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How Bad Could It Be? Alcohol Dampens Stress Responses to Threat of Uncertain Intensity

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Abstract
Stress response dampening is an important motive for alcohol use. However, stress reduction via alcohol (alcohol SRD) is observed inconsistently in the laboratory, and this has raised questions about the precise mechanisms and boundary conditions for these effects. Emerging evidence indicates that alcohol SRD may be observed selectively during uncertain but not certain threats. In a final sample of 89 participants, we measured stress response via potentiation of defensive startle reflex in response to threat of shock in blocks with certain (low and high) and uncertain shock intensity. Our alcohol-administration procedure produced blood alcohol concentrations (BACs) across a broad range (0.00%–0.12%) across participants. Increasing BACs were associated with linearly decreasing startle potentiation and self-reported anxiety. This SRD effect was greater during uncertain than certain threat. More broadly, these results suggest that distinct mechanisms are involved in response to threats of uncertain intensity and threats of certain intensity.

Keywords
drug and substance abuse, stress reactions, emotions, startle reflex

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> Imagine that you have arrived early to a restaurant, with the intention to break up with your significant other. You know this conversation will be stressful, but you cannot anticipate how strongly your partner will react. You could be met with any reaction ranging from uncomfortable silence to loud shouting and crying. You order a large glass of wine to steady your nerves in response to this uncertainty.

Will this glass of wine have the desired effect? Drinkers expect alcohol to reduce their negative affective response to stressors (Sher, 1987). Furthermore, both recreational and problem drinkers report that stress reduction is an important motive for their alcohol use (Cooper, 1994; Schroder & Perrine, 2007). However, three decades of research have yet to specify the precise mechanisms and boundary conditions for stress response dampening via alcohol, or *alcohol SRD* (Levenson, Sher, Grossman, Newman, & Newlin, 1980; Sher, 1987; for a review, see Curtin & Lang, 2007). Researchers need to clarify when, how, and for whom alcohol SRD occurs to answer fundamental questions about this popular drug's reinforcing effects and to improve treatments for its excessive use. In addition, answers to these questions promise to advance understanding of the psychological and neurobiological mechanisms involved in the affective response to stressors more generally.

Uncertain Versus Certain Threat

The opening scenario exemplifies anticipation of an uncertain stressful encounter. Stressors vary on several dimensions of threat uncertainty. For example, threats or other stressors can be probabilistically and temporally uncertain. Affective scientists have developed tasks to examine the mechanisms that mediate the impact of uncertainty about threat probability (*if* the threat will occur) and threat onset (*when* the threat will occur) in humans and animal models (Davis, Walker, Miles, &

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Grillon, 2010; Mobbs et al., 2007). Multiple lines of evidence suggest that these uncertain threats can be distinguished from certain threats by the emotional, behavioral, and cognitive-attentional responses they elicit, the time course of these responses, and the neural mechanisms mediating these responses (Davis, 2006).

For instance, uncertain and certain threats produce distinct emotional responses characterized in humans as anxiety in the former case and fear in the latter (Grillon, 2008). Uncertain threats elicit freezing and hypervigilance in animals, whereas certain threats elicit active avoidance, defensive attack, or both (Blanchard & Blanchard, 1989). Imminent, certain threats focus attention on the threat itself, whereas distal, temporally uncertain threats encourage distributed attention to the overall environment (Cornwell, Echiverri, Covington, & Grillon, 2008; Fanselow & Lester, 1988; Mobbs et al., 2007). Response to temporally uncertain threats appears to be sustained, whereas response to certain threats is phasic and time-locked to the threat (Davis et al., 2010). Finally, neuroscience research with rodents has shown that a pathway involving the lateral divisions of the central nucleus of the amygdala and the bed nucleus of the stria terminalis appears to selectively mediate sustained response to temporally uncertain threats, perhaps through sensitivity to corticotrophin-releasing factor and norepinephrine (Walker & Davis, 2008).

