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Association between problematic alcohol use and reactivity to uncertain threat in two independent samples

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Abstract

Background—Recent laboratory studies have shown that acute alcohol intoxication selectively and effectively dampens aversive responding to an uncertain threat. An emerging hypothesis is that individuals who exhibit heightened reactivity to an uncertain threat may be especially motivated to use alcohol to dampen their distress, setting the stage for negative reinforcement processes to drive excessive alcohol use. However, no study to date has directly examined whether current problematic drinkers exhibit heightened reactivity to an uncertain threat as would be expected.

Methods—The present study was therefore designed to examine the association between current problematic alcohol use and reactivity to an uncertain threat during sobriety in two, independent samples. In Study 1 ($n = 221$) and Study 2 ($n = 74$), adult participants completed the same well-validated threat-of-shock task which separately probes responses to temporally predictable and unpredictable threat. Startle potentiation was measured as an index of aversive responding. Problematic alcohol use was defined as number of binge episodes within the past 30 days in Study 1 and total scores on a self-report measure of hazardous drinking in Study 2.

Results—As hypothesized, across both studies greater levels of problematic drinking were associated with greater startle potentiation to an unpredictable threat. In Study 2, hazardous drinking scores were also positively associated with startle potentiation to predictable threat.

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Conflict of interest

All authors declare that they have no conflicts of interest.

Contributors

Stewart Shankman and K. Luan Phan were the principal investigators of Study 1 and Study 2, respectively. Lynne Lieberman contributed to the collection and management of data. Stephanie Gorka provided the rationale for the paper, conducted the statistical analyses and wrote the first draft of the manuscript. All authors contributed to the paper and have approved the final manuscript.

Uncited references

Lang (1995), and Roberto et al. (2006).

Conclusions—The findings are notably consistent with the notion that heightened reactivity to an uncertain threat is an important individual difference factor associated with the onset and/or maintenance of problematic drinking behaviors and may therefore be a novel prevention and intervention target.

Keywords

Alcohol use; Binge drinking; Uncertain threat; Startle potentiation

1. Introduction

Reduction or avoidance of negative affect is a major motive for excessive alcohol use (Koob, 2003, 2013). Alcohol intoxication is thought to bring perceived relief from negative affective states, such as anxiety, thereby negatively reinforcing alcohol consumption and increasing the likelihood of using alcohol in the future (Baker et al, 2004, Khantzian, 1997). Over time, individuals may begin to rely on alcohol as a means of avoidance-based coping which significantly contributes to the onset and worsening of alcohol use disorders (Kassel et al., 2000, Robinson et al., 2011, Schroder and Perrine, 2007). In support of this, survey data indicate that drinkers use alcohol to ameliorate negative affect (Bibb and Chambless, 1986; Robinson et al., 2009) and believe that alcohol effectively reduces their anxiety (Cox et al., 1993).

Importantly, however, laboratory studies have not consistently demonstrated that alcohol dampens negative affect or stress (Greeley and Oei, 1999; see Curtin and Lang, 2007 for a review), and it has been posited that alcohol may only be stress-dampening for certain individuals under certain conditions. Along these lines, Bradford et al. (2013), Hachiya et al. (2010), Hefner and Curtin (2012), Hefner et al. (2013), Moberg and Curtin (2009) have conducted a series of studies clarifying the conditions by which alcohol is anxiolytic by demonstrating that acute alcohol intoxication dampens aversive reactivity during an uncertain, but not certain, threat/stress. In a seminal paper, using startle potentiation as an index of aversive responding (Bradley et al., 1999), Moberg and Curtin (2009) reported that alcohol intoxication (blood alcohol concentration [BAC] of 0.08%) significantly reduced startle potentiation during cues signaling unpredictable electric shock, but not during cues that signaled predictable shock. Through a series of follow-up studies, it was confirmed that as threat uncertainty increases, so does the magnitude of alcohol's stress-dampening effects and this association is both dose-dependent and generalizable across different forms of threat uncertainty including manipulations in threat timing, probability and severity (Bradford et al., 2013; Hefner and Curtin, 2012; Hefner et al, 2013). Taken together, alcohol selectively and effectively dampens aversive responding to an uncertain threat and may therefore target the biological, affective and/or cognitive processes engaged by threat uncertainty.

