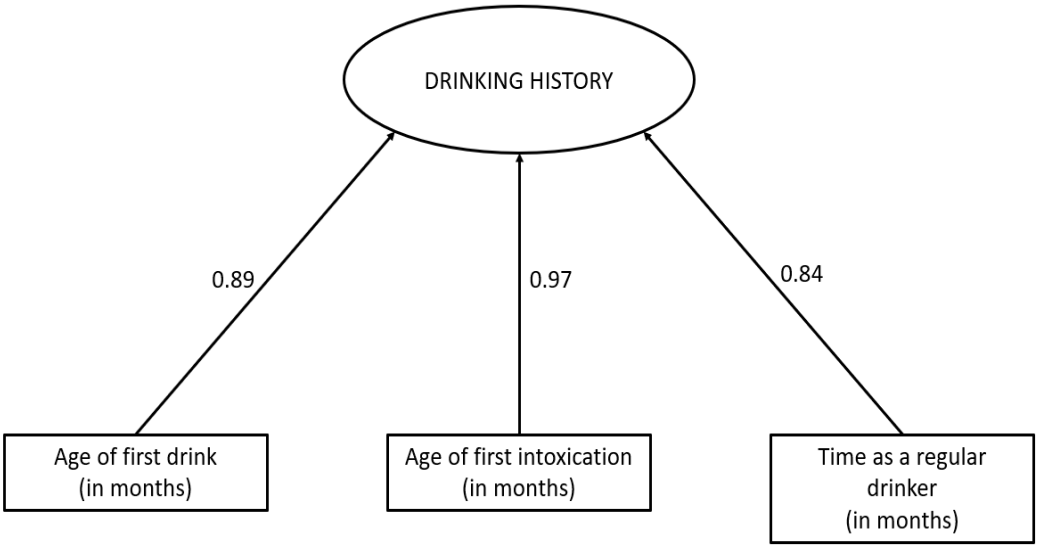

Figure 1. Drinking History Measurement Model Indicator Loadings.

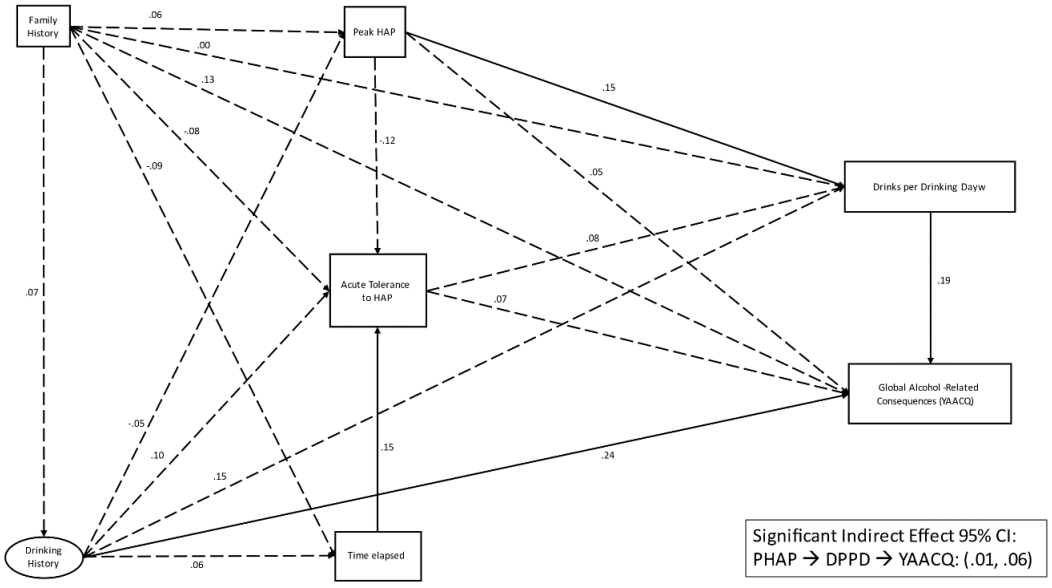

Figure 2. High Arousal Positive Model. Standardized path estimates are shown. Significant effects ($p < .05$) are represented by bold lines.