Grillon and his colleagues have manipulated uncertainty about if and when threats will occur in humans using their no-shock, predictable-shock, unpredictable-shock (NPU) task (Schmitz & Grillon, 2012). Predictable and unpredictable shock both potentiate the startle reflex, a cross-species physiological index of defensive reflexive responding. Patients with posttraumatic stress and panic disorders exhibit selectively increased startle potentiation during unpredictable but not predictable shock in the NPU task (Grillon et al., 2008; Grillon, Pine, et al., 2009). Medications prescribed to treat anxiety appear to have greater effect on startle potentiation during unpredictable shock than during predictable shock in the NPU task (Grillon, Chavis, Covington, & Pine, 2009).

Most research on alcohol SRD has not included attempts to vary threat uncertainty. However, Moberg and Curtin (2009) demonstrated that a moderate dose of alcohol (approximately four standard drinks over 1 hr in a 180-pound man) selectively reduced startle potentiation during threat of unpredictable but not predictable shock in the NPU task. In two follow-up experiments, Curtin and his colleagues confirmed that greater alcohol SRD during uncertain than during certain threat was observed with more precise, separate manipulations of expectations regarding if (probabilistic uncertainty; Hefner & Curtin, 2012) and when (temporal uncertainty; Hefner, Moberg, Hachiya, & Curtin, 2013) the threat would occur.

If, When, and How Bad?

Initial basic affective science and our laboratory's research on alcohol SRD have focused on uncertainty regarding if and when threats will occur (Davis et al., 2010; Hefner & Curtin, 2012; Hefner et al., 2013; Moberg & Curtin, 2009). It is now time to probe the boundary conditions of uncertainty to better define this construct. In the opening scenario, you are relatively certain about if and when your partner's reaction will occur. The uncertainty is constrained primarily to the severity dimension (i.e., how bad the reaction will be). In the experiment reported here, we followed emerging interest in this understudied dimension of threat uncertainty (Shankman, Robison-Andrew, Nelson, Altman, & Campbell, 2011) to test the novel prediction that alcohol SRD will be more robust when threat severity is uncertain than when it is certain.

Alcohol Dose Response and Uncertain Threat

In the opening scenario, you might expect the amount of wine to influence its effectiveness. In fact, Sher (1987) found that alcohol SRD was consistently observed with intoxicating doses of alcohol. Thus, initial theoretical accounts predicted that alcohol dose would moderate the magnitude of alcohol SRD but did not specify the form of the dose response function (e.g., linear, threshold, or asymptotic). However, only a handful of experiments on alcohol SRD have examined alcohol dose response (Donohue, Curtin, Patrick, & Lang, 2007; Moberg, Weber, & Curtin, 2011; Sher & Walitzer, 1986; Stewart, Finn, & Pihl, 1992). Furthermore, these experiments included no more than three active doses, and therefore did not allow clear specification of the dose response function (but see Moberg et al., 2011). None of these studies compared dose response effects on alcohol SRD during uncertain versus certain threats of any kind.

The Current Study

We manipulated threat uncertainty and severity by exposing participants to blocks of certain low-intensity shock, certain high-intensity shock, and uncertain-intensity shock. We administered various doses of alcohol to manipulate participants' blood alcohol concentrations (BACs) quantitatively across a broad range of ecologically meaningful levels from sobriety to moderately high intoxication (approximately six standard drinks over 1 hr in a 180-pound man). We assessed participants' stress response by measuring the potentiation of their defensive startle reflex during the threats. We tested the following two predictions: First, we expected alcohol SRD to be dose dependent, with increasing SRD (i.e., decreasing

startle potentiation) associated with increasing BAC. Second, we expected alcohol to produce selectively greater SRD during threat of uncertain-intensity shock than during threat of certain-intensity shock. We included two threats of certain intensity to evaluate a competing hypothesis that the magnitude of alcohol SRD varies with the intensity of the stress response rather than the uncertainty of the stressor. We conducted supplemental analyses to examine potential individual difference moderators of alcohol SRD. Finally, we included a measure of self-reported anxiety to index participants' subjective emotional response to the threats of certain and uncertain intensity.