A large body of rodent and human research indicates that an uncertain threat elicits a generalized feeling of apprehension not associated with a clearly identifiable source and heightened, sustained vigilance (labeled *anticipatory anxiety*; Barlow, 2000; Blanchard et al., 1993; Davis, 1998; Herry et al, 2007; Jackson et al., 2015). Meanwhile, predictable or certain threat elicits a phasic response to an identifiable stimulus that is time-locked to the

threat (*labeled* fear; Barlow, 2000; Davis et al, 2010). These aversive responses have been shown to be pharmacologically distinct (Grillon et al, 2006, 2011) and mediated by overlapping, but separable, neural circuits (Alvarez et al., 2011; Davis, 2006).

Considering this literature and findings from Curtin and Lang (2007) alcohol may be especially effective at dampening anticipatory anxiety. This is markedly consistent with early theories suggesting that alcohol intoxication impairs attentional capabilities such as sustaining vigilance and dividing attention (i.e., processes central to anticipatory anxiety; Steele and Josephs, 1990). Given that a major motive for using alcohol is the reduction or avoidance of aversive affective states, an emerging hypothesis is that those who are most sensitive and reactive to an uncertain threat, and thus experiencing chronic heightened anticipatory anxiety, are the most motivated to consume alcohol to dampen their distress, setting the stage for negative reinforcement processes to drive excessive, continuous alcohol use. In other words, individuals who excessively use alcohol may experience greater anticipatory anxiety in response to an uncertain threat and therefore find alcohol intoxication to be especially reinforcing. Although this points to the possibility that reactivity to an uncertain threat is an important individual difference factor that connotes risk for problematic alcohol use, no study to our knowledge has directly examined whether current problematic drinkers do indeed exhibit heightened anticipatory anxiety in response to an uncertain threat.

In preliminary support of this hypothesis, however, a recent investigation in a sample of undergraduates found that coping-related drinking motives were positively associated with individual differences in intolerance of uncertainty (a personality construct reflecting the view that uncertainty is distressing and intolerable), even when controlling for broad negative affectivity and anxiety sensitivity - a related personality trait which is known to be associated with problematic drinking (Kraemer et al., 2015). Thus, those who reported that they use alcohol to cope with their distress report a particular sensitivity to uncertainty. Moreover, a prior study by our laboratory found that individuals with current panic disorder (PD) and a *past* diagnosis of alcohol dependence exhibited greater startle potentiation during unpredictable, but not predictable, threat-of-shock relative to healthy controls and individuals with PD-only (Gorka et al., 2013), indicating that those with a history of problematic drinking displayed greater reactivity to an uncertain threat relative to those who did not. Together, these findings provide important preliminary evidence to suggest that individuals who engage in excessive, problematic alcohol use exhibit a hyper-sensitivity to an uncertain threat; however, this hypothesis remains to be directly tested. Based on prior studies, it is still unclear whether problematic drinking behaviors, rather than just coping motives, are related to sensitivity to an uncertain threat, and whether the findings from Gorka et al. (2013) were driven by the history of problematic drinking/alcohol dependence.

The present study was therefore designed to examine the association between current, problematic alcohol use and reactivity to an uncertain threat during sobriety in two, independent samples (Study 1 and Study 2). In both Study 1 and Study 2, participants completed the same well-validated threat-of-shock task designed to probe responses to an unpredictable and predictable threat. Startle potentiation was collected as an index of aversive responding. Current problematic alcohol use was assessed via self-reported number

of alcohol binge episodes within the past 30 days in Study 1. As both a replication and an extension, in Study 2, participants completed the Alcohol Use Disorders Identification Test (AUDIT; Babor et al., 1989) - a widely used self-report measure that includes information about current drinking frequency and hazardous and problematic drinking patterns. We hypothesized that more binge episodes (Study 1) and higher AUDIT/problematic drinking scores (Study 2) would be associated with greater startle potentiation to an unpredictable threat above and beyond current anxiety and depressive symptoms which have both been previously linked to threat reactivity (Grillon et al., 2013; Shankman et al., 2013).

2. Material and methods

2.1. Participants

Study 1 and Study 2 were designed to recruit adult volunteers with a range of psychiatric diagnoses, symptoms and alcohol use problems consistent with the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative. All participants were recruited via advertisements posted in the community, local psychiatric clinics, nearby college campuses and in area newspapers/websites. A variety of advertisements were used to target different populations (e.g., healthy controls, heavy drinkers, anxiety disorder patients) in an effort to enroll a diverse sample. Both studies took place at the University of Illinois-Chicago, in different laboratories, and were approved by the university Institutional Review Board. All participants provided written informed consent after review of the protocol. Study 1 and Study 2 required participants to complete a set of laboratory tasks, a battery of questionnaires and a semi-structured clinical interview. Laboratory tasks and questionnaires were administered in a counterbalanced order to eliminate potential order effects. Participants received cash as payment for participation.

