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Alcohol Selectively Reduces Anxiety but Not Fear: Startle Response During Unpredictable Versus Predictable Threat

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Recent theory and empirical research have suggested that fear and anxiety are distinct processes with separable neurobiological substrates. Furthermore, a laboratory procedure has been developed to manipulate fear versus anxiety independently via administration of predictable or unpredictable electric shock, respectively. Benzodiazepines appear to selectively reduce anxiety but not fear in this procedure. The primary aim of this experiment was to determine if alcohol produced a similar selective reduction in anxiety. Intoxicated (target blood alcohol concentration of .08%) and nonintoxicated participants viewed a series of colored squares separated by variable intertrial intervals (ITIs) in 3 conditions. In the predictable shock condition, shocks were administered contingently during every square. In the unpredictable shock condition, shocks were administered noncontingently during both squares and ITIs. In the no-shock condition, no shocks were administered at any time. Alcohol significantly reduced startle potentiation during cues signaling unpredictable but not predictable shock, consistent with the thesis that alcohol selectively reduces anxiety but not fear. In addition, alcohol's effect on startle potentiation during unpredictable shock was mediated by vigilance. This anxiolytic effect may clarify the nature of alcohol's reinforcing effects in social and problem drinkers.

Keywords: alcohol, startle response, anxiety, fear, stress response dampening

The stress-reducing properties of alcohol are well-known and occasionally pursued by all drinkers. However, individuals who drink primarily for stress reduction (vs. other motives, e.g., increasing positive emotions or social or celebratory motives) are at increased risk for developing alcohol use disorders (Cooper, Frone, Russell, & Mudar, 1995; Schroder & Perrine, 2007). Alcohol use disorders are also highly comorbid with certain anxiety disorders (Grant et al., 2004; Kushner, Sher, & Beitman, 1990). Moreover, stress exposure is a powerful precipitant for relapse to alcohol use among alcohol dependent users (Brown, Vik, Patterson, Grant, & Schuckit, 1995). Thus, identifying the mechanism(s) underlying alcohol's effect on stress is important if one is to better understand both social and problematic alcohol use. Recent basic and applied research with both animals (Davis, 1989; Sullivan et al., 2004; Walker & Davis, 1997a) and humans (Curtin, Lang, Patrick, Cacioppo, & Birbaumer, 2001; Grillon et al., 2006; Hogle & Curtin, 2006; Piper & Curtin, 2006) has synthesized precise laboratory manipulations of stress with sensitive measurement procedures to parse the stress response into its constituent components. In particular, this research has suggested that fear and anxiety arise from dissociable neurobiological substrates that can be disentangled by careful manipulation of stimulus contingencies. Of particular importance, recent research with these methods has demonstrated selective effects of anxiolytic drugs (i.e., benzodiazepines) on anxiety but not fear (Grillon et al., 2006). In this article, we report on the first experiment to use similar methods and measurement procedures to test if alcohol has comparable selective effects on anxiety in humans.

Alcohol Use and Stress

Few would debate the important role that stress plays in the patterns of alcohol use among both social and problem drinkers. *Stress response dampening* is one of the most common expectations that people, social and problem drinkers alike, report regarding the acute effects of alcohol use (Goldman, Brown, & Christiansen, 1987). Even children who have yet to use alcohol themselves expect stress relief from alcohol as a result of observing older drinkers (Christiansen, Goldman, & Inn, 1982). Not surprisingly, given these robust outcome expectancies associated with alcohol use, coping with stress is one of the primary motives that individuals report for their use of alcohol as well (Cooper et al., 1995).