Method

Participants

We recruited 89[1] participants (45 female, 44 male; mean age = 21.7 years, *SD* = 1.2 years) from the university community. All were at least 21 years old, had experience with the highest study dose of alcohol within the past year, and reported no history of alcohol-related problems (CAGE questionnaire; Mayfield, Mcleod, & Hall, 1974), no current use of psychiatric medication, and no medical condition that would contraindicate alcohol consumption. No participants were pregnant (verified by urine sample). Participants were instructed to abstain from alcohol and other drugs for 24 hr and from all food and beverages except water for 4 hr prior to their experimental session. We verified that all participants were sober on arrival via breathalyzer (Alcosensor IV; Intoximeters Inc., St. Louis, MO). We paid participants $10 per hour or class extra-credit points.

Baseline startle assessment

Participants' baseline startle response to acoustic startle probes was assessed in a pretask procedure during which they viewed a series of 12 colored squares presented on a CRT monitor for 5 s each with a variable intertrial interval (ITI; range = 10–20 s). Baseline startle response was included in analyses as a covariate to control for individual differences in startle potentiation (Hefner & Curtin, 2012; Hogle, Kaye, & Curtin, 2010; Moberg et al., 2011). (See the Supplemental Material available online for details on measurement of the startle response in the baseline and main tasks.)

BAC manipulation

Approximately equal numbers of male and female participants were randomly administered each of 12 alcohol doses (placebo and doses with target BACs from 0.01% to 0.11%, in increments of 0.01%). We assigned an additional 6 participants to both the placebo and the 0.11%-dose conditions to increase power. All participants were informed that they would receive a moderately impairing dose of alcohol that should produce a BAC of approximately 0.08%.

The alcoholic beverages consisted of 100-proof vodka (Smirnoff Blue Label), water, and a juice mixer, with the juice accounting for three quarters of the drink volume. We calculated the alcohol dose to produce the target BAC approximately 30 min after beverage consumption (see Curtin & Fairchild, 2003, for details regarding the dosing formula). Participants assigned to the placebo group received a beverage consisting of fruit juice mixed with water poured from a vodka bottle in their presence (participants who received alcohol similarly saw the vodka poured from a vodka bottle in their presence). The total volume of all beverages was matched to the volume of the beverage for the 0.11%-BAC group, with water replacing the equivalent volume of alcohol. Outside of participants' view, all drinks were misted with alcohol, and 2 ml of alcohol was floated on top of the beverages to provide sensory stimulation to support the placebo manipulation. Each participant's beverage was divided into four drinks, each consumed over 10 min, for a total drinking period of 40 min. The experimental session began 15 min after the end of the drinking period. We measured BAC immediately before, at the midpoint of, and immediately after completion of the main task. We used mean achieved BAC (average BAC across the three assessment times) in analyses evaluating alcohol's effects on startle potentiation.

Assessment of subjective shock tolerance

We measured participants' subjective shock tolerance following standardized procedures from our laboratory (e.g., Curtin, Patrick, Lang, Cacioppo, & Birbaumer, 2001; Moberg & Curtin, 2009). Five minutes after the drinking period, participants reported their response to a series of 200-ms electric shocks of increasing intensity. Shocks were administered across the distal phalanges of the index and ring fingers of the left hand. The procedure was stopped once participants reached the maximum level of shock that they could tolerate.

Cued-threat task

The main task was a cued-threat task consisting of eight blocks. In each block, participants viewed a series of five colored square cues that were presented on a CRT monitor for 5 s each and separated by a variable ITI (10–20 s, *M* = 15 s). We measured startle response to acoustic startle probes presented five times per block (three during cues, two during ITIs). There were four block types:

certain low-intensity shock, certain high-intensity shock, uncertain-intensity shock, and no shock. We instructed participants that shocks at the indicated intensity level would be administered 4.8 s after onset of each cue during all shock blocks and that no shocks would be administered during any ITI or at any time in no-shock blocks. We set the intensity levels for the low-shock and high-shock blocks, respectively, to 33% and 100% of each participant's maximum reported subjective shock tolerance. In uncertain-intensity blocks, we instructed participants that shock intensity would vary across cues but would never exceed the intensity of shocks delivered in the high-intensity blocks. In fact, low- and high-intensity shocks were equiprobable, intermixed randomly across cues in uncertain-intensity blocks.