As part of the larger aims for Study 1, a total of 161 biological, sibling dyads were recruited to examine familial threat and reward processes. Inclusion criteria for the larger family study included being between the ages of 18 and 30 years old and having at least one biological sibling in the same age range that was also willing and able to participate. Exclusion criteria included a personal or family history of mania or psychosis, a medical or neurological illness that may impact psychophysiological functioning (e.g., epilepsy), an inability to read or write English, a history of serious head trauma, and left-handedness. Of the 292 participants who enrolled and completed the study protocol, 71 were excluded from the study due to technical equipment failure during the startle task ($n = 19$), missing self-report data ($n = 20$), or poor quality startle eye-blink data ($n = 32$; 70% or more of the blinks in any one condition being coded as missing or non-responders or an inability to visually distinguish eyeblink responses from baseline activity). The final sample included 221 individuals (see Table 1).

Study 2 was similarly designed to examine threat processes in adults, but also how these processes change in response to treatment. As such, Study 2 included a subset of treatment seeking adults who reported depression and/or anxiety symptoms severe enough to warrant treatment (i.e., cognitive behavioral therapy [CBT] or selective serotonin reuptake inhibitor [SSRI]). Participants were required to be between the ages of 18 and 65 years. Exclusion criteria included an inability to provide consent and read and write in English, a major active

medical or neurological problem, lifetime history of mania or psychosis, any contraindication to receiving SSRIs, being already engaged in any form of psychiatric treatment (including medication), history of traumatic brain injury, left-handedness, and being pregnant. A total of 98 individuals were recruited; however, 26 were excluded for missing/corrupted raw startle data ($n = 5$), missing self-report data ($n = 6$), or poor quality startle data ($n = 15$; same criteria as above). The final sample included 74 individuals (see Table 1). All data presented below was assessed prior to treatment (i.e., baseline). Notably, unlike in Study 1, no individual was taking psychiatric medications at the time of the evaluation.

2.2. Procedure and threat task

The threat task and laboratory procedures for Study 1 and Study 2 were identical. Upon arrival to the lab, all individuals were assessed for acute alcohol intoxication via a breathalyzer and tested negative. After the screening, to prevent early exaggerated startle responding, participants completed a 2 min habituation task during which 6 acoustic startle probes were administered. Shock electrodes were subsequently placed on participants' non-dominant hand and a second habituation task was administered to ensure that attachment of the shock electrodes did not significantly re-potentiate early startle responses. Afterwards, a shock work-up procedure was completed in which participants received increasing levels of shock intensity until they reached a level that they described as "highly annoying but not painful." Ideographic shock levels were used to ensure equality in perceived shock aversiveness (Rollman and Harris, 1987) and to be consistent with prior studies (e.g., Shankman et al., 2013). The maximum shock was 5 mA.

Participants then completed the No-Predictable-Unpredictable (NPU) threat task which is modeled after the one developed by Schmitz and Grillon (2012) and has been previously used in our lab (Gorka et al., 2013, 2015; Shankman et al., 2013). The task includes three within-subject conditions – no shock (N), predictable shock (P), and unpredictable shock (U). Text at the bottom of the computer monitor informs participants of the current condition by displaying: "no shock" (N), "shock at 1" (P), or "shock at anytime" (U). Each condition lasted 145s, during which a 4s visual countdown (CD) was presented six times. The interstimulus intervals (ISIs; i.e., time between CDs) ranged from 15 to 21 s ($M = 18.0$ s) during which only the text describing the condition was on the screen. During the N condition, no shocks were delivered. During the P condition, participants received a shock every time the CD reached 1. During the U condition, shocks were administered at any time (i.e., during the CD or ISI). Startle probes were presented both during the CD (1–2s following CD onset) and ISI (4–13 s following ISI onset). The time interval between a shock and the following startle probe was always greater than 10 s to ensure that the subsequent startle response was not significantly affected by an immediately preceding stimulus. Each condition was presented two times in a randomized order (counterbalanced across participants). All participants received 24 total electric shocks (12 in P and 12 in U) and 60 total startle probes (20 in N, 20 in P, and 20 in U).

