Anxiety and Subjective Response to Alcohol: Moderating Effects of Drinking Context and Mediation by Cortisol Response to Alcohol

by

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A Dissertation Presented in Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

Approved May 2018 by the
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ARIZONA STATE UNIVERSITY

August 2018

ABSTRACT

Anxiety disorder diagnosis is a risk factor for alcohol use disorders (AUDs), but mechanisms of risk are not well understood. Studies show that anxious individuals receive greater negative reinforcement from alcohol when consumed prior to a stressor, but few studies have examined whether anxious individuals receive greater negative (or positive) reinforcement from alcohol in a general drinking context (i.e., no imminent stressor). Previous studies have also failed to examine possible moderating effects of specific drinking contexts (e.g., drinking in a group or alone). Finally, no studies have investigated mediating variables that might explain the relationship between anxiety and reinforcement from alcohol, such as physiological response to alcohol (e.g., cortisol response). Data for this study were drawn from a large alcohol administration study (N = 447) wherein participants were randomized to receive alcohol (target peak BAC: .08 g%) or placebo in one of four contexts: group simulated bar, solitary simulated bar, group sterile laboratory, solitary sterile laboratory. It was hypothesized that anxiety would be associated with positive subjective response (SR) under alcohol (above and beyond placebo), indicating stronger reinforcement from alcohol. It was also hypothesized that social and physical drinking context would moderate this relationship. Finally, it was hypothesized that anxiety would be associated with a blunted cortisol response to alcohol (compared to placebo) and this blunted cortisol response would be associated with stronger positive SR and weaker negative SR. Results showed that anxiety was not associated with positive SR in the full sample, but drinking context did moderate the anxiety/SR relationship in most cases (e.g., anxiety was significantly associated with positive SR (stimulation) under placebo in solitary contexts only). There was no evidence

that cortisol response to alcohol mediated the relationship between anxiety and SR. This study provides evidence that anxious drinkers expect stronger positive reinforcement from alcohol in solitary contexts, which has implications for intervention (e.g., modification of existing interventions like expectancy challenge). Null findings regarding cortisol response suggest alcohol's effect on cortisol response to stress (rather than cortisol response to alcohol consumption) may be more relevant for SR and drinking behavior among anxious individuals.

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Prevalence, Costs, and Comorbidity of Anxiety Disorders and Alcohol Use Disorders

Alcohol use disorders (AUDs) and anxiety disorders are highly prevalent in the general population (Grant et al., 2004; Kessler et al., 1997) and carry a high cost in terms of health care expenditures (Rehm et al., 2009; Simon et al., 1995). Furthermore, these costly conditions have been shown to co-occur at rates higher than would be expected by chance (Grant et al., 2004; Kessler et al., 1997). This presents a worrisome picture from a public health perspective, as comorbid mental health and substance use disorders have been shown to be associated with worse treatment outcomes than either type of disorder alone (Compton et al., 2003; Grella et al., 2001). However, the etiology underlying the co-occurrence of these conditions is still not well understood. Researchers have investigated the comorbidity problem from multiple perspectives, including investigating AUDs as a risk factor for the development of anxiety disorders (e.g., George et al., 1990), anxiety disorders as a risk factor for AUDs (e.g., Zimmerman et al., 2003), and possible shared etiological explanations involving genetics or environment (e.g., Kendler et al., 1995). In a 2000 review of research on the comorbidity between anxiety disorders and AUDs, Kushner concluded that each of these perspectives offers some insight into the comorbidity problem, and it is likely that comorbidity comes about as a result of a "vicious cycle" wherein anxiety symptoms contribute to risk for AUDs via negative reinforcement-motivated drinking (i.e., using alcohol to alleviate anxiety symptoms), and continued drinking and withdrawal worsen anxiety symptoms. Thus, research on any link in this cycle is likely to offer insight into the etiology of both disorders as well as the development of comorbidity.

Much research has focused on the causal influence of anxiety disorders on AUDs, and it has been shown in multiple studies that pre-existing anxiety disorders can predispose individuals to develop later AUDs. For example, Buckner et al. (2008) found that a diagnosis of social anxiety disorder or panic disorder by age 16 significantly increased risk for a diagnosis of alcohol dependence by age 30 (although the association for panic disorder became non-significant when controlling for other psychopathology). Similarly, Zimmerman et al. (2003) found that diagnosis of an anxiety disorder in adolescence or young adulthood was predictive of onset of alcohol abuse four years later and was marginally significantly predictive of the onset of any AUD (abuse or dependence) four years later. Finally, Kushner et al. (1999) found that diagnosis of an anxiety disorder as a freshman in college was associated with significantly higher odds of developing alcohol dependence seven years later.

Results are somewhat less consistent when examining the relationship between anxiety symptoms (versus diagnosed anxiety disorders) and initiation of use or heavy use (versus alcohol abuse or dependence), but a number of studies have shown positive associations (Kaplow et al., 2001; Stewart et al., 1995; Valentiner et al., 2004), suggesting that anxiety can influence the development of alcohol problems even at sub-clinical levels. Thus, research into the mechanisms by which anxiety predisposes individuals to develop problematic alcohol use and AUDs is warranted, even though this is only one link in the complex relationship between these two problems. Research investigating the comorbidity question has the potential to produce theoretical advancements in our understanding of the (potentially shared) etiology of these disorders

as well as novel prevention and intervention strategies tailored specifically to those with comorbid anxiety and AUDs.

Anxiety and the Reinforcing Value of Alcohol

Alcohol consumption results in a complex array of physiological effects that can be interpreted positively or negatively by the drinker (Levenson et al., 1980). Unsurprisingly, experiencing stronger positive subjective effects of alcohol (e.g., feeling stimulated or elated), and weaker negative subjective effects (e.g., feeling sedated or woozy) reinforces drinking behavior and leads to greater alcohol consumption and greater likelihood of developing alcohol problems in the future (King et al., 2011; Trim et al., 2009). In addition to experiencing positive and negative subjective effects (i.e., pleasure and displeasure) as a result of alcohol consumption, one can also theoretically receive negative reinforcement from alcohol via reduction of negative affect. Alcohol's ability to provide negative reinforcement is fairly well-established thanks to a number of studies utilizing the stress response dampening (SRD) model proposed by Levenson et al. (1980), which asserts that alcohol provides negative reinforcement by dampening physiological and subjective response to future stressful events. This model has been supported by a number of well-designed empirical studies wherein participants' physiological and subjective response to a standard stressor (e.g., shock or a social stressor like a self-disclosing speech) is assessed after consumption of alcohol or placebo. Generally, it has been found that alcohol "dampens" the intensity of response to a stressor to a greater degree than placebo (Levenson et al., 1980; Sher & Levenson, 1982; Sher & Walitzer, 1986).

There is some empirical evidence suggesting that individuals with elevated levels of anxiety receive greater negative reinforcement from alcohol, which is one plausible etiological mechanism to explain the comorbidity between anxiety and AUDs. However, the conditions under which this negative reinforcement occurs are narrowly defined because the vast majority of studies investigating this question utilize the stress response dampening (SRD) paradigm mentioned above, but with the added layer of comparing individuals based on anxiety status (variously defined, see below). For example, in a mixed-gender sample, Macdonald et al. (2000) found that alcohol (vs. placebo) significantly reduced affective and cognitive reactivity (i.e., negative thoughts) to a hyperventilation challenge among those high in anxiety sensitivity, but not among those low in anxiety sensitivity. Stewart & Pihl (1994) found that women high in anxiety sensitivity experienced greater alcohol-induced reductions in anticipatory emotional arousal and skin conductance prior to an aversive noise burst compared to women low in anxiety sensitivity (though there was no placebo condition in this study). Finally, Sinha et al. (1998) found that alcohol (vs. placebo) reduced heart rate and blood pressure reactivity to a social stressor in women with a family history of anxiety disorder, but alcohol *increased* blood pressure reactivity among men with a family history of anxiety disorder. In contrast to results supporting enhanced SRD in anxious women, and mirroring the results of Sinha et al. (1998), findings from other studies utilizing male samples have generally been negative. For example, in an all-male sample, Sher & Walitzer (1986) found that the presence of social anxiety did not moderate the effect of alcohol (vs. placebo) on subjective anxiety or heart rate during a social stressor. Additionally, Keane and Lisman (1980) found that alcohol consumption (vs. placebo)

had no effect on changes in self-reported anxiety among either socially anxious men or non-anxious men.

Taken together, these studies suggest that greater anxiety (or predisposition to anxiety by family history) may predispose individuals to experience greater stress response dampening effects from alcohol, but this effect may be exclusive to (or at least stronger in) women. Although this evidence provides some insight into the link between anxiety and pathological alcohol use (at least among women), the SRD model is limited in its ability to provide insight into how the full spectrum of anxiety symptoms and disorders might predispose individuals to develop alcohol problems for two reasons. First, the model only directly applies to situations in which alcohol is ingested immediately prior to stressful events, which covers a relatively narrow range of scenarios in which alcohol might be used to cope with anticipated anxiety or negative affect (e.g., drinking before a social event to reduce anxiety experienced during the event). The model does not map well onto types of anxiety that are more chronic or less predictable, such as panic attacks and generalized anxiety, which may spur alcohol use aimed at coping with negative affect in the present, as opposed to drinking in anticipation of negative affect. Second, the model's sole focus on negative reinforcement means that it does not address the possibility that anxiety could predispose one to seek positive, mood-enhancing alcohol effects (i.e., positive reinforcement; see below). In light of these limitations, studies investigating the relationship between anxiety and alcohol's reinforcing effects (including positive reinforcement) in the absence of an imminent stressor are needed.

Anxiety and Subjective Response to Alcohol - Moving Beyond Stress Response Dampening

Fortunately, validated measures now exist that allow researchers to assess alcohol's reinforcing effects in a general context (i.e., without reference to a stressor) in a valid and accurate way that was not possible when the SRD model was first proposed. The variety of subjective effects that can result from drinking alcohol (e.g., stimulation, sedation, agitation, relaxation) are collectively referred to by many researchers as "subjective response to alcohol." In one conceptualization, subjective response (SR) is defined as an endophenotype reflecting "individual differences in sensitivity to the pharmacological effects of alcohol" (Morean and Corbin, 2010). Multiple measures have been developed by different groups of researchers that attempt to assess subjective response. One such measure is the Biphasic Alcohol Effects Scale (BAES; Martin et al., 1993), which assesses the subjective feelings of stimulation (e.g., feeling "elated" or "energized") that predominate on the ascending limb of the blood alcohol curve as well as the subjective feelings of sedation (e.g., feeling "sluggish" or "down") that predominate on the descending limb of the blood alcohol curve.

Studies utilizing the BAES have found that individuals at high risk for developing AUDs (either as a result of family history of AUDs or a pattern of heavy drinking) tend to experience stronger subjective stimulation and less subjective sedation after consuming alcohol (Erblich et al., 2003; King et al., 2002). As mentioned above, this profile of subjective response has been shown to be predictive of future alcohol use and problems (King et al., 2011; Trim et al., 2009), supporting the usefulness of subjective response to alcohol as a marker of risk for future alcohol problems. However, one significant

limitation of the BAES is that it was not designed to capture low-arousal, positively valenced subjective effects (e.g., relaxation), which could theoretically be negatively reinforcing (especially for anxious individuals). As defined on the BAES, subjective feelings of stimulation would be experienced as positively reinforcing, whereas subjective feelings of sedation would be experienced as aversive, meaning that negatively reinforcing effects are not addressed.

Fortunately, a recently developed measure of subjective response, the Subjective Effects of Alcohol Scale (SEAS; Morean et al., 2013), was explicitly designed to tap aspects of subjective response to alcohol that were not assessed by previous measures like the BAES. The SEAS assesses the full arousal by valence space of possible subjective alcohol effects (high/low arousal is fully crossed with positive/negative valence). Crucially, one subscale of the SEAS specifically assesses the low-arousal, positively valenced subjective effects (e.g., feeling calm, relaxed) that would be critical in understanding negative reinforcement from alcohol among anxious individuals across a range of drinking scenarios. Because anxiety is characterized by chronic high arousal and the frequent experience of negative affect, individuals high in trait anxiety would seemingly be more likely to experience subjective alcohol effects like relaxation as negatively reinforcing across many situations. Thus, a measure assessing relaxing or calming effects of alcohol (relative to a pre-alcohol state) would be a useful tool in understanding the negatively reinforcing effects of alcohol in this population in particular.