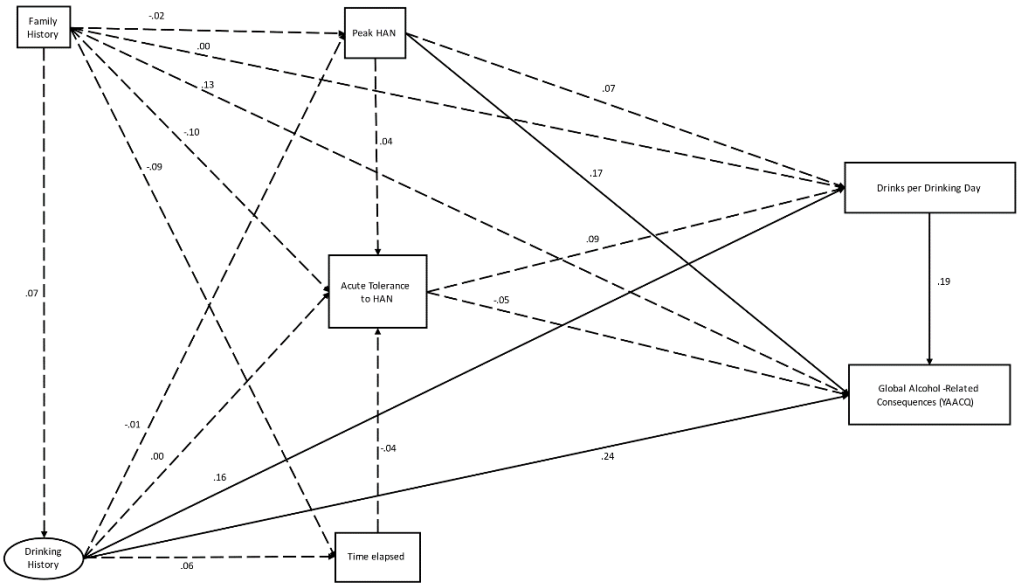

Figure 3. High Arousal Negative Model. Standardized path estimates are shown. Significant effects ($p < .05$) are represented by bold lines.

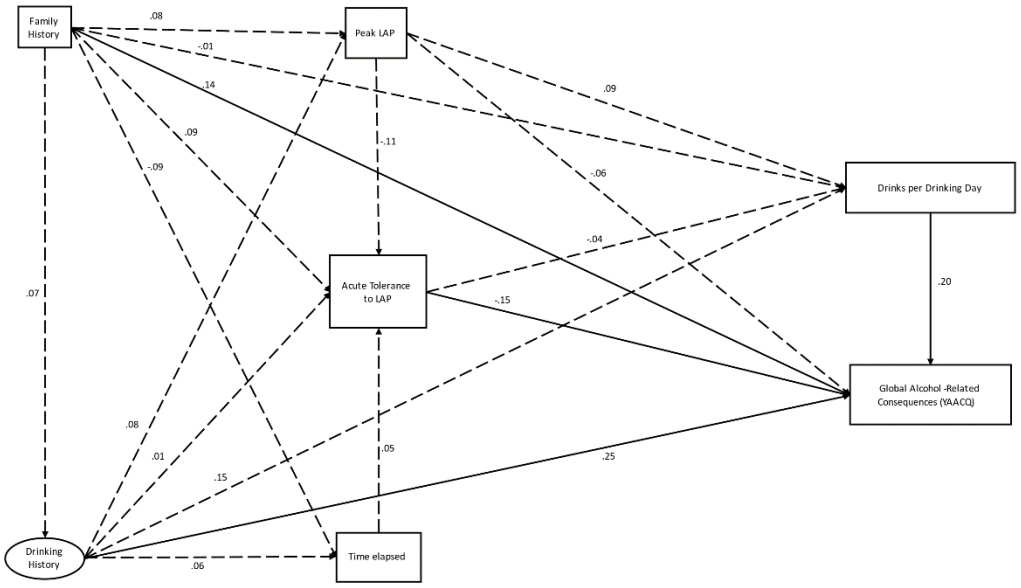

Figure 4. Low Arousal Positive Model. Standardized path estimates are shown. Significant effects ($p < .05$) are represented by bold lines.

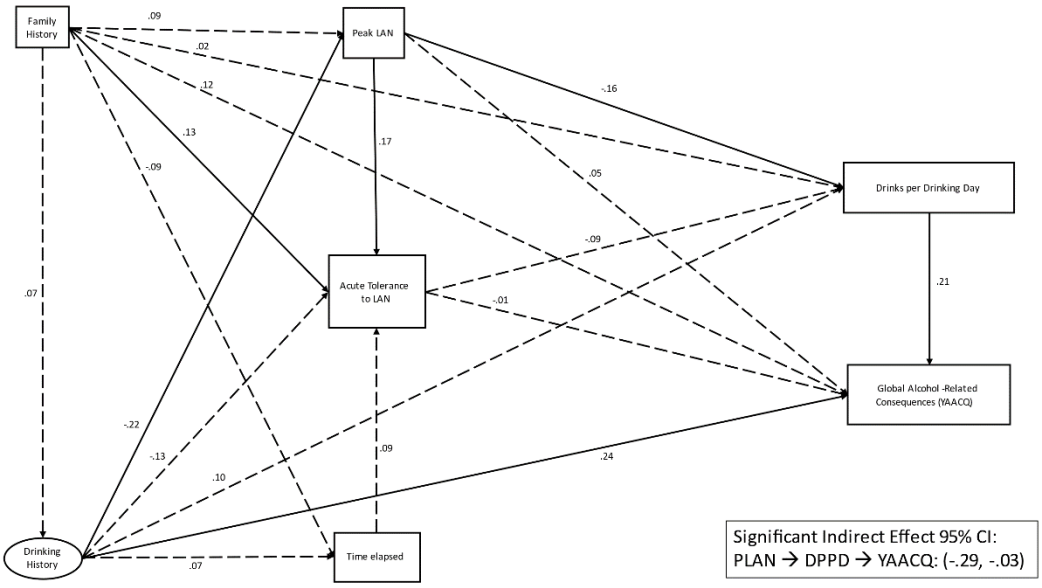

Figure 5. Low Arousal Negative Model. Standardized path estimates are shown. Significant effects ($p < .05$) are represented by bold lines.

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