In Study 1 only, after the task participants rated how intense, annoying, and anxiety provoking the shocks were, the degree to which they would avoid the shocks, and how aversive they found the acoustic startle probes on a 7-point Likert scale.

2.3. Startle data collection and processing

In both studies, startle data were acquired using BioSemi Active Two system (BioSemi, Amsterdam, The Netherlands). In Study 1, stimuli were administered using PSYLAB (Contact Precision Instruments, London, UK) and in Study 2, stimuli were administered using Presentation (Albany, CA). Acoustic startle probes were 40 ms duration, 103 dB bursts of white noise with near-instantaneous rise time presented binaurally through headphones. Electric shocks lasted 400 ms and were administered to the wrist of the participants' left hand.

Startle responses were recorded from two 4 mm Ag/AgCl electrodes placed over the orbicularis oculi muscle below the left eye. The ground electrode was located at the frontal pole (FPZ) of an electroencephalography (EEG) cap that participants were wearing as part of the larger studies. One startle electrode was placed 1-cm below the pupil and the other was placed 1 cm lateral of that electrode. Data were collected using a bandpass filter of DC-500Hz at a sampling rate of 2000 Hz.

Blinks were processed and scored according to published guidelines (Blumenthal et al, 2005). Data processing included applying a 28 Hz high-pass filter, rectifying, and then smoothing using a 40 Hz low-pass filter. Peak amplitude of the blink reflex was defined within 20–150 ms following the startle probe onset relative to baseline (i.e., average baseline EMG level for the 50 ms preceding the startle probe onset). Each peak was identified by software but examined by hand to ensure acceptability. Blinks were scored as non-responses if EMG activity during the 20–150 ms post-stimulus time frame did not produce a blink peak that is visually differentiated from baseline activity. Blinks were scored as missing if the baseline period was contaminated with noise, movement artifact, or if a spontaneous or voluntary blink began before minimal onset latency and thus interfered with the startle probe-elicited blink response. Blink magnitude values (i.e., condition averages include values of 0 for non-responses) were used in all analyses.

2.4. Study 1: problematic alcohol use

Current alcohol use was assessed during the clinical interview using the Time-Line Follow-Back technique (Sobell and Sobell, 1992). Specifically, participants were presented with a calendar of the past 30 days and asked to indicate on what days they “binged” and how many drinks they had. Binge episodes were defined as having 5 standard drinks for men, and 4 drinks for women, in two hours (NIAAA, 2014). Of note, binge drinking is conceptualized as a form of problematic drinking as it is linked to serious adverse emotional, behavioral and health-related outcomes (Jennison, 2004).

Although the current sample was diverse, the continuous variable of number of binge episodes within the past 30 days was skewed (2.5, SE = 0.15) and kurtotic (9.1, SE = 0.29; $M = 1.5 \pm 2.5$). To correct for this distribution issue, number of binges was re-coded into a 3-

level variable such that 0 = no binges ($n = 116$), 1 = one binge ($n = 41$), and 2 = two or more binges within the past 30 days ($n = 64$).

2.5. Study 2: problematic alcohol use

To assess hazardous and problematic alcohol use, participants completed the widely-used AUDIT – a 10-item self-report measure developed by the World Health Organization (WHO). AUDIT total scores are a combined measure of alcohol consumption frequency (including binges), alcohol use problems, and dependence symptoms, and have been shown to be a sensitive measure of problematic drinking in diverse populations (Saunders et al., 1993a, 1993b). In the current study, reliability of the measure was good ($\alpha = 0.73$). Total scores were normally distributed ($M = 3.7 \pm 3.4$; range: 0–15; skew = 0.8; kurtosis = 0.3) and 23% of the sample had total AUDIT scores at or above the total cut-off for problematic drinking (Babor et al, 1989).