In contrast to the many and varied studies investigating the negatively reinforcing properties of alcohol among anxious individuals, there are very few alcohol

administration studies that aim to address the question of whether anxiety is linked to stronger positive reinforcement from alcohol (another possible etiological mechanism connecting anxiety to risk for alcohol use disorders). This oversight is surprising given that multiple studies have found associations between elevated anxiety and stronger expectancies for positively reinforcing alcohol effects (e.g., stimulation; Brown and Munson, 1987; Ham et al., 2002; Ham et al., 2010) and enhancement-related drinking motives (i.e., drinking to increase positive affect; Allan et al., 2015; Buckner et al., 2006; Villarosa et al., 2014). Even studies that explicitly aim to connect anxiety to negative reinforcement-related expectancies and motives provide hints (upon closer examination) that anxiety may also be associated with positive reinforcement-related expectancies and motives.

For example, anxiety has been found to be associated with stronger coping-related drinking motives in many studies (e.g., Comeau et al., 2001; Lewis et al., 2008), and this has traditionally been interpreted to mean that anxious individuals use alcohol because they expect it to decrease their negative affect (negative reinforcement). However, given the relatively high correlation between the coping and enhancement subscales of the DMQ (r = .46 in Cooper, 1994), which is the most widely-used measure assessing coping motives, it seems plausible that coping motives for drinking could also (at least partially) reflect motivation to obtain positive alcohol effects to counter negative affect. This notion is supported by the somewhat ambiguous wording of items on the DMQ's coping motives subscale, which asks subjects to rate how often they drink for the following reasons: "to forget your worries," "because it helps you when you feel depressed or nervous," "to cheer up when you are in a bad mood," "because you feel more self-

confident and sure of yourself," and "to forget about your problems." On the surface, these items seem ambiguous enough to potentially tap positive reinforcement-related motives in addition to negative reinforcement motives for drinking, suggesting that elevated coping motives observed among anxious individuals may some combination of seeking positively and negatively reinforcing alcohol effects to counter negative affect.

Despite multiple studies in the expectancies and motives literature suggesting a connection between anxiety and stronger positive reinforcement from alcohol, there is only one alcohol administration study whose results speak to this question. In a 1995 study, Chutuape & DeWit found that individuals who met criteria for an anxiety disorder reported both decreased subjective anxiety (negative reinforcement) and increased "elation" (positive reinforcement) after consuming alcohol (relative to placebo); control subjects did not report decreased anxiety or increased elation under alcohol (relative to placebo). However, the finding regarding positively reinforcing alcohol effects received no mention in the discussion, highlighting the general lack of attention to positive reinforcement from alcohol in the anxiety literature. Though this study provides preliminary evidence that anxious individuals experience stronger positive subjective effects from alcohol, it was limited by its use of a non-validated measure of subjective response as well as a weak placebo control (the authors provided color codes differentiating alcohol from placebo beverages and the majority of participants were able to correctly identify which was which). So, in addition to studies investigating the relationship between anxiety and negative reinforcement from alcohol in the absence of an imminent stressor (as in the SRD paradigm), studies investigating the link between

anxiety and positively reinforcing effects of alcohol are also needed (preferably ones that utilize a validated measure of subjective response as well as a strong placebo control).

Moderating Effects of Drinking Context on the Relationship between Anxiety and Subjective Response to Alcohol

Another key factor to consider in the relationship between anxiety and the development of alcohol problems, and one that no studies have directly addressed to date, is the effect of environmental context on subjective response to alcohol. A recent study from our laboratory found that participants in a low-stimulation drinking context (a sterile laboratory environment) reported stronger low-arousal, positively valenced subjective effects (e.g., feeling calm, relaxed) under alcohol compared to placebo. However, there was no difference in subjective effects between alcohol and placebo participants in a high-stimulation drinking context (a simulated bar environment) (Corbin et al., 2015). All participants in this study consumed their beverages in groups, meaning that the only contextual variable that differed was the physical environment. This indicates that the physical context in which alcohol is consumed can interact with the pharmacological effects of alcohol to produce varying profiles of subjective response, making alcohol consumption in certain environments more or less reinforcing than in others.

Social context also has been shown to affect subjective response to alcohol. For example, Sher (1985) found that participants who received placebo beverages in a group setting reported greater "warmth-glow" compared to participants who received placebo in a solitary setting (indicating a main effect of drinking context). Additionally, participants who received placebo in a group setting were no different in "warmth-glow" compared to participants who received alcohol in either a group or solitary setting, meaning that social

setting alone seemed to produce positive subjective effects that were similar to those produced by alcohol across all settings. In a similar study, Pliner and Cappell (1974) found that alcohol interacted with social context such that participants who received alcohol in a group reported feeling significantly friendlier, less unhappy, and more euphoric than subjects who received placebo in a group, whereas there were no alcohol/placebo differences in subjective effects among participants in a solitary condition. This suggests that social context not only influences placebo response (as in Sher, 1985) but it can also interact with the pharmacological effects of alcohol to produce unique subjective effects when drinking takes place in a group versus solitary context.

Given that physical and social context are to be able to alter the reinforcing value of alcohol, investigating contextual effects as a moderator of the relationship between anxiety and subjective response seems warranted. For example, in light of evidence showing that positive subjective effects are experienced more strongly in low-stimulation contexts in the laboratory, low-stimulation drinking situations in the real world (e.g., drinking alone at home) might be especially risky for anxious individuals in terms of developing future alcohol problems. Supporting this idea, preliminary evidence from our laboratory shows that in a general sample (i.e., not selected for anxiety), solitary drinking predicts alcohol problems, and this effect is mediated through coping-related drinking motives (Corbin, Ladensack, & Scott, under revision). Given that anxious individuals report elevated coping motives for drinking (Comeau et al., 2004; Lewis et al., 2008), it seems plausible that low-stimulation drinking environments could be especially reinforcing for anxious individuals via stronger positive subjective effects of alcohol (specifically, low-arousal, positively valenced effects like relaxation). On the other hand,

evidence showing that anxious individuals also report elevated enhancement motives (Allan et al., 2015; Buckner et al., 2006; Villarosa et al., 2014) suggests that high-stimulation environments (e.g., bar, group drinking) could amplify the positive subjective effects of alcohol among anxious individuals; specifically high-arousal, positively valenced effects like stimulation (and perhaps this effect is mediated through enhancement motives, similar to coping motives mediating the anxiety/solitary drinking effect).

If drinking context does significantly impact the experience of subjective response to alcohol among anxious individuals, this would have important implications for prevention and intervention efforts to reduce alcohol use and problems in this population. For example, anxious individuals who report solitary drinking could be targeted for tailored prevention efforts (e.g., motivational interviewing, coping skills training, etc.). Alternatively, it is possible that anxious individuals hold exaggerated expectancies regarding the positive effects of alcohol in low-stimulation drinking contexts (i.e., they expect more positive effects from alcohol but don't actually receive them). In this case, expectancy challenge interventions (wherein expectancies for positive alcohol effects are reduced, as in Neighbors et al., 2004) could be tailored to be context-specific, challenging the idea that drinking in such environments produces more positive alcohol effects. In either case, further investigation of the role of drinking context in the relationship between anxiety and positive subjective effects of alcohol is warranted. Specifically, alcohol administration studies with a strong placebo control are needed to distinguish between alcohol-related expectancies and pharmacological effects of alcohol, both with

regards to the general relationship between anxiety and subjective alcohol effects as well as moderating effects of context.

Cortisol Response to Alcohol as a Mediator of the Relationship between Anxiety and Subjective Response to Alcohol

While investigating the relationship between anxiety and subjective response (as well as possible moderating effects of context) is an important step in understanding comorbidity between anxiety and alcohol use disorders, understanding the mechanisms underlying subjective response to alcohol in anxious individuals would be particularly useful for guiding prevention and intervention efforts aimed at reducing alcohol use and problems in this population. Researchers have proposed and investigated a handful of possible mechanisms underlying subjective response in the general population, including family history of alcoholism (Schuckit et al., 1984; Morzorati et al., 2002; O'Malley & Maisto, 1985) and personal drinking history (Holdstock et al., 2000; King et al., 2002). Another potential mechanism that has received a fair amount of attention in the literature is cortisol response to alcohol. Cortisol is the end product of activation of the HPA axis, a major component of the brain's stress response system. In response to a sufficiently intense stressor, the hypothalamus releases corticotropin-releasing hormone (CRH), which signals the anterior pituitary gland to release adrenocorticotropic hormone (ACTH), which then signals the adrenal cortex to release cortisol. Cortisol travels through the bloodstream and acts on many different target tissues and in the brain, generally suppressing some functions (e.g., reproductive activity, immune function) and increasing the availability of energy in the short-term (via glucogenesis, blocking of insulin activity, etc.; Tsigos & Chrousos, 2002). Cortisol also provides negative feedback

to the hypothalamus via binding to glucocorticoid receptors in the brain, downregulating hypothalamic release of CRH and eventually returning the system to baseline activity (de Kloet, 2004; Tsigos & Chrousos, 2002).

In light drinkers, alcohol consumption acutely activates the HPA axis and results in elevations in salivary cortisol on the descending limb of the blood alcohol curve, but in heavy drinkers this cortisol response is blunted (King et al., 2006; King et al., 2011). Heavy drinkers also report stronger positive subjective effects (stimulation) and weaker negative subjective effects (sedation) compared to light drinkers (King et al., 2002; King et al., 2011). Along similar lines, Schuckit and colleagues reported in a series of studies that individuals with a family history of alcohol use disorders have both a blunted cortisol response to alcohol and experience weaker negative subjective effects of alcohol (specifically the impairing, intoxicating effects of alcohol) compared to family history negative individuals (Schuckit et al., 1987; Schuckit & Gold, 1988). Taken together, these studies suggest that cortisol response to alcohol may influence subjective response to alcohol, perhaps because elevated cortisol is aversive in and of itself, leading drinkers to negatively interpret the ambiguous effects of alcohol when cortisol levels increase. This idea is supported by studies showing that stronger cortisol response to stressors in the lab, such as the cold pressor test and the Trier Social Stress Test, is associated with both increased negative affect in general (McRae et al., 2006) as well as experiencing stronger negative subjective alcohol effects (Brkic et al., 2016). It is also possible that the lack of a cortisol response to alcohol (as seen in light drinkers and family history negative individuals) allows more positive subjective alcohol effects to emerge (as seen in King et

al., 2011), meaning that alcohol consumption would be both less aversive and more reinforcing among those with a blunted cortisol response.

Existing evidence suggests that blunted cortisol response to alcohol among heavy drinkers develops over time as a result of chronic activation and upregulation of the HPA axis (Bernardy et al., 1996; Errico et al., 1993). This is significant, because it suggests that other processes leading to chronic activation and eventual dysregulation of the HPA axis might also lead to a similar profile of blunted cortisol response to alcohol (and potentially experiencing weaker negative subjective alcohol effects and/or stronger positive subjective effects). Anxiety is one such potential process, wherein the repeated stresses associated with experiencing high physiological arousal and negative affect upregulate the activity of the HPA axis and eventually result in lower baseline levels of cortisol as well as a blunted cortisol response to stress (Boyer et al., 2000). A blunted cortisol response to psychosocial stress in the lab has been found among both heavy drinkers (Errico et al., 1993; Errico et al., 2002) and those with anxiety disorders (Petrowski et al., 2010; Petrowski et al., 2013), suggesting that chronic anxiety can dysregulate HPA axis reactivity in a comparable manner to heavy drinking. Thus, HPA dysregulation associated with anxiety could serve as a potential explanatory mechanism connecting anxiety to risk for alcohol problems. If anxiety-induced dysregulation of the HPA axis predisposes individuals to experience weaker negative subjective effects and/or stronger positive subjective effects due to blunted cortisol response to alcohol, this would make alcohol less aversive and more reinforcing, leading to greater risk for the development of alcohol problems.

Present Study

The present study investigated the relationship between anxiety symptoms and subjective response to alcohol, as well as possible moderating effects of drinking context. Cortisol response to alcohol was also examined as a potential mediating variable in the relationship between anxiety and subjective response to alcohol. These aims were accomplished utilizing data from a large-scale, placebo-controlled alcohol administration study designed to assess the effects of various drinking contexts on human alcohol response.

Aims/Hypotheses

The study had three primary aims. First, the relationship between anxiety symptoms and positive subjective alcohol effects (i.e., stimulation and relaxation) was examined. It was hypothesized that higher anxiety would be associated with stronger positive subjective effects (HAP and LAP effects) under both alcohol and placebo, but this relationship was expected be significantly stronger under alcohol (reflecting greater positive and negative reinforcement from alcohol among those higher in anxiety).