A preblock message on the monitor informed participants of the next block type. A two-character condition abbreviation was presented in the center of each cue to further reinforce condition information: "LO" during low-intensity blocks, "HI" during high-intensity blocks, "??" during uncertain-intensity blocks, and "NS" during no-shock blocks. We used three different block orders, which were counterbalanced across subjects. We scored mean startle potentiation (i.e., increase in startle response to acoustic startle probes during threat blocks relative to no-threat blocks) separately for the three threat types (uncertain intensity vs. high intensity vs. low intensity).

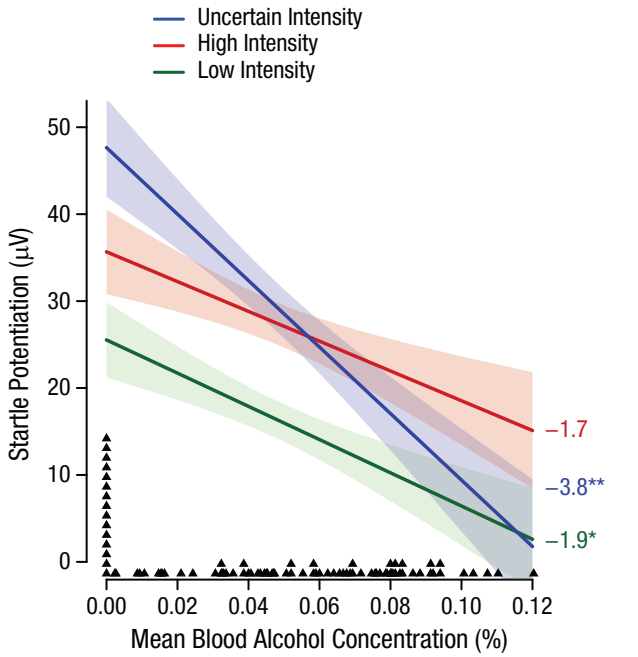

Fig. 1. Startle potentiation as a function of mean blood alcohol concentration (BAC) and threat type. The translucent bands indicate confidence envelopes (±1 *SE*) around the point estimates (dark lines) of mean startle potentiation from the general linear model. The strip plot (triangles) along the *x*-axis shows the observed mean BACs for all participants. The numbers in the right margin are coefficients from the general linear model, showing the simple effect of BAC for each threat type (*$p < .05$; **$p < .001$).

Post-threat-task measures

After the cued-threat task and final BAC assessment, participants rated how anxious they were when they saw each threat cue, using a 5 point rating scale (1 = *not at all anxious*; 5 = *extremely anxious*). They then completed self-report individual difference measures of personality and alcohol use. Finally, participants were debriefed, compensated, and dismissed once reaching a BAC below 0.03%.

Results

We analyzed data with R (R Development Core Team, 2013). The mean BAC for participants who were administered alcohol was 0.058% (*SD* = 0.03%) immediately before the main task, 0.059% (*SD* = 0.03%) in the middle of the task, and 0.059% (*SD* = 0.03%) immediately after the task. The strip plot in Figure 1 shows the mean BAC for all individuals.

Startle potentiation

We analyzed startle potentiation in a general linear model (GLM) with repeated measures for threat type (uncertain vs. high vs. low). Fully interactive between-subjects regressors for mean BAC, baseline startle, gender, and block order were included in the GLM.[2] We report unweighted BAC effects across the baseline-startle, gender, and block-order covariates. (The effects of these covariates and of individual difference moderators related to personality and alcohol use are discussed in the Supplemental Material). To test our predictions, we examined two planned orthogonal contrasts for threat type: (a) startle potentiation in uncertain-intensity blocks versus average startle potentiation across low-intensity and high-intensity blocks and (b) startle potentiation in high-intensity blocks versus startle potentiation in low-intensity blocks. We report raw GLM coefficients (*b*) and partial eta-squared (η_p^2) to document effect sizes.