Support for an important role of the alcohol use–stress relationship in *problem drinking* is also well established. For example, drinkers who report emotion regulation broadly as a primary motive for their alcohol use (i.e., drinking either to increase positive emotion or to decrease stress) display increased alcohol use. However, drinking with the primary intention of decreasing stress has unique connections to alcohol problems (Cooper et al., 1995; Schroder & Perrine, 2007). The

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high rates of comorbidity between alcohol use disorders and a subset of anxiety disorders (e.g., generalized anxiety disorder, posttraumatic stress disorder) also highlight the risk for clinically significant problems associated with stress-related drinking (Creamer, Burgess, & McFarlane, 2001; Grant et al., 2004; Kessler, Sonnega, Bromet, Hughes, & Nelson, 1995). In addition, stressors reliably reinstate alcohol and other drug use among abstinent alcohol or drug-dependent humans and animals (Brown et al., 1995; Lê et al., 1998; Shaham, Erb, & Stewart, 2000; Shiffman, 1989).

Research on alcohol–emotion interactions has been dominated by the stress-response-dampening model. This model proposes that alcohol affects emotional response to aversive events broadly, across situations and stimuli (Sher, 1987). Using a variety of eliciting stimuli and measurement techniques, these studies have had inconsistent results (Curtin & Lang, 2007; Greeley & Oei, 1999). Over the past 15 years, several more complex models that focus on attention and appraisal mechanisms have been developed (Sayette, 1993; Steele & Josephs, 1990). Although these newer models appear promising, more precise tools for eliciting and measuring emotional response are needed to clarify the mechanisms involved.

Fear Versus Anxiety: Methods, Mechanisms, and Measures

The startle reflex (Davis, 1989) provides an attractive, noninvasive methodology for examining the effects of drugs on affective response in animals and humans. The startle response to an abrupt, intense stimulus (e.g., loud noise) increases above baseline when elicited in the presence of a cue that has been paired contingently with an aversive unconditioned stimulus (e.g., electric shock; Curtin et al., 2001; Grillon, Ameli, Woods, Merikangas, & Davis, 1991; Grillon & Davis, 1997). This effect is referred to as *fear-potentiated startle*, and substantial research with animals has confirmed that projections from the central nucleus of the amygdala (CeA) to the primary startle circuit are responsible for this startle potentiation (for a review, see Davis, 1992).

More recently, research has identified other manipulations that also potentiate the startle reflex in animals and humans. For example, corticotropin-releasing factor (CRF; a stress hormone) has been observed to potentiate startle when administered to rats (Liang et al., 1992; Swerdlow, Geyer, Vale, & Koob, 1986). Walker and Davis (1997a) demonstrated that exposure to bright light increases startle above baseline in rats, a nocturnal species. Similarly, in humans, exposure to darkness (Grillon, Duncko, Covington, Kopperman, & Kling, 2007; Grillon, Pellowski, Merikangas, & Davis, 1997b) and unpredictable electric shock (Grillon, Baas, Lissek, Smith, & Milstein, 2004) also increase startle response magnitude.

There are important differences in the nature of the response produced by CRF, noncontingent (unpredictable) shocks, and light–darkness manipulations versus cue-contingent (predictable) electric shock administration. Specifically, cue-contingent administration of electric shock produces phasic fear-potentiated startle only during the punctate cues that predict imminent shock administration. In contrast, CRF, unpredictable shock, and light–darkness manipulations produce more sustained potentiation of the startle reflex. Moreover, Davis and colleagues have demonstrated elegant double dissociations in the neural substrates underlying startle potentiation across these two classes of manipulations in animals (Walker & Davis, 1997b, 2008; Walker, Toufexis, & Davis, 2003). Specifically, lesions of the CeA abolished fear-potentiated startle to predictable shocks but not potentiation of startle to CRF and bright light exposure. In contrast, lesions of the bed nucleus of the stria terminalis (BNST) abolished startle potentiation to CRF and bright light exposure but not fear-potentiated startle to cues predicting shock. Similar involvement of the BNST has been confirmed during unpredictable shock administration (Walker & Davis, 2008).