Second, the moderating effects of drinking context on the relationship between anxiety and positive SR were examined. It was hypothesized that higher anxiety would be more strongly associated with LAP effects under alcohol (vs. placebo) in low-stimulation contexts (solitary and lab), but not high-stimulation contexts (group and bar). Conversely, it was hypothesized that higher anxiety would be more strongly associated with HAP effects under alcohol (vs. placebo) in high-stimulation contexts but not low-stimulation contexts. In other words, the two-way interactions between beverage condition and

anxiety were expected to be significant in low-stimulation contexts only when predicting LAP SR and high-stimulation contexts only when predicting HAP SR.

Third, cortisol response to alcohol was examined as a potential mediating variable between anxiety and subjective response to alcohol. Specifically, it was hypothesized that higher anxiety would be negatively associated with cortisol response to alcohol (vs. placebo), and in turn, lower cortisol response to alcohol would be associated with weaker negative subjective alcohol effects and stronger positive subjective alcohol effects (relative to placebo).

METHOD

Design Overview

The present study utilized data from an NIAAA-funded R01 study investigating the effects of physical and social context on subjective and physiological response to alcohol (and placebo). Data was collected at an in-person interview session as well as an alcohol administration session.

Participants

Participants (total N = 447, n = 349 for cortisol analyses) were 21-25 years old (M = 22.3, SD = 1.25), 57% male, and were representative of the community of a large metro area in the southwestern United States in terms of race (67% Caucasian), ethnicity (25% Hispanic/Latino) and student status (79% current students). Participants were required to report consuming 4 drinks (female) or 5 drinks (male) at least once in the past month to be eligible for the study. Exclusion criteria included past-month alcohol dependence, past-month mood or anxiety disorder diagnosis, serious medical conditions, regular use of prescription psychotropic or pain medication, history of negative reactions to alcohol, daily marijuana use, history of abstinence-oriented alcohol treatment, and pregnancy or nursing.

Procedure

Survey Session: Once participants were deemed eligible via phone screen or online screener (online screeners were implemented later in the study), they were invited to an interview/survey session which included a structured clinical interview assessing past-month (exclusion criterion) and past-year alcohol, mood, and anxiety disorders.

Participants also completed self-report survey measures (including self-reported anxiety) and a standardized interview assessing past 30-day drinking.

Alcohol Administration Session: The alcohol administration session took place approximately 1 week following the interview/survey session. Participants were randomized to receive either alcohol or placebo in one of four contexts: group simulated bar (total n = 115, n = 70 in alcohol, n = 45 in placebo), solitary simulated bar (total n = 109, n = 67 in alcohol, n = 42 in placebo), group sterile lab (total n = 108, n = 67 in alcohol, n = 41 in placebo), and solitary sterile lab (total n = 115, n = 66 in alcohol, n = 49 in placebo). Participants were randomized to beverage condition within each context at a ratio of 60% in the alcohol condition to 40% in the placebo condition. See Table 1 for a breakdown of participant randomization and cell sizes. Participants in the alcohol condition consumed 3 beverages containing vodka, cranberry juice, citrus soda, and lime juice to achieve a target peak breath alcohol concentration (BrAC) of .08 g%. Participants in the placebo condition consumed 3 beverages with flat tonic water in place of vodka (along with a very small amount of vodka floated on the surface of the drink for scent/taste cues). Previous studies using this placebo manipulation have achieved placebo response rates above 80% in terms of estimated BAC and estimated number of drinks in the placebo group relative to the alcohol group (Corbin et al., 2015), indicating success in convincing placebo participants that they had received a non-trivial amount of alcohol.

In group contexts, participants consumed their beverages and completed measures/tasks in the company of 1-2 other participants, while in solitary contexts participants drank and completed measures/tasks alone. In simulated bar contexts participants drank in a simulated bar environment that includes alcohol-related cues (e.g.,

Table 1

Participant Randomization Breakdown by Cell

Total **N = 447**	**Alcohol** **n = 270**	**Placebo** **n = 177**
Group Bar	70	45
Group Lab	67	41
Solitary Bar	67	42
Solitary Lab	66	49

stemware, neon signs, liquor bottles) and music, whereas participants in sterile lab contexts drank in laboratory environments that did not contain alcohol-related cues, music, or other stimuli. Measures of subjective response to alcohol were completed during the ascending and descending limb of the blood alcohol curve (at matched target BrACs of approximately .06 g%), as well as at peak BrAC. Each placebo participant was matched to an alcohol participant who had already completed the protocol in order to match the timing of ascending and descending limb assessments. A modified measure of subjective response (with reference to alcohol removed) was also completed at baseline so that baseline subjective state could be controlled for in analyses. Salivary cortisol was collected at baseline prior to beverage administration and at matched ascending and descending target BrACs of approximately .06 g%.

Measures

Anxiety Symptoms: The Depression Anxiety and Stress Scales (DASS; Lovibond & Lovibond, 1995) is a 42-item measure assessing depression, anxiety, and stress symptoms over the past two weeks. Only the 14-item anxiety subscale was utilized in the present study. The anxiety subscale includes items such as "I felt scared without any good reason," "I found myself in situations that made me so anxious I was most relieved when they ended," and "I perspired noticeably (e.g., hands sweaty) in the absence of high temperatures or physical exertion." Cronbach's alpha for the anxiety subscale was in the acceptable range (.76).

Subjective Response: The Subjective Effects of Alcohol Scale (SEAS; Morean et al., 2013) is a 14-item scale assessing subjective response (SR) to alcohol. Questions assess the degree to which participants feel various subjective effects as a result of consuming

alcohol (though at baseline references to alcohol are removed in order to assess pre-drinking subjective state). The SEAS spans the full arousal by valence affective space, including high arousal positive (HAP) effects (e.g., "vigorous"), high arousal negative (HAN) effects (e.g., "aggressive"), low-arousal positive (LAP) effects (e.g., "relaxed"), and low-arousal negative (LAN) effects (e.g., "woozy"). The HAP and LAP subscales were of primary interest in analyses assessing the relationship between anxiety and subjective response (because they assess positive subjective effects), but all subscales were utilized as outcome measures in analyses involving cortisol. Cronbach's alpha values for the various SEAS subscales at baseline, on the ascending limb, at peak BAC, and on the descending limb (respectively) were as follows: HAP (.87, .92, .93, .95); HAN (.77, .74, .81, .80); LAP (.78, .79, .82, .88); LAN (.72, .85, .89, .91).

Cortisol Response: Saliva was collected via 8mm by 125mm foam swabs placed under the tongue. Participants were instructed to engage in a chewing motion with the swab under the tongue for a duration of two minutes, after which a research assistant removed the swab and placed it in a plastic vial for later assay. Approximately 1ml of saliva was collected at each sampling point. Each saliva sample was split in two and assayed separately using a highly sensitive enzyme immunoassay (Salimetrics, Carlsbad, CA) by the Institute for Interdisciplinary Salivary Bioscience Research at Arizona State University. The immunoassays return the cortisol level present in each sample (expressed in micrograms per deciliter). The mean of the two assays for each subject at each timepoint was utilized in analyses. The inter-sample correlations at baseline, ascending limb, and descending limb timepoints were extremely high (*r*'s > .96).

Family History of Alcohol Problems: Family history of alcohol problems was assessed using the Family Tree Questionnaire (Mann et al., 1985), wherein participants classify parents, siblings, and grandparents as non-drinkers, social drinkers, possible problem drinkers, and definite problem drinkers. Analyses utilized parental family history as a binary variable (1 = one or both parents classified as "definite" problem drinkers, 0 = neither parent classified as a "definite" problem drinker). Previous studies have shown that classification of first-degree relatives as "definite" problem drinkers has very high test-retest reliability (Cohen's Kappa of .93-1.0; Mann et al., 1985)

Alcohol Use: Frequency and quantity of alcohol use over the past 30 days was assessed using the Timeline Follow-Back (TLFB) interview (Sobell & Sobell, 1992). Total number of drinks in the past 30 days were utilized in analyses. The TLFB has been shown to be valid and highly reliable for assessing recent alcohol use in college students (Sobell et al., 1986; Pedersen et al., 2012).

Statistical Analyses

Preliminary Analyses: Analyses were carried out in Mplus version 7 (Muthen & Muthen, 2012) using maximum likelihood estimation with robust standard errors (MLR; robust to non-normal data, estimates missing data) except in aim 3, when maximum likelihood estimation without robust standard errors (ML) was used. ML is still robust to non-normal data (and estimates missing data) and was used in aim 3 analyses because MLR cannot be used with bootstrapping, which was required to generate asymmetric confidence intervals for indirect effects. Given the use of MLR and ML, common transformations (e.g., logarithmic) were not conducted based on distributional characteristics like skewness. However, extreme values for individual salivary cortisol

samples have been reported in prior studies (Lai et al., 2005; Shirtcliff et al., 2012), and given that Winsorization of these extreme values is common practice (values > 3 standard deviations above the mean are assigned a value just higher than the highest non-extreme value in the sample, preserving rank-order of the data), Winsorization was employed when necessary.

Aim 1 - Relationship between Anxiety and Subjective Response: To examine the hypothesized relationship between anxiety symptoms and subjective response to alcohol, an SEM model was constructed to test whether the interaction of DASS anxiety and beverage condition (alcohol vs. placebo) predicts 1) high-arousal positive (HAP) effects on the ascending limb of the BAC curve and 2) low-arousal positive (LAP) effects on the descending limb of the BAC curve. Baseline HAP/LAP scores, drinking context, parental history of alcohol problems, gender, and past 30-day alcohol use (total drinks) were included as covariates in this model. See Figure 1 for a conceptual model (covariates not shown). In cases where the interaction between beverage condition and anxiety was not significant, the interaction term was removed from the model to facilitate interpretation of main effects.

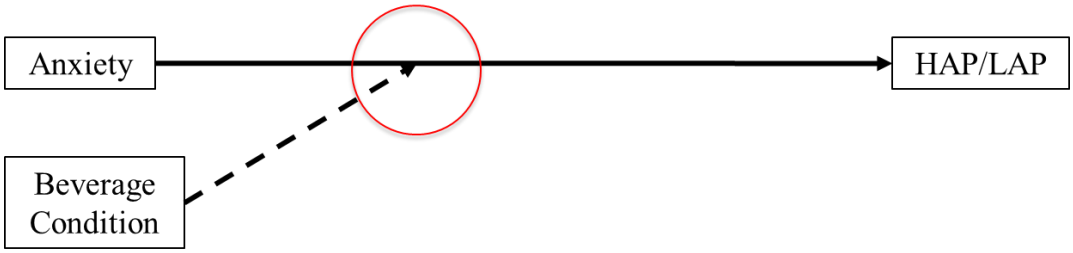
Aim 2 - Moderating Effects of Drinking Context: To examine moderating effects of drinking context on the anxiety/beverage condition/SR relationship, multi-group SEM models were constructed to test whether the magnitude of the interaction between anxiety and beverage condition predicting HAP/LAP effects differs by 1) physical context (bar vs. lab) and 2) social context (group vs. solitary). Baseline HAP/LAP scores, parental history of alcohol problems, gender, and past 30-day alcohol use (total drinks) were again included as covariates in these models. Each set of multi-group analyses (one set grouped

Figure 1. Conceptual Model of Aim 1

by social context and one set grouped by physical context) consisted of nested model comparisons with one degree of freedom difference between models. An unconstrained model with all paths freely estimated across both drinking contexts was compared to 1) a model wherein the interaction term (anxiety by beverage condition; red circle in Figure 2) predicting HAP was constrained to be equal across drinking contexts and 2) a model wherein the interaction term predicting LAP was constrained to be equal across drinking contexts. If a significant decrement in model fit was observed (via a change in Satorra-Bentler scaled chi-square (Satorra & Bentler, 2001)), it was concluded that the nature of the interaction differs by drinking context, and the two-way interaction was decomposed within each context. In the case of a statistically significant two-way anxiety/beverage condition interaction within one or both contexts, simple slopes of the anxiety/SR relationship under alcohol and placebo were examined within the context(s). See Figure 2 for a conceptual model (covariates not shown).