Mean startle potentiation was significant (nonzero) across threat types at a BAC of 0.00%, $b = 36.2$, $t(65) = 9.10$, $p < .001$, $\eta_p^2 = .56$ (Fig. 1). Startle potentiation was increased significantly during uncertain-intensity threat compared with the average startle potentiation across certain high-intensity and low-intensity threat, $b = 17.1$, $t(65) = 3.69$, $p < .001$, $\eta_p^2 = .17$. In addition, startle potentiation was significantly increased during certain high-intensity threat relative to certain low-intensity threat, $b = 10.1$, $t(65) = 2.04$, $p = .046$, $\eta_p^2 = .06$. Despite differences

across threat type, startle potentiation was significant (nonzero) for each threat type (ps < .001).

As predicted, the overall effect of mean BAC across threat types was significant, such that startle potentiation decreased 2.5 μV for every 0.01% increase in BAC, b = −2.5, $t(65)$ = 3.48, p = .001, η_p^2 = .16. Also as predicted, interaction contrasts indicated that this mean BAC effect was significantly greater during uncertain threat (b = −3.8) than during certain (average of high and low) threat (b = −1.8), b = −2.0, $t(65)$ = 2.44, p = .018, η_p^2 = .08. In contrast, the magnitude of the mean BAC effect was comparable across certain high (b = −1.7) and certain low (b = −1.9) threat, b = 0.2, $t(65)$ = 0.22, p = .825, η_p^2 = .00.

Linearity of the BAC effect on startle potentiation

We assessed the linearity of the BAC effect on startle potentiation in two ways. First, via linear inspection, we confirmed that the patterns of residuals for the BAC effect in component-plus-residual plots were consistent with linear effects during both certain and uncertain threat (Fox, 2008); specifically, the residuals were symmetrically distributed around the BAC regression line for all BACs (Fig. 2). Second, we included regressors for higher-order (i.e., quadratic and cubic) BAC effects in supplemental GLMs. The effects of these higher-order regressors were not significant for either certain-threat contrasts (quadratic: p = .479; cubic: p = .408) or uncertain-threat contrasts (quadratic: p = .233, cubic: p = .484).

Self-reported anxiety in response to cues

We conducted analyses of self-reported anxiety during the cues in a GLM using the same model that we used to analyze startle potentiation. (We report the effects of the covariates from this analysis, as well as correlations between self-reported anxiety and startle potentiation, in the Supplemental Material.) At a BAC of 0.00%, self-reported anxiety was significantly greater during uncertain threat compared with the average anxiety during certain high and certain low threat, b = 0.84, $t(65)$ = 4.65, p < .001, η_p^2 = .25 (Fig. 3). Self-reported anxiety was also greater during certain high threat relative to certain low threat, b = 1.47, $t(65)$ = 7.23, p < .001, η_p^2 = .45.

The overall effect of mean BAC across threat types was significant, such that self-reported anxiety decreased 0.09 units for every 0.01% increase in BAC, b = −0.09, $t(65)$ = 3.06, p = .003, η_p^2 = .13. Interaction contrasts indicated that this mean BAC effect was significantly greater during uncertain threat (b = −0.14) than during certain (average of high and low) threat (b = −0.07), b = −0.07, $t(65)$ = 2.09, p = .041, η_p^2 = .06. In contrast, the magnitude of the mean BAC effect was comparable across certain high (b = −0.06) and certain low (b = −0.08) threat, b = 0.02,