2.6. Current depression and anxiety symptoms

Participants in both studies completed the Inventory of Depression and Anxiety Symptoms (IDAS-II; Watson et al., 2012) – a 99-item self-report measure assessing symptoms of emotional disorders during the previous two weeks. Participants are asked to respond to each item using a 5-point Likert scale ranging from 1 (*not at all*) to 5 (*extremely*) and scores are summed to create subscales related to DSM-IV (APA, 2000) mood and anxiety symptoms. Prior research has demonstrated that the IDAS has excellent psychometric properties including internal consistency, test-retest reliability, and convergent and discriminant validity (Watson et al., 2007). For the current study, the IDAS depression subscale and a composite of the IDAS anxiety disorder subscales (i.e., social anxiety, panic, traumatic intrusions and avoidance, and claustrophobia) were used as covariates in the analyses below. Reliability of the IDAS in Study 1 ($\alpha = 0.81$) and Study 2 ($\alpha = 0.94$) was excellent.

2.7. Data analysis plan

First, as a manipulation check, we conducted a 3 (Condition: N, P, U) $\times$ 2 (Cue: CD, ISI) repeated measures ANOVA to confirm that the task elicited startle to P- and U-threat as designed. Consistent with prior studies (e.g., Gorka et al, 2013), we then confirmed that alcohol binges and AUDIT scores were not significantly associated with startle magnitude during the no-threat, control conditions of the NPU task (i.e., N_{CD} and N_{ISI} ; all $ps > 0.27$). Given the null findings, we created average startle potentiation scores (using the control conditions) for the P- and U-threat conditions to account for baseline individual differences in startle magnitude. For P-threat, we subtracted startle magnitude during N_{CD} from P_{CD} . For U-threat, we subtracted average startle magnitude during N_{CD} and N_{ISI} from average startle magnitude during U_{CD} and U_{ISI} because both phases of the U conditions (and N conditions) had the same meaning during the task. The P- and U-threat startle potentiation scores were used as dependent variables in the subsequent analyses.

For Study 1, the effect of alcohol binges on startle potentiation was tested using a flexible multilevel mixed model, which allows for the shared variance between biological siblings to be modeled and statistically accounted for. Threat condition (P or U) and alcohol binges were specified as fixed effects and gender, age, and IDAS depression and anxiety scores

were included as covariates. The multilevel model used restricted maximum likelihood (REML) estimation and an unstructured covariance matrix. Any significant variable $\times$ threat condition interactions were followed-up using two separate post-hoc multilevel mixed models examining the effect of the variable on startle potentiation during each threat condition (i.e., P and U separately). Hedges' g , an index of effect size that accounts for differences in the number of participants in each group (Hedges, 1982), is reported for significant findings.

For Study 2, the effect of AUDIT scores on startle potentiation was tested using a repeated measures analysis of variance (ANOVA). Threat condition was specified as a two-level within-subjects variable whereas AUDIT scores were specified as a between-subjects variable. Identical to above, age, gender and IDAS depression and anxiety scores were included as covariates. Any significant variable $\times$ threat condition interactions were followed-up similar to above by conducting post-hoc linear regressions examining the effect of the variable on startle potentiation during each threat condition separately. Partial correlation coefficients (controlling for all covariates listed above) between startle potentiation and AUDIT scores are reported as estimates of effect size for significant associations.

3. Results

3.1. Manipulation check

In Study 1, participants provided self-report ratings of how aversive they perceived the electric shock during the threat task. On average, participants rated the shocks as moderate to extremely intense ($M = 4.5 \pm 1.1$), annoying ($M = 5.6 \pm 1.3$), and anxiety provoking ($M = 4.7 \pm 1.5$), and rated that they would avoid receiving the shocks again to a high degree ($M = 5.0 \pm 1.6$).

Across both studies, results assessing the effects of the NPU-task indicated a main effect of condition, $F(2, 586) = 140.52, p < 0.001$, and cue, $F(1, 293) = 111.72, p < 0.001$, and a condition $\times$ cue interaction, $F(2, 586) = 34.66, p < 0.001$. During the CD, startle significantly differed among the conditions such that $N_{CD} < P_{CD} < U_{CD}$ ($ps < 0.001$). During the ISIs, startle also differed such that U_{ISI} was greater than P_{ISI} and N_{ISI} ($ps < 0.001$), whereas P_{ISI} and N_{ISI} did not differ. The task therefore elicited startle magnitude to threat conditions as designed (Figs. 1 and 2). Of note, Study did not moderate the effect of cue or condition, or the condition $\times$ cue interaction, indicating that the pattern of results did not differ across the two samples. There was, however, a main effect of Study $F(1, 292) = 4.45, p < 0.05$, such that startle was higher, on average, in Study 1 than in Study 2.