Aim 3 - Cortisol Response as a Mediator of the Anxiety/Subjective Response Relationship: To examine cortisol response as a potential mediating variable, moderated indirect effects models were constructed in Mplus using syntax adapted from the MODMED series of routines in SAS (Preacher et al., 2007), which are specifically designed to test moderation of mediated effects. Four models (one with each SEAS subscale as the ultimate outcome) were tested. In each model, anxiety symptoms interacted with beverage condition to predict cortisol level on the descending limb (controlling for baseline cortisol levels), which in turn predicted SR on the descending limb (controlling for baseline SR). Descending limb cortisol (rather than ascending limb) was chosen as the mediating variable of interest because this timepoint most closely

Figure 2. Conceptual Model of Aim 2

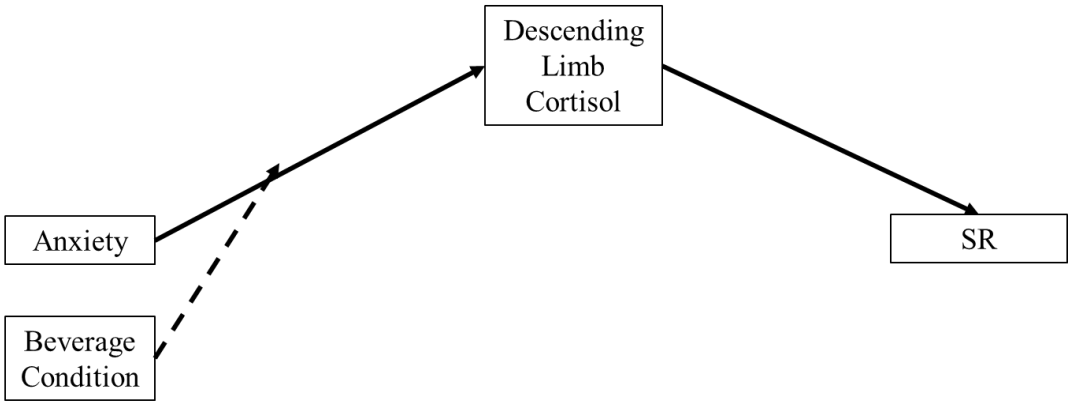


corresponds with peak cortisol response to alcohol seen in previous studies (King et al., 2011). Thus, descending limb SR was chosen as the outcome variable of interest to examine contemporaneous effects of cortisol response to alcohol on SR. If the interaction of anxiety and beverage condition did not significantly predict descending limb cortisol (a precondition of the moderated mediation hypotheses), simple mediation (indirect effect) models were substituted for MODMED models in order to facilitate interpretation of possible indirect effects. In addition to baseline SR scores and baseline cortisol level, drinking context, family history of alcohol problems, gender, and past 30-day alcohol use (total drinks) were included as covariates in these models. See Figure 3a for a conceptual model (covariates not shown).

In order to fully utilize all available cortisol data (baseline, ascending limb, and descending limb assessments), an additional set of growth models was constructed to examine cortisol response as a mediator of the effects of anxiety on SR. Specifically, a series of multi-group growth models (with indirect effects) were constructed with the slope of cortisol change (from baseline assessment to the descending limb assessment) as a mediator between anxiety symptoms and all descending limb SEAS SR subscales (models also estimated the intercept of cortisol, but slope of change was of primary interest). In this context, a steeper negative slope (or a shallower positive slope) of cortisol change from baseline to descending limb would be interpreted as a lower cortisol response (and again, a lower cortisol response under alcohol was hypothesized to predict stronger positive SR and weaker negative SR).

Models were grouped by beverage condition (alcohol vs. placebo) in order to determine whether indirect effects of anxiety on SR via cortisol slope significantly

Figure 3a. Conceptual Model of Aim 3 – Moderated Indirect Effects

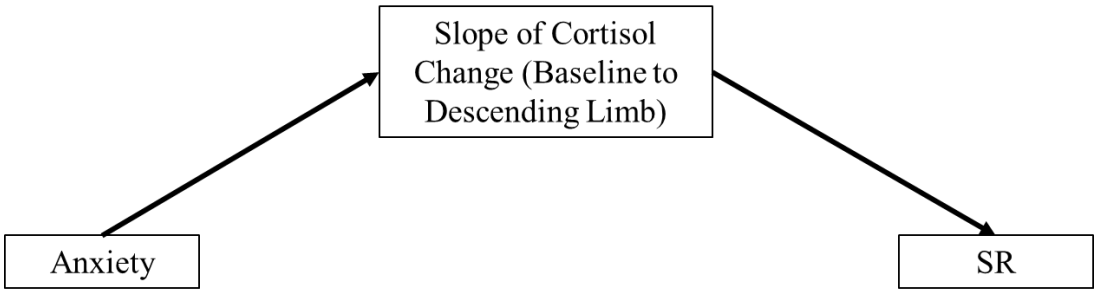


differed by beverage condition. As in the MODMED models for aim 3, baseline SR scores, baseline cortisol level, drinking context, family history of alcohol problems, gender, and past 30-day alcohol use (total drinks) were included as covariates in these growth models. See Figure 3b for a conceptual model (covariates not shown). A simple chi-square difference test of model fit (Satorra-Bentler scaled chi-square was not required here because MLR was not used) was conducted to determine whether the relationship between anxiety and cortisol slope differed by beverage condition. Specifically, a model in which the path from anxiety to cortisol slope was constrained to be equal across beverage conditions was compared to a model in which that path was allowed to vary by beverage condition, and if a significant decrement in model fit was observed (as indexed by the chi-square difference test), it was concluded that the nature of this relationship was different under alcohol vs. placebo. If this conclusion was reached, estimates of indirect effects of anxiety on SR via cortisol slope were examined separately by beverage condition.

Overall, this multi-group growth modeling approach is similar to the aim 3 MODMED analyses wherein the interaction of anxiety and beverage condition predicts cortisol level on the descending limb (which then predicts SR), but the growth model approach allows all cortisol data to be utilized and also generates separate estimates of indirect effects within each beverage condition.

In both sets of models for aim 3, bias-corrected bootstrapped confidence intervals for indirect effects were generated in Mplus to account for asymmetric distribution of products of coefficients (MacKinnon et al., 2004).

Figure 3b. Conceptual Model of Aim 3 – Multi-Group Growth with Indirect Effects



RESULTS

Preliminary Analyses, Descriptive Statistics, and Correlation Matrices

Due to the use of MLR and ML, variables were not transformed or altered based on their distributional characteristics except in two instances: First, 10 participants had at least one cortisol value Winsorized, meaning that an individual cortisol value at baseline, ascending limb, and/or descending limb was greater than 3 standard deviations above the mean for that timepoint and was assigned a value at the top of the distribution to retain rank order while reducing outliers. Second, two participants reported extreme values of drinking on the TLFB that were unlikely to be accurate (e.g., in excess of 500 standard drinks in the past month), so these cases were Winsorized to retain these heavy drinkers in the sample without overly skewing the data.

Descriptive statistics of study variables within each beverage condition are presented in Table 2, and correlation matrices of all study variables are provided in Tables 3a (placebo condition), 3b (alcohol condition), and 3c (full sample).

Aim 1 - Relationship between Anxiety, Beverage Condition, and Subjective Response

Contrary to hypotheses, the interaction of anxiety and beverage condition did not significantly predict either ascending limb HAP SR (b = -.05, SE = .044, p = .25) or descending limb LAP SR (b = -.019, SE = .047, p = .69). Model fit indices for the hypothesized model were as follows: $\chi^2(2) = 15.35$, $p < .001$, RMSEA = .122, CFI = .976, SRMR = .019. In order to correctly interpret main effects of anxiety and covariates on the SR outcomes, the non-significant interaction terms were removed from the model, and results of this simpler model are presented in Table 4. Model fit indices for this

Table 2

Descriptive Statistics by Beverage Condition

	Alcohol Condition			Placebo Condition				
	Mean	**SD**	**%**	**Mean**	**SD**	**%**	**Range**	**Valid N**
DASS Anxiety	16.1	3.1	-	15.9	2.6	-	14-37	447
Gender (% Male)	-	-	56%	-	-	58%	-	447
TLFB Total Drinks	34.3	28.4	-	36.4	31.5	-	2-201	446
Family History of Problem Drinking	-	-	12%	-	-	17%	-	447
Baseline HAP	4.7	2.1	-	4.5	2.1	-	0-10	445
Baseline HAN	.45	1.0	-	.39	.97	-	0-10	443
Baseline LAP	6.9	1.7	-	7.0	1.6	-	0-10	445
Baseline LAN	.19	.66	-	.16	.63	-	0-10	443
Descending Limb HAP	4.9	2.4	-	3.8	2.4	-	0-10	444
Descending Limb HAN	.53	1.1	-	.20	.60	-	0-10	444
Descending Limb LAP	6.4	2.1	-	6.2	2.2	-	0-10	446
Descending Limb LAN	.96	1.5	-	.22	.60	-	0-10	446
Baseline Cortisol	.22	.16	-	.19	.11	-	.02-.68	348
Ascending Limb Cortisol	.16	.11	-	.15	.10	-	.02-.58	347
Descending Limb Cortisol	.10	.06	-	.10	.06	-	.01-.33	349

Table 3a

Correlation Matrix: Placebo Participants

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Anxiety	1	.061	.059	.018	-.046	.159*	-.116	.032	.030	.140	-.014	-.029	.063	.032	.022
2. Gender	.061	1	.126	.052	.183*	.081	-.042	.186*	.274**	.081	-.010	.038	.358**	.346**	.268**
3. TLFB	.059	.126	1	-.062	.143	-.064	.086	-.041	.115	-.011	.030	-.091	.096	.086	.147
4. FH	.018	.052	-.062	1	.032	.054	.004	.101	.020	.074	-.025	.013	.006	-.080	.044
5. BHAP	-.046	.183*	.143	.032	1	.101	.199**	.141	.654**	.060	.244**	.039	.000	.054	-.023
6. BHAN	.159*	.081	-.064	.054	.101	1	-.200**	.399**	.230**	.356**	-.122	.204**	-.055	.016	-.021
7. BLAP	-.116	-.042	.086	.004	.199**	-.200**	1	-.080	.104	-.032	.524**	.017	-.018	.018	-.019
8. BLAN	.032	.186*	-.041	.101	.141	.399**	-.080	1	.164*	.267**	-.077	.488**	.138	.085	.186*
9. DLAP	.030	.274**	.115	.020	.654**	.230**	.104	.164*	1	.099	.332**	.075	.156	.112	.096
10 DLAN	.140	.081	-.011	.074	.060	.356**	-.032	.267**	.099	1	-.011	.397**	-.051	-.036	-.072
11. DHAP	-.014	-.010	.030	-.025	.244**	-.122	.524**	-.077	.332**	-.011	1	.020	-.075	.005	-.088
12. DHAN	-.029	.038	-.091	.013	.039	.204**	.017	.488**	.075	.397**	.020	1	.015	.133	.220**
13. BL Cort	.063	.358**	.096	.006	.000	-.055	-.018	.138	.156	-.051	-.075	.015	1	.443**	.456**
14. AL Cort	.032	.346**	.086	-.080	.054	.016	.018	.085	.112	-.036	.005	.133	.443**	1	.602**
15. DL Cort	.022	.268**	.147	.044	-.023	-.021	-.019	.186*	.096	-.072	-.088	.220**	.456**	.602**	1

Note: TLFB: Timeline Followback, FH: Family History of Alcoholism, BHAP-BLAN: Baseline SR, DHAP-DLAN: Descending Limb SR, BL Cort: Baseline Cortisol, AL Cort: Ascending Limb Cortisol, DL Cort: Descending Limb Cortisol

Table 3b

Correlation Matrix: Alcohol Participants

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Anxiety	1	-.018	.069	.085	.012	.155*	-.132*	.009	.021	.336**	-.050	.106	.194**	.081	.060
2. Gender	-.018	1	.116	.083	.145*	.087	.056	.123*	.250**	.081	.065	.119	.182**	.150*	.060
3. TLFB	.069	.116	1	-.030	.100	.037	.028	.040	.041	.018	-.025	-.127*	.055	.057	.015
4. FH	.085	.083	-.030	1	-.020	-.019	.117	.085	.052	.041	.083	-.092	.041	.018	.017
5. BHAP	.012	.145*	.100	-.020	1	.175**	.353**	.105	.575**	.060	.349**	.094	.133	.028	-.008
6. BHAN	.155*	.087	.037	-.019	.175**	1	-.117	.266**	.129*	.510**	-.058	.204**	.035	.089	.056
7. BLAP	-.132*	.056	.028	.117	.353**	-.117	1	-.054	.250**	-.046	.607**	-.079	.035	.018	-.002
8. BLAN	.009	.123*	.040	.085	.105	.266**	-.054	1	.103	.196**	.037	.255**	.036	.017	-.021
9. DLAP	.021	.250**	.041	.052	.575**	.129*	.250**	.103	1	.099	.407**	.311**	.142*	.056	.026
10. DLAN	.336**	.081	.018	.041	.060	.510**	-.046	.196**	.099	1	-.112	.314**	.056	.089	.052
11. DHAP	-.050	.065	-.025	.083	.349**	-.058	.607**	.037	.407**	-.112	1	.047	.155*	.115	.078
12. DHAN	.106	.119	-.127*	-.092	.094	.204**	-.079	.255**	.311**	.314**	.047	1	.029	-.021	.064
13. BL Cort	.194**	.182**	.055	.041	.133	.035	.035	.036	.142*	.056	.155*	.029	1	.533**	.457**
14. AL Cort	.081	.150*	.057	.018	.028	.089	.018	.017	.056	.089	.115	-.021	.533**	1	.628**
15. DL Cort	.060	.060	.015	.017	-.008	.056	-.002	-.021	.026	.052	.078	.064	.457**	.628**	1