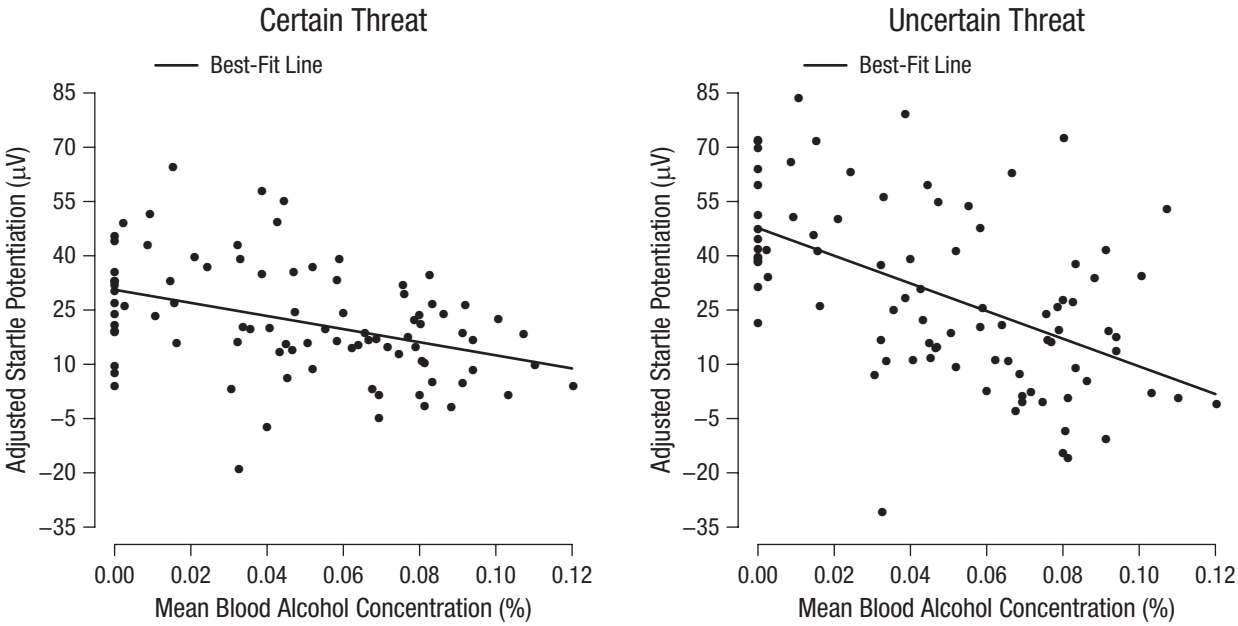

Fig. 2. Component-plus-residual plots for the effect of blood alcohol concentration (BAC) on startle potentiation during certain and uncertain threat. Component-plus-residual plots are used to assess linearity of effects in general linear models (Fox, 2008). Startle potentiation scores in these plots were adjusted to control for all regressors in the models other than BAC.

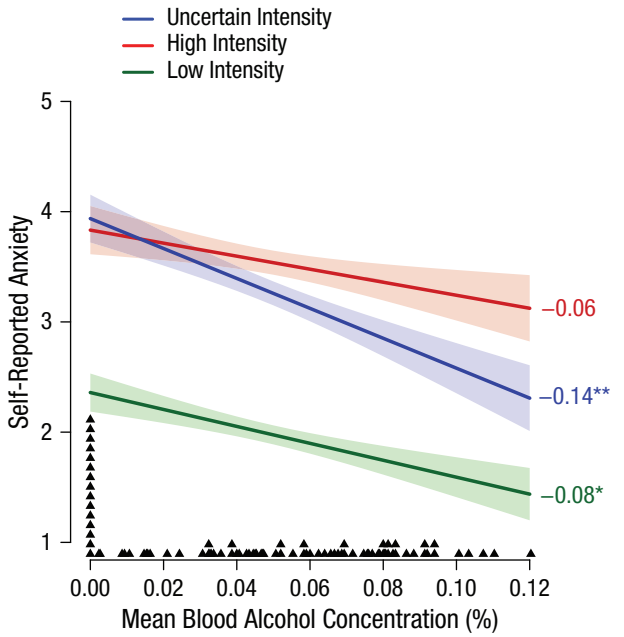

Fig. 3. Self-reported anxiety (1 = *not at all anxious*; 5 = *extremely anxious*) as a function of mean blood alcohol concentration (BAC) and threat type. The translucent colored bands indicate confidence envelopes (±1 *SE*) for point estimates (dark lines) of self-reported anxiety from the general linear model. The strip plot (triangles) along the *x*-axis shows the observed mean BACs for all participants. The numbers in the right margin are coefficients from the general linear model, showing the simple effect of BAC for each threat type (*$p < .05$; **$p < .001$).

$t(65) = 0.49$, $p = .629$, $\eta_p^2 = .00$. In sum, the pattern of results for self-reported anxiety matched closely that for startle potentiation.