3.2. Alcohol use and startle potentiation

Results from Study 1 are presented in Table 2. There was a significant positive association between number of binge episodes within the past 30 days and overall startle-potentiation which was qualified by a significant alcohol binges $\times$ threat condition interaction. Follow-up analyses revealed that more alcohol binges were significantly associated with greater startle potentiation to U-threat, $b = 16.87, t = 4.44, p < 0.001$ (Fig. 1A); however, number of alcohol

binges was not associated with startle potentiation to P-threat, $b = 2.09$, $t = 0.75$, *ns*. Post-hoc paired comparisons indicated that individuals who reported two or more binge episodes within the past 30 days exhibited greater startle potentiation relative to those who did not binge ($p < 0.001$; Hedges' $g = 0.58$), and marginally greater startle relative to those with only one binge ($p = 0.07$; Hedges' $g = 0.26$). There were no differences between those who reported no binge and those who reported one binge ($p = 0.13$), though this finding approached a trend. There were no other main effects or interactions, including no effects of gender.

Results from the Study 2 indicated that there was a significant main effect of AUDIT scores on overall startle potentiation (i.e., both P- and U-threat; Fig. 1B; P-threat $r = 0.24$, U-threat $r = 0.32$). The AUDIT x condition interaction only approached a trend ($p = 0.12$), though the direction of effects was consistent with Study 1. There were no other main effects or interactions, including no effects of gender.

4. Discussion

Accumulating evidence suggests that reactivity to an uncertain threat may be a key individual difference factor related to excessive alcohol use. However, prior studies had never directly examined whether current problematic drinking is indeed associated with greater reactivity to an uncertain threat, which was the premise of the current study. In two separate, diverse samples, the present findings indicate that greater levels of problematic drinking are significantly associated with greater startle potentiation to an uncertain threat. This was notably demonstrated across two indices of problematic drinking – number of alcohol binges within the past 30 days and self-reported harmful and hazardous drinking patterns (i.e., AUDIT scores). Together, these findings provide additional support for the hypothesis that those who display high levels of anticipatory anxiety in response to an uncertain threat may be the most motivated to engage in excessive alcohol use since laboratory studies have shown that acute alcohol intoxication is particularly effective at alleviating anticipatory anxiety (Moberg and Curtin, 2009; Bradford et al, 2013). In other words, individuals who are highly reactive to an uncertain threat likely find alcohol intoxication to be highly negatively reinforcing which sets the stage for continued and escalated drinking (Koob, 2003, 2013).

Given that all of the research addressing this question have been cross-sectional, including the current study, it is important to note that additional studies are needed to disentangle whether heightened reactivity to an uncertain threat is a risk factor and/or an acquired factor associated with problematic alcohol use. As mentioned above, it is possible that heightened reactivity to an uncertain threat precedes problematic alcohol use, is evident early in development, and connotes *risk* for continuing to use alcohol after it is initiated. It is also possible that heightened reactivity to an uncertain threat is a consequence of problematic alcohol use as repeated alcohol exposure is known to cause cumulative neuroadaptations in the brain that alter neurotransmission and increase anxiety and negative affect (Koob and Le Moal, 2001; Koob and Volkow, 2010). Therefore, alcohol exposure in-and-of-itself increases anxiety and stress (Sinha, 2008) and may relatedly increase reactivity to an uncertain threat, which could maintain rather than initially cause problematic drinking behaviors.

It is worth noting that these two possibilities are not mutually exclusive and it is plausible that baseline individual differences in reactivity to an uncertain threat connote risk for problematic drinking *and* over time, repeated alcohol use exacerbates reactivity. This would ultimately result in an increased need and desire to maintain frequent use. In light of the current findings and the large to moderate observed effect sizes, prevention and/or intervention techniques aimed at reducing problematic drinking may therefore consider targeting reactivity to an uncertain threat to disrupt the feed-forward cycle between anticipatory anxiety and alcohol intoxication. This could involve screening adolescents for heightened reactivity to uncertain threat and employing targeted counseling, behavioral and/or educational-based efforts to deter the onset of problematic drinking. It could also involve the development of novel pharmacological replacement therapies which alleviate anticipatory anxiety and/or remedy disrupted neural circuits or recruit healthy ancillary circuits to normalize reactivity to uncertainty.