Note: TLFB: Timeline Followback, FH: Family History of Alcoholism, BHAP-BLAN: Baseline SR, DHAP-DLAN: Descending Limb SR, BL Cort: Baseline Cortisol, AL Cort: Ascending Limb Cortisol, DL Cort: Descending Limb Cortisol

Table 3c

Correlation Matrix: Full Sample

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Anxiety	1	.010	.064	.055	-.007	.157**	-.128**	.018	.030	.288**	-.035	.084	.156**	.065	.046
2. Gender	.010	1	.120*	.070	.159**	.084	.018	.147**	.251**	.074	.034	.087	.235**	.225**	.142**
3. TLFB	.064	.120*	1	-.042	.116*	-.005	.052	.007	.064	.004	-.003	-.114*	.068	.069	.069
4. FH	.055	.070	-.042	1	.000	.010	.071	.089	.021	.034	.032	-.080	.018	-.030	.030
5. BHAP	-.007	.159**	.116*	.000	1	.148**	.293**	.120*	.599**	.063	.307**	.084	.089	.037	-.014
6. BHAN	.157**	.084	-.005	.010	.148**	1	-.150**	.317**	.171**	.454**	-.083	.193**	.006	.062	.026
7. BLAP	-.128**	.018	.052	.071	.293**	-.150**	1	-.065	.179**	-.047	.571**	-.065	.017	.018	-.009
8. BLAN	.018	.147**	.007	.089	.120*	.317**	-.065	1	.130**	.209**	-.008	.280**	.069	.042	.047
9. DHAP	.030	.251**	.064	.021	.599**	.171**	.179**	.130**	1	.127**	.374**	.288**	.158**	.084	.051
10. DHAN	.288**	.074	.004	.034	.063	.454**	-.047	.209**	.127**	1	-.075	.353**	.051	.066	.020
11. DLAP	-.035	.034	-.003	.032	.307**	-.083	.571**	-.008	.374**	-.075	1	.046	.082	.075	.013
12 DLAN	.084	.087	-.114*	-.080	.084	.193**	-.065	.280**	.288**	.353**	.046	1	.050	.022	.085
13. BL Cort	.156**	.235**	.068	.018	.089	.006	.017	.069	.158**	.051	.082	.050	1	.503**	.451**
14. AL Cort	.065	.225**	.069	-.030	.037	.062	.018	.042	.084	.066	.075	.022	.503**	1	.617**
15. DL Cort	.046	.142**	.069	.030	-.014	.026	-.009	.047	.051	.020	.013	.085	.451**	.617**	1

Note: TLFB: Timeline Followback, FH: Family History of Alcoholism, BHAP-BLAN: Baseline SR, DHAP-DLAN: Descending Limb SR, BL Cort: Baseline Cortisol, AL Cort: Ascending Limb Cortisol, DL Cort: Descending Limb Cortisol

Table 4

Main Effects of Anxiety and Covariates on Ascending HAP/LAP SR

	Outcome: Ascending HAP			**Outcome: Descending LAP**		
	Beta	**SE**	***p***	**Beta**	**SE**	***p***
DASS Anxiety	.02	.02	.28	.03	.03	.25
Beverage Condition	1.53	.15	< .001*	.22	.17	.19
Gender	.47	.16	.003*	.11	.17	.52
TLFB Total Drinks	.01	.01	.61	-.01	.01	.32
Parent Problem Drinking	.01	.18	.97	-.07	.23	.77
Physical Context	-.24	.15	.11	-.27	.16	.10
Social Context	.78	.15	< .001*	.23	.17	.17
Baseline HAP/LAP	.65	.04	< .001*	.72	.05	< .001*

*****Statistically significant effect at $p < .05$ or below

simpler model were as follows: $\chi^2(2) = 15.44$, $p < .001$, RMSEA = .123, CFI = .975, SRMR = .02.

Significant predictors of ascending limb HAP SR included beverage condition (greater stimulation under alcohol vs. placebo), gender (greater stimulation among males), social context (greater stimulation in group contexts), and baseline HAP SR (higher stimulation at baseline was associated with higher stimulation on the ascending limb). The only significant predictor of descending limb LAP SR was baseline LAP SR (higher relaxation at baseline was associated with higher relaxation on the descending limb). Notably, beverage condition was not significantly associated with LAP SR, though being in the alcohol condition was non-significantly positively associated with descending limb LAP SR. Anxiety was not significantly associated with either SR outcome.

Aim 2 - Moderating Effects of Drinking Context on the Relationship between Anxiety and Subjective Response

Moderating Effects of Social Context (Solitary vs. Group): To determine whether social context moderated the relationship between anxiety, beverage condition, and SR, a grouping statement was added to the hypothesized model from aim 1 to group participants by social context (solitary bar and solitary lab vs. group bar and group lab). In this model, all parameters were allowed to vary across social context. This freely estimated (fully unconstrained) model was compared to 1) a model constraining the anxiety by beverage condition interaction predicting HAP SR to be equal across social contexts and 2) a model constraining the interaction predicting LAP SR to be equal across social contexts.

Constraining the interaction term predicting HAP SR to be equal across social contexts resulted in a significantly worse model fit compared to the freely estimated model (Satorra-Bentler Scaled $\chi^2(1) = 12.42$, $p < .001$), while constraining the interaction predicting LAP SR did not result in a significantly worse fit (Satorra-Bentler scaled $\chi^2(1) = .037$, $p = .85$). Thus, the final model presented in Table 5 constrains the interaction of anxiety and beverage condition predicting descending LAP to be equal across social context (solitary vs. group) while all other parameters are freely estimated (i.e., allowed to vary across social context). Model fit indices for this model were as follows: $\chi^2(5) = 19.76$, $p < .001$, RMSEA = .115, CFI = .972, SRMR = .024.

As shown in Table 5, the anxiety by beverage condition interaction predicting HAP SR was statistically significant in solitary contexts ($b = -.14$, SE = .049, $p = .004$), but not in group contexts ($b = .02$, SE = .067, $p = .76$). See Figure 4 for a visual comparison of these two-way interactions within each social context. Given the statistically significant interaction in solitary contexts, simple slopes for the anxiety/SR relationship under alcohol and placebo in solitary contexts were also examined. Within the alcohol condition in solitary contexts, anxiety was not significantly related to HAP SR ($b = -.024$, SE = .029, $p = .42$). However, within the placebo condition in solitary contexts, anxiety was significantly positively associated with HAP SR ($b = .106$, SE = .044, $p = .02$). Thus, social context moderates the relationship between anxiety, beverage condition, and HAP SR such that anxiety is positively associated with HAP SR under placebo (but not alcohol) in solitary conditions, while no such interaction exists in group conditions.

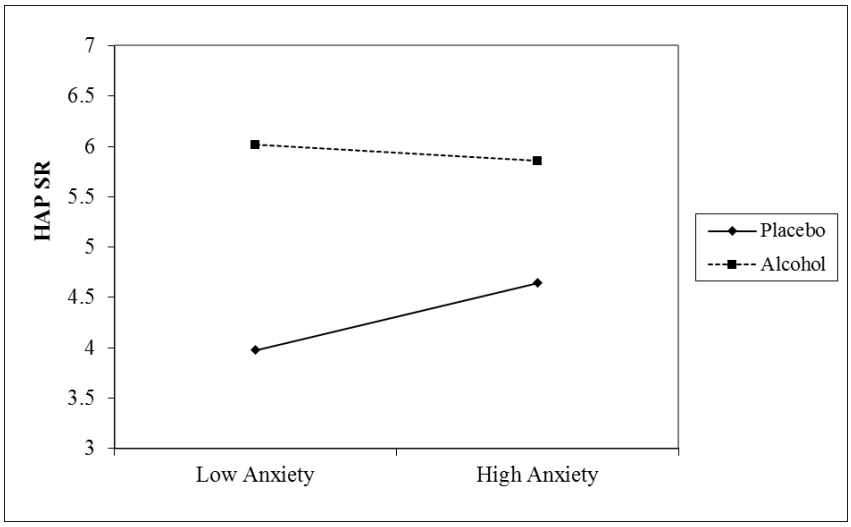
Table 5

Moderation of Anxiety/SR Relationship by Social Context

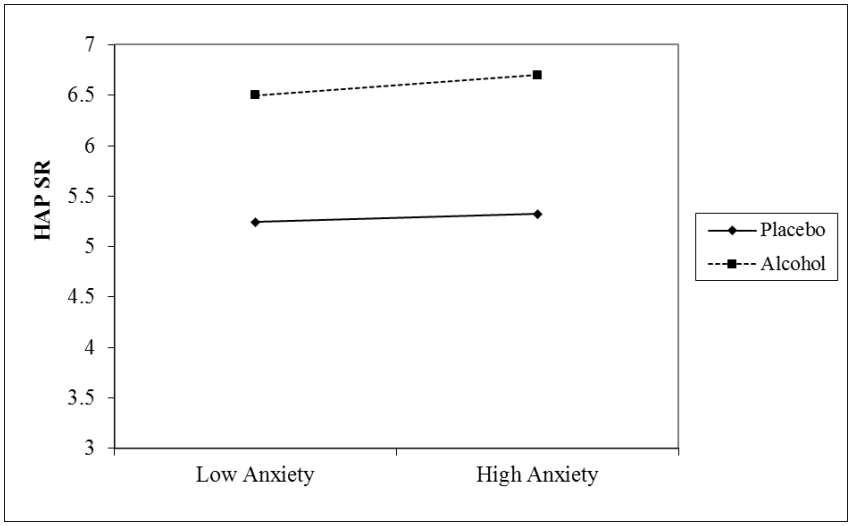
	Outcome: Ascending HAP						**Outcome: Descending LAP**					
	Solitary Contexts			**Group Contexts**			**Solitary Contexts**			**Group Contexts**		
	b	**SE**	***p***	***b***	**SE**	***p***	***b***	**SE**	***p***	***b***	**SE**	***p***
DASS Anxiety	.11	.04	.006*	.01	.05	.77	.03	.05	.50	.04	.04	.28
Beverage Condition	1.62	.19	< .001*	1.32	.21	< .001*	.12	.25	.63	.34	.23	.14
Anxiety*Beverage Condition	-.14	.05	.004*	.02	.07	.76	-.01	.05	.80	-.01	.05	.80
Gender	.70	.21	< .001*	.23	.23	.30	.03	.25	.91	.20	.22	.37
TLFB Total Drinks	.01	.01	.79	.01	.01	.64	-.01	.01	.29	-.01	.01	.81
Parent Problem Drinking	.07	.26	.80	.03	.25	.89	.11	.28	.70	-.26	.38	.51
Baseline HAP/LAP	.75	.05	< .001*	.50	.08	< .001*	.74	.07	< .001*	.70	.07	< .001*

*****Statistically significant effect at $p < .05$ or below

Figure 4. Interaction of Anxiety and Beverage Condition Predicting HAP SR in Solitary and Group Contexts (Aim 2)



Solitary Contexts (p = .004)



Group Contexts (p = .76)

The nature of this moderation is contrary to hypotheses. It was predicted that anxiety would be more strongly associated with HAP SR under alcohol (vs. placebo) in group contexts compared to solitary contexts. Additionally, the hypothesis that social context would moderate the relationship between anxiety, beverage condition, and LAP SR was not supported, as evidenced by the lack of change in model fit when constraining the interaction predicting LAP SR to be equal across contexts.

Moderating Effects of Physical Context (Lab vs. Bar): To determine whether physical context moderated the relationship between anxiety, beverage condition, and SR, a grouping statement was again added to the hypothesized model from aim 1, this time grouping participants by physical context (solitary lab and group lab vs. solitary bar and group bar). In this model, all parameters were allowed to vary across physical context. This freely estimated (fully unconstrained) model was compared to 1) a model constraining the anxiety by beverage condition interaction predicting HAP SR to be equal across physical contexts and 2) a model constraining the interaction predicting LAP SR to be equal across physical contexts.