Discussion

This experiment provides clear evidence that the magnitude of alcohol SRD is greater when there is uncertainty about the severity of the upcoming threat than when the threat is well defined. This finding emerged in a task in which conditions were carefully matched for threat probability and timing (100% cue-shock pairings at 4.8 s after cue onset), amount and density of aversive stimulation (10 shocks with a 15-s mean ITI in each condition), and perceptual demands for processing threat cues (all cues were simple colored squares). The careful matching of these threat characteristics increases confidence that the differences in alcohol SRD across conditions resulted from differences in uncertainty about the intensity of the threat.

Uncertain threat intensity elicited a more robust defensive response than did comparably intense (i.e., high and low) certain threats. This finding appears to confirm the proverb, "better the devil you know than the devil you don't." It also raises the possibility that the increased alcohol SRD observed during uncertain threat resulted from the increased defensive responding in that condition rather than uncertainty per se (e.g., Moberg et al., 2011). However, this appears unlikely given that we observed comparable alcohol SRD during certain threats of high and low intensity, even though certain high threat elicited significantly greater startle potentiation than certain low threat. This significant moderation of alcohol SRD by threat uncertainty (uncertain vs. certain) but not threat intensity (certain high vs. certain low) strongly implicates threat uncertainty as the necessary characteristic for increased alcohol SRD. In other words, intoxicated drinkers may be less anxious about "the devil you don't know" than about "the devil you know," which in turn may lead to increases in certain types of risk taking when people drink (Corte & Sommers, 2005).

The current results join previous research that demonstrated an increase in alcohol SRD when participants were uncertain if and when shocks would occur (Hefner & Curtin, 2012; Hefner et al., 2013; Moberg & Curtin, 2009). Our study thus provides an important conceptual replication of these prior findings at a time when psychological science has been criticized for its inattention to the replicability of research findings (see, e.g., Pashler & Wagenmakers, 2012, a special section on replication in *Perspectives on Psychological Science*). More important, uncertainty about the nature of a threat, including its severity or intensity, appears to be qualitatively different from uncertainty about the occurrence of that threat. However, the two types of uncertainty have comparable impact on the magnitude of alcohol SRD. This suggests that threat uncertainty is a broadly relevant threat characteristic regardless of the source of the uncertainty and begins to implicate higher-level cognitive processes, including appraisal and attention that may be involved in response to uncertain threats generally (Curtin et al., 2001; Sayette, 1993). Direct measurement of these cognitive processes with varied methods (e.g., event-related potentials, startle prepulse inhibition, self-report of subjective risk and controllability) will be an important next step on the path to specifying mechanisms of action.

Our confidence in the conclusion that the magnitude of alcohol SRD is greater during uncertain than during certain threat is increased by our supplemental analyses of self-reported anxiety. This program of research on alcohol SRD during uncertain threat builds on basic affective neuroscience research with rodents (Davis et al., 2010) that relies on startle potentiation as the primary dependent measure of threat response (Hefner & Curtin, 2012; Hefner et al., 2013; Moberg & Curtin, 2009). This study is the first to include explicit measurement of self-reported anxiety during uncertain and certain threat. The finding of comparable BAC effects across both physiological and self-report measures in the same experiment

eliminates many alternative methodological or measurement explanations of the pattern of results. It also generalizes the alcohol SRD effect to the domain of subjective emotional experience and suggests that participants are aware to some degree of the greater alcohol SRD reinforcement available during uncertain threat.

Early theory and research on alcohol SRD identified alcohol dose as a potential important moderator of SRD effects, regardless of whether the threats were certain or uncertain. The influence of dose on SRD effects also has important implications for understanding how alcohol SRD will influence real-world drinking. Unfortunately, the majority of SRD research has used only a single, moderate dose of alcohol. We used a novel quantitative manipulation of BAC to probe the alcohol dose response function across a broader range of BACs. We established that alcohol SRD is linear during both certain and uncertain threat up to a moderately high BAC (0.12%). This suggests that alcohol use is negatively reinforced even from the first drink (i.e., at very low BACs) within a drinking occasion, which may indicate that preliminary, modest reinforcing effects are available to most drinkers. However, our results indicate that the magnitude of reinforcement from alcohol SRD may increase with increasing BACs. Thus, higher BACs associated with heavier, binge-drinking episodes may be more strongly reinforced despite the longer-term negative consequences associated with heavy drinking.