Importantly, before these approaches are explored, it would be useful to first uncover at what point heightened reactivity to an uncertain threat emerges in the progression to problematic alcohol use, and identify the mechanisms that contribute to this exaggerated affective response style. It has been posited that heightened reactivity to an uncertain threat may stem from several related abnormalities including increased threat attention, inflated estimates of threat harm, deficient safety learning, and maladaptive cognitive control (Grupe and Nitschke, 2013). It has also been suggested that personality traits such as anxiety sensitivity (AS), or the tendency to interpret anxiety-related sensations as fearful and distressing (Reiss et al, 1986), also contribute to reactivity to an uncertain threat (Lejuez et al., 2000; Melzig et al, 2008; Nelson et al, 2015), and that AS in particular may be an overlapping, yet distinct, factor related to problematic alcohol use (Carleton et al., 2007; DeMartini and Carey, 2011). To date, no study has attempted to disentangle the roles of these potential processes and how they contribute to reactivity to an uncertain threat and problematic drinking behaviors. This knowledge will be critical as we seek to develop mechanistically-driven interventions, which are delivered at opportune phases in disease development, to ultimately reduce the burden of alcohol use disorders.

In addition to an uncertain threat, the results from Study 2 indicated that higher AUDIT scores were associated with greater startle potentiation to predictable threat. This was notably not the case in Study 1 as number of binge episodes was uniquely associated with reactivity to an uncertain threat. These findings may imply that problematic drinking behaviors, beyond just binge drinking, relate to overall threat responding including both fear and anticipatory anxiety. However, it is also important to highlight that the Study 2 sample size was relatively small and the age range of participants was larger, which is noteworthy given that age is associated with greater baseline startle and affect modulated startle potentiation (e.g., Quevedo et al., 2010; Smith et al., 2005). The AUDIT scores by threat condition interaction in Study 2 also approached a trend level. Given that Study 1 did not show that alcohol use was related to startle reactivity to predictable threat, this specific finding from Study 2 warrants caution in interpretation. Nevertheless, future studies should consider the possibility that problematic drinkers exhibit broad abnormalities in threat responding but that the drinking behaviors themselves may (or may not) be reinforced by alcohol's acute effects on anticipatory anxiety.

Interestingly, a few recent studies also suggest that individual differences in reactivity to an uncertain threat may impact vulnerability to substances in addition to alcohol, including both nicotine and cannabis. For instance, Hogle et al. (2010) have demonstrated that within smokers, nicotine deprivation selectively increases startle potentiation to an unpredictable threat and that both anticipating smoking a cigarette *and* actually smoking a cigarette significantly dampens this reactivity (Bradford et al, 2015). Meanwhile, heavy marijuana users have been shown to exhibit heightened aversive reactivity to an uncertain threat and an uncertain reward (Hefner et al., 2015; Gloria et al, 2015, in preparation), highlighting the possibility that substance users evidence a broad sensitivity to uncertainty and find unpredictable threats and rewards aversive. Taken together, reactivity to uncertainty, particularly an uncertain threat, has emerged as an important construct related to several forms of substance use and future studies should therefore continue to clarify its role in substance use initiation, maintenance and relapse.

Although the current study has several strengths including replication in two independent samples, across two indices of problematic drinking, there are several limitations worth noting. First, although both studies included individuals with a range of problematic drinking behaviors, the overall mean of binge drinking and AUDIT scores was somewhat low and reflected the fact that the samples were mostly drawn from the general community rather than substance abuse clinics. Thus, additional research is needed to assess whether the present findings would generalize to more severe and dependent alcohol use samples. Second, the sample was diagnostically heterogeneous and included both healthy controls and individuals with current psychiatric disorders. Although depressive and anxiety symptoms were included covariates in the analyses, the extent to which specific disorders and/or patterns of comorbidity may have influenced the results is unclear. Third, only two measures of problematic drinking (i.e., binge episodes and AUDIT scores) were examined in the current study and there is a need for additional studies to explore whether the present associations extend to other aspects of risky drinking such as alcohol use motives and expectancies. Lastly, as was noted above, the current study is cross-sectional and thus, the directionality of the current findings cannot be determined. Future prospective studies assessing individual differences in reactivity to an uncertain threat prior to and following problematic drinking onset are greatly needed.