Constraining the anxiety by beverage condition interaction predicting HAP SR to be equal across physical contexts resulted in a significantly worse model fit (Satorra-Bentler Scaled $\chi^2(1) = 6.42$, $p = .01$) compared to the freely estimated model. Additionally, constraining the interaction predicting LAP SR to be equal across social contexts resulted in a significantly worse fit compared to the freely estimated model (Satorra-Bentler Scaled $\chi^2(1) = 5.87$, $p = .02$). Thus, the final model presented in Table 6 is a freely estimated model wherein all parameters were allowed to vary across physical

Table 6

Moderation of Anxiety/SR Relationship by Physical Context

	Outcome: Ascending HAP						**Outcome: Descending LAP**					
	Lab Contexts			**Bar Contexts**			**Lab Contexts**			**Bar Contexts**		
	b	**SE**	***p***	***b***	**SE**	***p***	***b***	**SE**	***p***	***b***	**SE**	***p***
DASS Anxiety	.03	.03	.33	.14	.07	.04*	.02	.04	.60	.10	.08	.25
Beverage Condition	1.83	.22	< .001*	1.20	.20	< .001*	.22	.24	.37	.22	.24	.36
Anxiety*Beverage Condition	-.07	.06	.29	-.10	.07	.16	.06	.07	.36	-.12	.09	.19
Gender	.46	.25	.06	.45	.20	.03*	.03	.24	.90	.20	.23	.39
TLFB Total Drinks	-.01	.01	.65	.01	.01	.42	.01	.01	.98	-.01	.01	.15
Parent Problem Drinking	-.25	.26	.34	.18	.28	.51	-.13	.27	.64	-.12	.40	.76
Baseline HAP/LAP	.67	.06	< .001*	.69	.06	< .001*	.72	.07	< .001*	.72	.08	< .001*

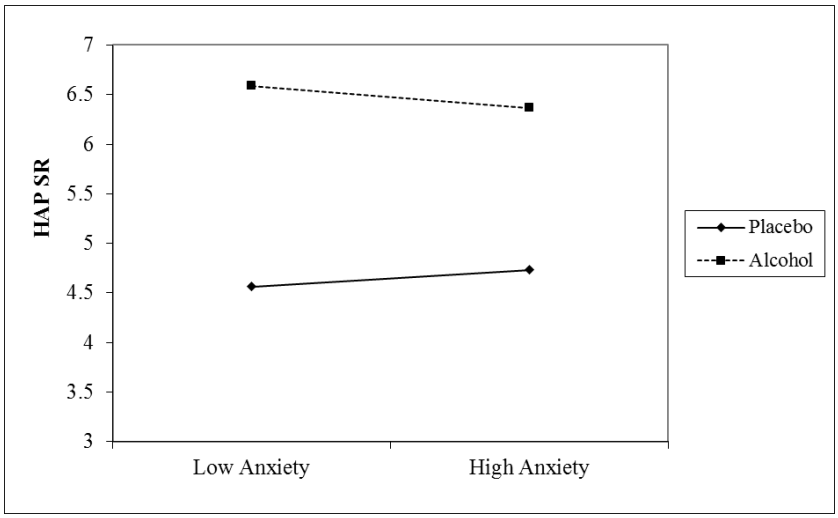
*****Statistically significant effect at $p < .05$ or below

contexts. Model fit indices for this model were as follows: $\chi^2(4) = 16.62$, $p = .002$, RMSEA = .112, CFI = .975, SRMR = .024.

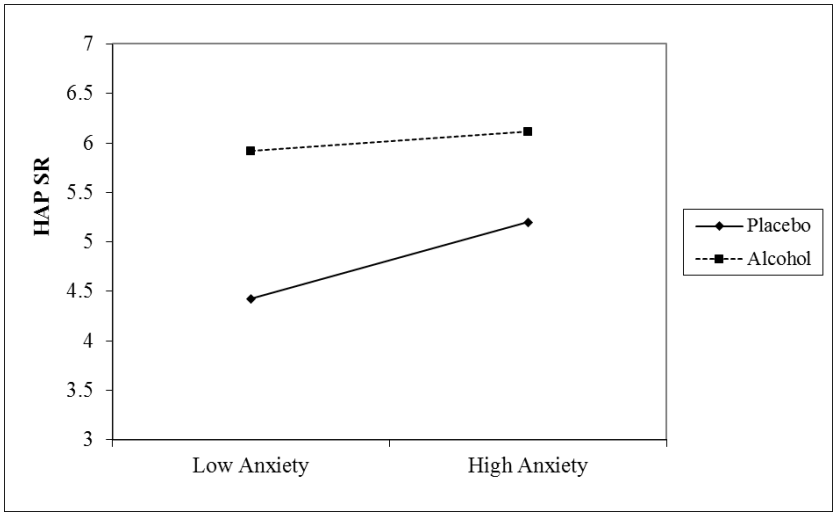
As shown in Table 6, the anxiety by beverage condition interaction predicting HAP SR was not significant in either laboratory ($b = -.067$, SE = .064, $p = .29$) or bar ($b = -.102$, SE = .072, $p = .16$) contexts. See Figure 5 for a visual comparison of these two interactions within each social context. Visual inspection suggests some signal for a relationship between anxiety and HAP SR under placebo in the bar contexts, whereas anxiety does not seem to be associated with HAP SR under alcohol in the bar contexts. In the lab contexts anxiety does not seem to be differentially associated with HAP SR under alcohol vs. placebo. However, given that neither of these two-way interactions was statistically significant, any interpretation of differential anxiety/SR relationships under alcohol vs. placebo is speculative.

As shown in Table 6, the anxiety by beverage condition interaction predicting LAP SR was also not significant in either laboratory ($b = .062$, SE = .067, $p = .36$) or bar ($b = -.121$, SE = .092, $p = .19$) contexts. See Figure 6 for a visual comparison of these two interactions within each social context. Visual inspection of these interactions suggest that anxiety may have a small positive association with LAP SR under alcohol in lab contexts, in contrast to bar contexts where anxiety may have a small positive association with LAP SR under placebo. While neither of these interactions was statistically significant within either physical context, their opposing nature likely accounts for the observed decrement in model fit when the interaction terms were constrained to be equal across physical contexts.

Figure 5. Interaction of Anxiety and Beverage Condition Predicting HAP SR in Lab and Bar Contexts (Aim 2)

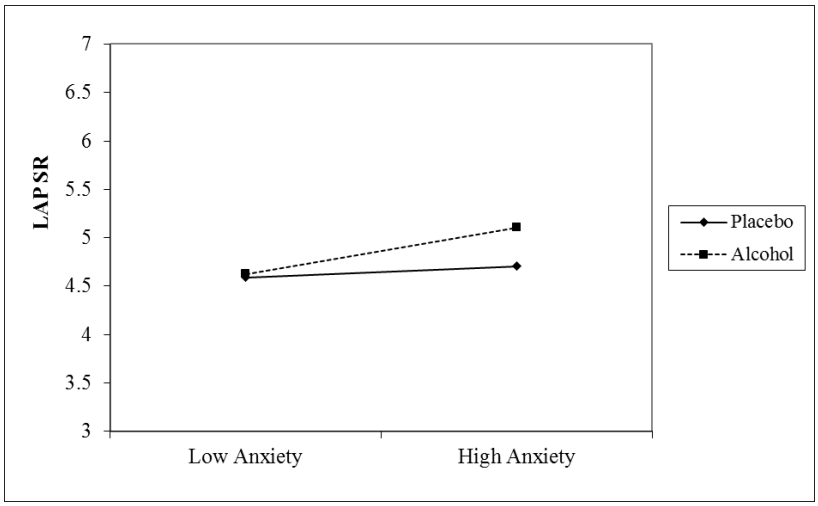


Lab Contexts (p = .29)

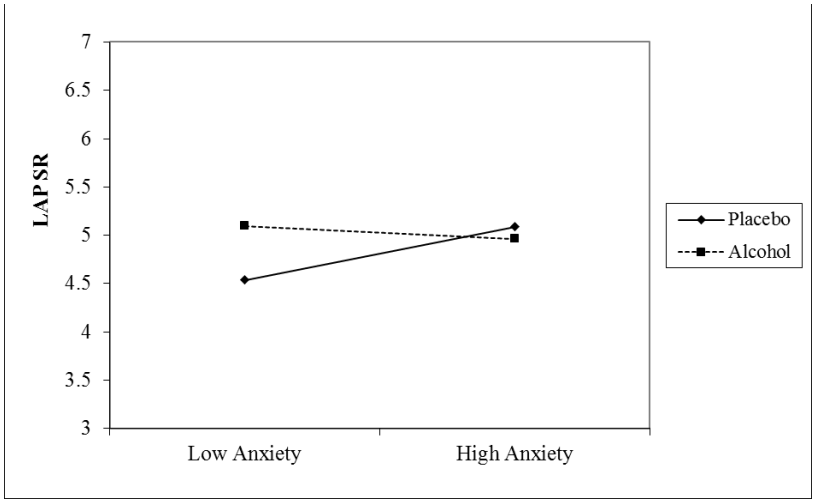


Bar Contexts (p = .16)

Figure 6. Interaction of Anxiety and Beverage Condition Predicting LAP SR in Lab and Bar Contexts (Aim 2)



Lab Contexts (p = .36)



Bar Contexts (p = .19)

These results regarding moderation of the anxiety/beverage condition/SR relationship by physical context do not align with hypotheses in the sense that none of the two-way interactions within a particular physical context were statistically significant (it was hypothesized that anxiety would be more strongly associated with HAP SR under alcohol in bar contexts and more strongly associated with LAP SR under alcohol in lab contexts). There was some signal for an association between anxiety and LAP SR under alcohol in lab contexts, as hypothesized, but the lack of statistical significance precludes further interpretation.

Aim 3 - Cortisol Response as a Mediator of the Relationship between Anxiety and Subjective Response

Moderated Indirect Effects Models: To determine whether cortisol response mediates the relationship between anxiety, beverage condition, and SR, four MODMED models were constructed wherein the interaction of anxiety and beverage condition predicted descending limb cortisol response, and descending limb cortisol response predicted descending limb SR. Contrary to hypotheses, the interaction between anxiety and beverage condition did not significantly predict descending limb cortisol in any of the four SR subscale models (all p values > .65). Model fit indices for the hypothesized MODMED models ranged from excellent to poor (descending HAP outcome: $\chi^2(25) = 52.52$, $p = .001$, RMSEA = .056, CFI = .898, SRMR = .041; descending HAN outcome: $\chi^2(25) = 47.43$, $p = .004$, RMSEA = .051, CFI = .892, SRMR = .037; descending LAP outcome: $\chi^2(25) = 25.54$, $p = .43$, RMSEA = .008, CFI = .997, SRMR = .028; descending LAN outcome: $\chi^2(25) = 56.373$, $p < .001$, RMSEA = .060, CFI = .800, SRMR = .045).

In order to correctly interpret any indirect effects of anxiety on SR (through descending limb cortisol), the non-significant interaction term was removed from the models, leaving four mediation models (anxiety predicting the four SR subscales through descending limb cortisol). With the exception of the LAP SR outcome model (where fit of the hypothesized model was already excellent), model fit was improved in the simpler models compared to the hypothesized MODMED models (descending HAP outcome: $\chi^2(22) = 31.34$, $p = .09$, RMSEA = .035, CFI = .965, SRMR = .033; descending HAN outcome: $\chi^2(22) = 22.85$, $p = .41$, RMSEA = .011, CFI = .996, SRMR = .029; descending LAP outcome: $\chi^2(22) = 25.10$, $p = .29$, RMSEA = .020, CFI = .985, SRMR = .030; descending LAN outcome: $\chi^2(22) = 22.65$, $p = .42$, RMSEA = .009, CFI = .996, SRMR = .028).

Table 7 presents a summary of these four indirect effects models. The path from anxiety to descending limb cortisol (the "a" path) was not significant in any model, nor was the path from descending limb cortisol (the "b" path) to any of the SR subscales. Thus, the preconditions for mediation were not met, which is reinforced by the fact that the asymmetric, bootstrapped 95% confidence intervals for indirect effects of anxiety on SR through cortisol all contained 0. No hypotheses regarding the relationship between anxiety, cortisol, and subjective response were supported.