Our supplemental analyses of individual differences (see the Supplemental Material) indicated that the magnitude of alcohol SRD during uncertain threat was reduced among individuals who reported that they typically binge-drink alcohol outside the laboratory. Additional developmental and longitudinal research is necessary to determine if this individual difference moderator reflects a premorbid etiological risk factor for alcoholism (Schuckit & Smith, 2006; Schuckit et al., 2009) or the development of tolerance following frequent heavy use. Regardless, these drinkers may need to pursue particularly heavy, hazardous levels of alcohol to obtain rewarding alcohol SRD effects.

Alcohol SRD during uncertain threat may contribute meaningfully to the putative reward that drinkers receive from alcohol. The moderating roles of alcohol dose and binge use patterns suggest that this presumed reinforcement mechanism may encourage heavy, high-BAC, hazardous use. The alcohol SRD effects were manifest in both drinkers' defensive physiology and their subjective emotional response to uncertain threats. A next step would be to contrast these effects of alcohol with those of other relevant drugs (e.g., anxiolytics, sedatives; Grillon et al., 2006), The current findings should be directly linked to alcohol use itself via simultaneous measurement of stress and ad lib drinking in the laboratory and real world.

In real-world contexts (e.g., our opening scenario), both certain and uncertain threats are often appraised to some degree prior to drinking. Sayette (1993) has suggested that the timing of drinking relative to threat appraisal may have an important moderating effect on the magnitude of alcohol SRD. This thesis was outside the scope of our current experiment. However, future research should examine the impact of these temporal factors on alcohol SRD in the face of uncertain threats.

Compensatory neuroadaptation in the response to uncertain threats following chronic alcohol or other drug use and early chronic stress have been implicated in addiction (Koob & Volkow, 2010). In other recent research, we have provided preliminary evidence of neuroadaptation in response to uncertain threat among smokers (Hogle et al., 2010). Confirmation of a similar effect among alcoholics would implicate this mechanism in the etiology of alcoholism.

More broadly, these results join an emerging body of evidence from affective neuroscience about response to uncertain threat. Research with rodents suggests that distinct neural mechanisms are involved in response to uncertain versus certain threats (Davis et al., 2010). Clinical research implicates exaggerated response to uncertain but not certain threats in the etiology of anxiety disorders in humans (Grillon et al., 2008; Grillon, Pine, et al., 2009). The use of alcohol in the current experiment can be viewed as a coarse pharmacological manipulation that allowed us to dissociate the putatively distinct mechanisms underlying uncertain versus certain threat in humans (see Hefner et al., 2013, for additional discussion). Future neuropharmacological challenge with corticotrophin-releasing factor and norepinephrine agonists and antagonists in humans can more precisely probe these neural mechanisms that have been implicated in the response to uncertain threats (Davis et al., 2010).

Author Contributions

J. J. Curtin and D. E. Bradford developed the study concept and design. Data collection was performed by D. E. Bradford and B. L. Shapiro. D. E. Bradford performed the data analysis and interpretation under J. J. Curtin's supervision. D. E. Bradford drafted the manuscript, and J. J. Curtin provided critical revisions. All authors approved the final manuscript.

Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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Supplemental Material

Additional supporting information may be found at http://pss.sagepub.com/content/by/supplemental-data

Notes

1. Four additional participants were regression outliers (i.e., studentized residual with Bonferroni-corrected $p < .05$) in preliminary analyses of startle potentiation. We removed these participants from the sample.
2. BAC was multiplied by 100 to increase interpretability of its GLM coefficients, such that a 1-unit increase represented a 0.01% increase in BAC. Baseline startle was mean-centered. Unit-weighted, centered orthogonal regressors were included for gender (male = 0.5, female = −0.5) and block order (Helmert coding).

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