Taken together, the current study supports existing research and theory suggesting that heightened reactivity to an uncertain threat is an important individual difference factor associated with problematic drinking. The findings also converge with a broader, developing literature suggesting that intolerance of uncertainty, or the tendency to find uncertain outcomes distressing and aversive, underlies the motivation to use multiple drugs of abuse. Given that startle potentiation to threat is both psychometrically reliable and easy-to-measure (Shankman et al., 2013), additional research focused on its utility as a marker for substance use risk, disease or recovery is warranted. Studies should also continue to uncover the mechanisms that underlie heightened reactivity to an uncertain threat in an effort to identify novel prevention and/or intervention targets for problematic drinking and develop more mechanistically-driven clinical approaches for the treatment of addiction.

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Fig. 1.
Mean startle magnitude values during each condition of the threat task. N = no-shock; P = predictable shock; U = unpredictable shock; CD = countdowns; ISI = inter-stimulus interval. Bars reflect standard error.

Fig. 2.

A) Within Study 1, mean startle potentiation to an unpredictable threat at each level of binge episodes within the past 30 days. Bars reflect standard error. B) Within Study 2, scatter plot depicting the association between AUDIT total scores and startle potentiation to an unpredictable threat. U-threat = unpredictable threat; AUDIT = Alcohol Use Disorders Identification Test.

Table 1

Demographics and clinical characteristics.

Demographics	Study 1 (N = 221)	Study 2(N = 74)
Age(years)	23.1 (7.2) _a	26.56 (9.4) _b
Sex (% female)	62.0% _a	74.0% _a
Race/Ethnicity		
Caucasian	42.7% _a	49.0% _a
African American	11.4% _a	12.3% _a
Hispanic	24.1% _a	11.3% _a
Asian	14.5% _a	19.2% _a
Mixed Race	4.1% _a	1.4% _a
Other	3.2% _a	6.8% _a
Clinical Variables		
IDAS Depression	37.5 (12.5) _a	48.3 (18.3) _b
IDAS Anxiety	7.7 (2.4) _a	9.0 (3.1) _a
Lifetime Depression Diagnosis	34.6% _a	49.3% _a
Lifetime Anxiety Disorder Diagnosis	55.7% _a	61.6% _a
Lifetime Alcohol Use Disorder	34.1% _a	6.8% _b
Lifetime Substance Use Disorder	35.5% _a	9.6% _b
Taking Psychiatric Medication	7.7% _a	0.0% _b
Current Daily Cigarette Smoker	7.1% _a	6.8% _a
Used Cannabis in Past Six Months	34.7% _a	18.9% _b
Used Illicit Drugs * in Past Six Months	19.0% _a	10.8% _a
Startle Variables		
Potentiation to U-Threat	43.8 (51.2) _a	21.6 (31.4) _b
Potentiation to P-Threat	20.0 (73.8) _a	18.9 (34.4) _a

Note. Means or percentages with different subscripts across rows were significantly different in pairwise comparisons ($p < 0.05$, chi-square test for categorical variables and Tukey's honestly significant difference test for continuous variables). Diagnoses were assessed using DSM-IV criteria. IDAS = Inventory for Depression and Anxiety Symptoms.

* Illicit drugs include all recreational substances other than cannabis.

Table 2

Results from Study 1 and Study 2.

Variable	Study 1			Study 2		
	<i>b</i>	<i>t</i>	<i>p</i> -value	<i>df</i>	<i>F</i>	<i>p</i> -value
Condition	-36.13	-1.97	0.05	1.58	0.38	0.54
Age	-1.24	-1.08	0.28	1.58	2.00	0.16
Gender	8.38	0.49	0.62	1.58	0.86	0.36
Depression	0.56	0.53	0.60	1.58	0.23	0.63
Anxiety	-0.69	-0.12	0.90	1.58	0.11	0.75
Problematic Alcohol Use	22.44	2.38	0.01*	11.58	2.68	0.04*
Condition × Age	0.62	0.89	0.38	1.58	0.68	0.41
Condition × Gender	10.25	1.00	0.32	1.58	0.53	0.47
Condition × Depression	-0.39	-0.61	0.54	1.58	0.23	0.63
Condition × Anxiety	0.68	0.20	0.84	1.58	0.62	0.43
Condition × Problematic Alcohol Use	-13.11	-3.50	<0.0***	11.58	1.61	0.12

*Note.****
 $p < 0.01$,*
 $p < 0.05$.

Problematic alcohol use is defined as number of binge episodes within the past 30 days in Study 1 and total Alcohol Use Disorder Identification Test (AUDIT) scores in Study 2. Depression and Anxiety symptoms assessed via the Inventory of Depression and Anxiety Symptoms (IDAS-II).