Multi-Group Growth Models with Indirect Effects:

To determine whether slope of cortisol response (change in cortisol from baseline to descending limb) mediates the relationship between anxiety, beverage condition, and SR, a series of multi-group growth models with indirect effects were constructed. Models were grouped by beverage condition (alcohol vs. placebo), and in each model anxiety

Table 7

Indirect Effects of Anxiety on SR through Descending Limb Cortisol

	Anxiety to Descending Cortisol ("A" Path)			**Descending Cortisol to SR ("B" Path)**			**Total Indirect Effect**	
	b	**SE**	***p***	***b***	**SE**	***p***	**Point Estimate**	**95% CI**
HAP SR Model	-.001	.001	.52	1.75	1.88	.35	-.001	-.009 - .002
LAP SR Model	-.001	.001	.52	.66	1.45	.65	.000	-.006 - .001
HAN SR Model	-.001	.001	.51	-.01	.60	.98	.000	-.001 - .001
LAN SR Model	-.001	.001	.52	1.22	.97	.21	-.001	-.006 - .001

symptoms predicted cortisol intercept and slope, which in turn predicted each subscale of SR on the descending limb. To test the hypothesis that the relationship between anxiety and cortisol slope would differ by beverage condition, a model with all paths freely estimated was compared to a model in which the path from anxiety to cortisol slope was constrained to be equal across beverage conditions. A significant decrement in model fit was not observed ($\chi^2(1) = 2.63$, $p = .10$), indicating that the association between anxiety and cortisol slope did not differ by beverage condition (similar to the results of the MODMED analyses above). However, results were partially consistent with predictions: specifically, anxiety was more strongly negatively associated with cortisol slope in the alcohol condition ($b = -.34$, $p = .08$; negative sign indicating a steeper negative cortisol slope among those higher in anxiety) than in the placebo condition ($b = -.03$, $p = .79$).

Contrary to hypotheses, there was no indication of a significant association between cortisol response and SR on the descending limb in either beverage condition (all p values > .50). Thus, the second component of the mediation hypothesis (that cortisol response would be associated with SR) was also not supported. Model fit for the freely estimated model ($\chi^2(112) = 158.66$, $p = .03$, RMSEA = .049, CFI = .946, SRMR = .044) and constrained ($\chi^2(113) = 161.28$, $p = .02$, RMSEA = .050, CFI = .944, SRMR = .045) models were both acceptable.

Given the lack of evidence that the relationship between anxiety and cortisol slope varies by beverage condition, Table 8 presents estimates of indirect effects from the constrained model (wherein the path from anxiety to cortisol slope is constrained to be equal across beverage conditions). None of the indirect effects of anxiety on SR via cortisol slope were statistically significant in either beverage condition (all confidence

Table 8

Indirect Effects of Anxiety on SR via Cortisol Slope: Constrained Model

	Anxiety to Cortisol Slope ("A" Path)			**Cortisol Slope to SR ("B" Path)**			**Total Indirect Effect**	
	b	**SE**	***p***	***b***	**SE**	***p***	**Point Estimate**	**95% CI**
HAP SR Alcohol	-.192	.124	.12	-.047	.553	.93	.009	-.028 - .350
LAP SR Alcohol	-.192	.124	.12	-.016	.211	.94	.003	-.022 - .098
HAN SR Alcohol	-.192	.124	.12	.006	.070	.93	-.001	-.038 - .012
LAN SR Alcohol	-.192	.124	.12	.056	.237	.81	-.011	-.193 - .010
HAP SR Placebo	-.192	.124	.12	-.056	.476	.91	.011	-.032 - .348
LAP SR Placebo	-.192	.124	.12	-.084	.347	.81	.016	-.022 - .215
HAN SR Placebo	-.192	.124	.12	-.012	.091	.90	.002	-.008 - .063
LAN SR Placebo	-.192	.124	.12	.052	.080	.52	-.010	-.074 - .002

intervals contained 0). For descriptive purposes, Table 9 presents estimates of indirect effects from the fully unconstrained model (wherein the path from anxiety to cortisol slope was allowed to vary by beverage condition). Again, no indirect effects were significant in either beverage condition (all confidence intervals contained 0).

Table 9

Indirect Effects of Anxiety on SR via Cortisol Slope: Unconstrained Model

	Anxiety to Cortisol Slope ("A" Path)			**Cortisol Slope to SR ("B" Path)**			**Total Indirect Effect**	
	b	**SE**	***p***	***b***	**SE**	***p***	**Point Estimate**	**95% CI**
HAP SR Alcohol	-.339	.195	.08	-.047	.523	.93	.016	-.045 - .504
LAP SR Alcohol	-.339	.195	.08	-.016	.199	.94	.005	-.034 - .153
HAN SR Alcohol	-.339	.195	.08	.002	.011	.85	-.002	-.059 - .017
LAN SR Alcohol	-.339	.195	.08	.055	.191	.77	-.019	-.355 - .016
HAP SR Placebo	-.032	.120	.79	-.058	.513	.91	.002	-.030 - .161
LAP SR Placebo	-.032	.120	.79	-.087	.321	.79	.003	-.031 - .104
HAN SR Placebo	-.032	.120	.79	-.012	.092	.90	.000	-.006 - .036
LAN SR Placebo	-.032	.120	.79	.053	.079	.50	-.002	-.029 - .013

DISCUSSION

Objective

The objective of the current study was to investigate the relationship between anxiety symptoms and subjective response (SR) to alcohol, as well as possible moderating effects of drinking context and possible mediating effects of cortisol response to alcohol. The current study possessed unique strengths compared to previous studies in this area, both in terms of methodology and theory. Regarding methodology, the present study was the first investigation of anxiety and SR in the absence of an imminent stressor (i.e., outside of the stress response dampening (SRD) paradigm) to utilize a strong placebo control, which is necessary to discriminate between expectancies for alcohol effects and true pharmacological effects of alcohol. It was also the first to use a validated measure of SR that captures both positively and negatively reinforcing subjective effects of alcohol (the Subjective Effects of Alcohol Scale; Morean et al., 2013) and it utilized data from a very large (N = 447) representative sample of emerging adults, ensuring adequate power to address questions requiring group comparisons (e.g., effects of beverage condition and drinking context). Finally, the study addressed a number of important theoretical questions that have not been investigated previously, each of which is enumerated below in the context of the relevant specific aim.

Anxiety and Subjective Response – Results and Conclusions

The first specific aim of the study was to investigate the relationship between anxiety symptoms and positive SR to alcohol (both positively reinforcing, stimulation-like effects and negatively reinforcing, relaxation-like effects). This aim addressed a novel question given that prior studies have focused almost exclusively on the

relationship between anxiety and negatively reinforcing subjective effects, and almost always under the relatively narrow parameters of the SRD model, which only directly applies to situations involving drinking prior to an imminent stressor (as in Macdonald et al., 2000; Sinha et al., 1998, etc.). The one prior study that directly investigated the relationship between anxiety and positive SR outside of the SRD context was limited by a weak placebo control and the use of unvalidated measures of SR (Chutuape & DeWit, 1995).

It was hypothesized that anxiety symptoms would be associated with positive SR (specifically high-arousal, stimulation-like effects and low-arousal, relaxation-like effects) under both alcohol and placebo, but that this relationship would be significantly stronger under alcohol. This hypothesis was not supported, as anxiety was not more strongly associated with high-arousal positive (HAP) SR or low-arousal positive (LAP) SR in the alcohol condition compared to the placebo condition. In addition, although main effects of anxiety on positive SR (collapsed across both beverage conditions) were in the predicted direction, these effects were not statistically significant.

The lack of an interaction between anxiety and beverage condition in predicting SR was unexpected given that a prior study (Chutuape & DeWit, 1995) found that individuals who met criteria for an anxiety disorder reported increased "elation" and decreased "anxiety" following alcohol consumption (relative to placebo), whereas control subjects did not experience these differential effects from alcohol. But as mentioned previously, a weak placebo control calls these results into question. If the majority of participants knew they were consuming placebo (which was suggested by their manipulation check), then comparison of the alcohol vs. placebo condition was more akin

to comparison of an alcohol vs. no alcohol condition, which does not preclude the possibility of placebo effects. Further, the lack of a validated measure of SR makes it difficult to predict whether their results would generalize to the SEAS.

However, even if the increased positive alcohol effects among anxious individuals observed by Chutuape & DeWit (1995) were driven by expectancies, results were still inconsistent with their findings as there was no evidence for a main effect of anxiety on SR (collapsed across beverage conditions) in the present study. Results of the present study are also at odds with non-experimental evidence of elevated expectancies for positive subjective effects among anxious individuals (Brown and Munson, 1987; Ham et al., 2002; Ham et al., 2010) as well as elevated enhancement and coping motives for drinking (Allan et al., 2015; Buckner et al., 2006; Comeau et al., 2001; Lewis et al., 2008; Villarosa et al., 2014). If anxious individuals expect to receive stronger positive effects from alcohol, one would have expected anxiety to be significantly associated with SR collapsed across beverage condition, indicating an expectancy/placebo effect among individuals with higher anxiety.

One possible explanation for these null results is that the prevalence of anxiety symptoms in the current the sample was too low to detect a relationship between anxiety and SR. Individuals with a current anxiety disorder were excluded from participation, resulting in less than 10% of the sample being above the “normal” range of anxiety symptoms on the DASS (Lovibond & Lovibond, 1995). However, the majority of studies investigating the relationship between anxiety and alcohol expectancies or anxiety and drinking motives have also utilized general population samples that are not recruited for elevated anxiety symptoms or anxiety disorder diagnosis (with a few exceptions, such as

Ham et al., 2002). So, it does not seem that a highly anxious sample is required to detect an expectancy effect. Another possibility is that results from explicit measures of alcohol expectancies and drinking motives do not fully translate to alcohol administration studies, in which placebo response is an implicit rather than explicit measure of expectancies. It is also possible that the relationship between anxiety and positive SR to alcohol is restricted to situations involving an imminent stressor, as in the SRD paradigm (Macdonald et al., 2000; Sinha et al., 1998; Steward & Pihl, 1994). Given that anxious individuals seem to experience a greater dampening of physiological and cognitive stress responses to imminent stressors, perhaps these individuals come to expect stronger positive effects from alcohol in all situations even though they only receive those enhanced effects under the relatively narrow circumstances specified by the SRD model.

One additional explanation for the lack of significant relations between anxiety and SR is that such relations are context dependent. In other words, perhaps anxiety relates to SR only when alcohol is consumed in contexts that are conducive to such effects. This possibility was addressed in aim 2 of the current study as discussed below.

Moderating Effects of Context – Results and Conclusions

The second specific aim of the study was to investigate possible moderating effects of drinking context (social and physical context) on relations between anxiety symptoms and positive SR to alcohol. No previous study has investigated this question despite evidence that drinking context can influence SR to alcohol in the general population (Corbin et al., 2015; Pliner & Cappell, 1974; Sher, 1985).

It was hypothesized that social and physical context would moderate relations between anxiety symptoms and SR to alcohol (vs. placebo). Specifically, it was

hypothesized that anxiety would be more strongly associated with LAP SR under alcohol (vs. placebo) in low-stimulation contexts (solitary and lab contexts) but not high-stimulation contexts (group and bar contexts). The reverse was hypothesized for HAP SR: the relationship between anxiety and HAP SR was expected to be significantly stronger under alcohol (vs. placebo) in high-stimulation contexts (group and bar) relative to low-stimulation contexts (solitary and lab). These specific hypotheses regarding the nature and direction of the moderating effects were generally not supported, but some significant moderating effects of both social and physical context did emerge.

Specifically, social context significantly moderated the interactive effect of anxiety and beverage condition on HAP SR, and both social and physical context significantly moderated the interactive effect of anxiety and beverage condition on LAP SR (as evidenced by significant decrement in model fit when multi-group models forced equality of relations between anxiety and SR across physical/social contexts). As noted above, the nature of these moderated effects did not conform to hypotheses. Although three-way interactions were hypothesized, there was only one case in which the two-way interaction between anxiety and beverage condition was significant in one context but not the other. Specifically, the beverage condition by anxiety interaction predicting HAP SR was significant in solitary but not group contexts. The nature of the effect was such that the association between anxiety and HAP SR was stronger under placebo (vs. alcohol) in solitary contexts but not in group contexts (see Table 5 and Figure 4). This was in direct contrast with the hypothesis that anxiety would be most strongly linked to HAP SR under alcohol and in the group context. In the other two cases where constraining the model to be equivalent across context resulted in a significant decrement in model fit (HAP SR by

physical context and LAP SR by social context), none of the two-way interactions between anxiety and beverage condition were significant in any contexts, so these effects were not interpreted further.

Although not hypothesized, the finding that anxiety was associated with stronger HAP SR under placebo when drinking alone raises interesting questions for future studies. This finding suggests that individuals higher in anxiety expect stronger positively reinforcing subjective effects when drinking alone compared to individuals with lower anxiety. Studies have shown that alcohol expectancies can drive increased drinking behavior whether or not the expectancies accurately reflect the pharmacological effects of alcohol (Christiansen et al., 1989; Hasking, Lyvers, & Carlopio, 2011). Thus, elevated expectancies for positively reinforcing effects from solitary drinking could drive anxious individuals to drink more or more frequently in solitary situations. This is significant not only because increased drinking in any context could lead to increased risk for developing alcohol use disorders, but also because there is specific evidence linking solitary drinking with increased likelihood of alcohol problems (Gonzalez, Collins, & Bradizza, 2009; Keough et al., 2016).

At a minimum, this result suggests that future studies of the moderating effects of context on the anxiety/SR relationship are needed. If the moderating effect of social context on the anxiety/HAP relationship in the present study is replicated, this has implications for the prevention and treatment of alcohol use disorders among anxious individuals. Anxious solitary drinkers and those with elevated positive expectancies for solitary drinking would be important targets for intervention, perhaps through modification of established interventions to include components specific to anxiety and

solitary drinking. One possible candidate for this is BASICS (Dimeff et al., 1999), a motivational interviewing and skills training intervention that has been shown to be effective in emerging adults (Tollison et al., 2008; Vasilaki, Hosier, & Cox, 2006). BASICS provides clients with personalized feedback about their own drinking, information about normative drinking behavior among their peers, education about the effects of alcohol, and enhanced coping skills as a means to reduce drinking, all in a non-confrontational framework designed to enhance motivation to change (Murphy et al., 2001). Creating a context-specific version of a BASICS tailored to anxious drinkers would be straightforward. For example, facilitators could ask clients about the contexts in which they typically drink as well as specific expectancies for alcohol effects in those contexts, and if a client endorsed solitary drinking or positive expectancies specific to that context, facilitators would provide education regarding the link between solitary drinking and negative alcohol outcomes. There is empirical evidence that BASICS interventions are not as effective for individuals with elevated social anxiety (Terlecki et al., 2011), so perhaps even modest tailoring of existing programs could result in increased effectiveness among anxious drinkers.

Another intervention that could be similarly modified is expectancy challenge, which involves educating participants about alcohol expectancies (specifically how expectancies for positive effects are often exaggerated) with the goal of reducing positive expectancies (Darkes & Goldman, 1993; Wiers et al., 2004). These interventions are often conducted via experiential group learning wherein participants are individually randomized to receive alcohol or placebo and then, after a period of social interaction, are asked to guess which beverage they and their groupmates received (with correct guesses

reliably hovering around chance level of 50%). The difficulty in correctly identifying who received alcohol and who received placebo is then used as an entry point into teaching participants about expectancies. While this group format may not be ideal for addressing expectancies regarding solitary drinking, expectancy challenge conducted via didactic presentation has also been shown to be effective (Scott-Sheldon et al., 2012) and may be more amenable to modification with the insertion of content specific to solitary drinking.

Mediating Role of Cortisol Response – Results and Conclusions

The final specific aim of the study was to investigate cortisol response to alcohol as a possible mediating variable in the relationship between anxiety and SR. Results from previous studies comparing heavy drinkers to light drinkers (King et al., 2002; King et al., 2011) and comparing drinkers with and without a family history of alcohol use disorder (Schuckit et al., 1987; Schuckit & Gold, 1988) have suggested that blunted cortisol response to alcohol may be linked to a more positive SR profile, but this question has not been investigated directly. Chronic anxiety has also been linked to a dysregulated HPA axis and a blunted cortisol response to stress in the laboratory (Petrowski et al., 2010; Petrowski et al, 2013), but no study has investigated whether anxiety might also be associated with a blunted cortisol response to alcohol (similar to that seen in heavy drinkers) and a more positive profile of subjective response to alcohol.

It was hypothesized that cortisol response to alcohol would mediate the relationship between anxiety symptoms and subjective response to alcohol (vs. placebo). Specifically, it was hypothesized that higher anxiety would be associated with a blunted cortisol response under alcohol (compared to placebo), and this blunted cortisol response

to alcohol would in turn be associated with stronger positive SR and weaker negative SR. Hypotheses regarding the full moderated mediation model were not supported as anxiety was not significantly more strongly related to cortisol response under alcohol compared to placebo, though effects were in the predicted direction. For example, results of the growth model analyses show that the association between anxiety and cortisol slope was more strongly negative in the alcohol condition compared to the placebo condition (in the unconstrained model; see Table 9). Statistical significance was not reached in terms of the relevant individual paths, interaction effects, or model fit analyses, so it cannot be concluded that this component of the hypothesis was supported, but the general pattern of results suggests that the relationship between anxiety and cortisol response under alcohol may be worth investigating in future studies.

The lack of support for this component of the moderated mediation hypothesis could again be accounted for by the relatively restricted range of anxiety symptoms present in the sample (i.e., cortisol response to alcohol may only become significantly dysregulated/blunted at higher levels of chronic anxiety), but the relatively high level of drinking in the sample may have also played a role. As mentioned previously, prior studies investigating cortisol response to alcohol have found a significantly stronger cortisol response among light drinkers compared to heavy drinkers (King et al., 2002; King et al., 2011), and the light drinkers in these studies typically consumed very little alcohol. In King et al. (2011), the light drinking group was comprised of individuals who consumed less than 5 alcoholic drinks per week and generally engaged in binge drinking (5+ drinks in an occasion for men, 4+ drinks for women) less than 5 times per year. The heavy drinking group was comprised of individuals who consumed at least 10 alcoholic

drinks per week and who engaged in binge drinking 1 to 5 times per week. In the present study participants were required to report at least one binge drinking episode in the past month to be eligible, meaning that all participants engaged in binge drinking more frequently than the light drinkers in King et al. (2011). Thus, if cortisol response to alcohol was minimal for all participants in the present study due to a relatively high level of baseline drinking, detecting a relationship between anxiety and cortisol response would be difficult. It is not possible to determine with certainty whether the level of drinking in the sample played a causal role in the null findings, but given that the general trend for cortisol response in the present study was a steep downward slope from baseline in both the placebo and alcohol group (see Table 2), this explanation seems plausible.

In addition to the lack of support for the hypothesized relationships between anxiety, beverage condition, and cortisol response, there was no support for the second component of the moderated mediation hypothesis: a relationship between blunted cortisol response and subjective response to alcohol. There was no indication in any analyses that descending limb cortisol (see Table 7) or slope of cortisol change from baseline to descending limb (see Tables 8 and 9) was consistently associated with positive or negative SR. This finding was surprising given multiple previous studies showing a co-occurrence of blunted cortisol response to alcohol and a more positive/less negative profile of subjective response (King et al., 2002; King et al., 2011; Schuckit et al., 1987; Schuckit & Gold, 1988). Once again, the lack of lighter drinkers in the sample could have precluded detecting a relationship between cortisol response and any outcome of interest due to a restricted range of cortisol response to alcohol. However, it is also possible that personal drinking history and family history of alcohol problems have a

causal effect on SR but cortisol response to alcohol does not, despite its correlation with personal drinking history and family history.

The other possible implication of null findings regarding cortisol response as a mediator of the anxiety/SR relationship is that cortisol response is not particularly meaningful with regards to SR outside of a stress response dampening framework. It may be that the effect of alcohol on cortisol response to a specific stressor is more relevant to anxious individuals' SR than is cortisol response to alcohol consumption itself. Even if this is the case, the contextual moderation effects observed in the present study offer potentially novel avenues of investigation for future SRD studies. Anxious individuals' expectancies regarding the reinforcing effects of alcohol may be context-dependent, which could influence the situations in which they choose to drink and how much they choose to drink, which could in turn influence the degree to which alcohol dampens stress response.

Conclusions, Limitations, and Future Studies

The present study investigated relations between anxiety symptoms and subjective response to alcohol, along with moderating effects of drinking context and mediating effects of cortisol response to alcohol. No evidence was found for a relationship between anxiety symptoms and positive SR, but there was evidence for moderating effects of social and physical context on the relationship between anxiety and positive SR. These context-specific results have implications for the prevention of alcohol use disorders among anxious individuals (e.g., targeting anxious drinkers for expectancy challenge, providing education regarding negative outcomes associated with solitary drinking). There was also no support for hypotheses regarding the mediating role

of cortisol response to alcohol in the anxiety/SR relationship, although there was a signal in the data that anxiety symptoms may be associated with a blunted cortisol response to alcohol (vs. placebo), suggesting that future studies should investigate this relationship. Finally, there was no evidence that cortisol response to alcohol was linked to subjective response to alcohol. The general pattern of null findings may be an indication that the most relevant paradigm for studying the relationship between anxiety, SR, and cortisol response is the stress response dampening paradigm (but with added nuances regarding drinking context).

The study's methodological strengths (strong placebo control, large representative sample, validated measure of SR) and investigation of novel theoretical questions make it a significant contribution to the literature. That being said, there are a number of limitations that must be considered when interpreting results. First, as previously mentioned, the relatively low level of anxiety symptoms in the sample may have contributed to the lack of effects of anxiety on SR and cortisol response. Participants were ineligible for the study if they met DSM-IV criteria for a current anxiety or mood disorder, limiting the possible range of anxiety symptoms and thus potentially limiting power to detect effects. Future studies could address this by allowing individuals with current anxiety disorders to participate (though this raises some ethical questions given our knowledge of comorbidity between anxiety disorders and alcohol use disorders) or by recruiting individuals with elevated levels of anxiety symptoms relative to the general population.

Another possible limitation is the nature of the measure that was used to assess anxiety symptoms. The 14-question anxiety subscale of the DASS (Lovibond &

Lovibond, 1995) assesses a fairly broad range of physiological and cognitive anxiety symptoms (e.g., sweaty palms, shortness of breath, feeling close to panic), but it does not provide sufficient resolution to reliably assess distinct forms of anxiety that may be differentially associated with SR to alcohol (or cortisol response to alcohol), nor does it assess traits that may underlie anxiety symptoms (such as anxiety sensitivity). This is potentially significant, as social anxiety seems to be the form of anxiety most commonly linked to increased positive alcohol expectancies (e.g., Ham et al., 2010) and coping motives (e.g., Lewis et al., 2008), whereas anxiety sensitivity has been the most consistent predictor of greater stress response dampening under alcohol (Macdonald et al., 2000; Stewart & Pihl, 1994). Thus, future studies should utilize multiple measures of anxiety symptoms and assess traits like anxiety sensitivity in order to fully flesh out the nature of the relations between anxiety, SR, and cortisol response.

Finally, as mentioned above, the relatively high level of baseline drinking in the current sample could have also contributed to the lack of support for hypotheses regarding the mediating role of cortisol response in the relationship between anxiety and SR. Previous studies suggesting an association between cortisol response to alcohol and SR (King et al., 2002; King et al., 2011) included relatively light drinkers that likely would not have met minimum drinking criteria for inclusion in the current study. This is significant given that an elevated cortisol response to alcohol was observed specifically among light drinkers in previous studies. Thus, it may be the case that all participants in the present study have a relatively blunted cortisol response to alcohol compared to lighter drinkers, which would result in a restricted range of cortisol response and reduced power to detect effects. Future studies should explicitly recruit light drinkers in order to

determine whether cortisol response to alcohol is in fact blunted among individuals higher in anxiety and whether cortisol response is associated with SR to alcohol. However, as noted above, it is possible that cortisol response to alcohol is not significantly associated with anxiety and/or SR in drinking contexts that do not include an imminent stressor. It may be the case that the null results in the current study reflect a true lack of association between anxiety, cortisol, and SR in conditions outside of the SRD paradigm. In order to fully address this question, future studies should directly compare drinking conditions that include an imminent stressor to drinking conditions with no imminent stressor. This would allow for all outcomes of interest to be consistently operationally defined under SRD and non-SRD conditions. The present study provides a blueprint for the design of future investigations into the relationships between anxiety, cortisol response to alcohol, cortisol response to stress, and subjective response to alcohol (and possible moderating effects of context). Such studies are needed to enhance our understanding of how anxious individuals receive reinforcement from alcohol under various drinking conditions, which will inform prevention and intervention efforts aimed at reducing negative alcohol outcomes in this vulnerable population.

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