Given the nature of the eliciting stimuli and the time course of the response across these two categories of manipulations, researchers have offered these manipulations as laboratory models of fear versus anxiety (Davis, 2006; Grillon et al., 2006). Specifically, contingent cue–electric shock pairings involve simple, punctate stimuli that are highly predictive of imminent aversive stimulation (electric shock administration in the next few seconds). The phasic fear potentiation of startle, limited specifically to the cue period in response to this manipulation, is proposed to model the fear response. In contrast, noncontingent (unpredictable) shock, light–darkness, and CRF involve more complex, diffuse contextual cues that are more static or of longer duration and provide little information about when aversive stimulation will occur. The sustained potentiation of startle response for longer periods of time in response to these latter manipulations is proposed to model anxiety.

Alcohol and Other Drug Effects on Fear Versus Anxiety

Recent research has tested for differential effects of various benzodiazepines on fear versus anxiety in humans using these methods. In a series of studies, Baas et al. (2002) found that diazepam blocked the potentiation of startle induced by darkness but did not affect startle potentiation to a specific threat cue. This work suggests that explicit-cue fear conditioning is insensitive to the effects of diazepam. Grillon et al. (2006) manipulated shock predictability to elicit fear versus anxiety. Specifically, by pairing a distinct cue with shock and instructing participants that shocks could only occur during cue presentation, they were able to evoke fear to that cue. Alternatively, during periods in which shock administration was unpredictable, they generated a sense of anxiety in participants. The authors found that benzodiazepines selectively reduced startle potentiation during unpredictable shock blocks but not during blocks where shock was specifically paired with a distinct threat cue.

Melia, Ryabinin, Corodimas, Wilson, and LeDoux (1996) provided preliminary data to support the predicted dissociation between alcohol's effect on fear versus anxiety in rodents. Specifically, they examined alcohol's effect in rats on acquisition of phasic fear response (measured by behavioral freezing) to tones contingently paired with electric shock versus sustained fear response when placed in the training cage context without tone presentation. In this study, alcohol had minimal effect on freezing during tone presentation. In contrast, sizable dose-dependent effects of alcohol on freezing were observed

when the rats were placed in the cage (where shock had been administered) but without explicit tone presentation. These results dovetail nicely with the report of selective effects of benzodiazepines on anxiety in humans reported above.

Curtin and colleagues have used fear-potentiated startle in humans to examine alcohol's effect on fear during simple, punctate cues that predict electric shock (Curtin et al., 2001; Curtin, Lang, Patrick, & Stritzke, 1998). In both studies, alcohol did not reduce fear-potentiated startle when these simple cue were the focus of attention.[1] To our knowledge, no research has synthesized these lines of research to examine specific dissociations between the effects of alcohol on fear versus anxiety in humans.

The Current Study

On the basis of this brief review, we hypothesized that a moderate dose of alcohol would selectively reduce anxiety but not fear in human participants. To test this thesis, we used a variant of the methods developed by Grillon et al. (2006) to precisely manipulate fear versus anxiety (via the administration of predictable vs. unpredictable electric shock, respectively) and measured eyeblink startle response potentiation to index affective response. Predictable shock was expected to produce brief, phasic potentiation of the startle response only during the cues that predicted electric shock administration, consistent with the elicitation of a punctate fear response to these cues that indicated high probability of imminent threat. In contrast, unpredictable shock was expected to produce a sustained potentiation of the startle response across both cues and intertrial intervals (ITIs), consistent with the elicitation of a more sustained anxiety response in these blocks where clear information about threat probability and imminence was not provided. We predicted that alcohol would selectively reduce startle potentiation during unpredictable but not predictable shock blocks.

Method

Participants

Sixty-four participants (32 women) were recruited from the community via online advertisements. Preliminary study eligibility was assessed during a phone screening session. Participants were required to be between 21–35 years of age and to report recent experience with the dose of alcohol to be administered in the study. Participants were excluded if they reported a history of alcohol-related problems or a medical condition for which alcohol use was contraindicated. Participants who met these criteria were scheduled for an experimental session and told to abstain from alcohol use for 24 hr and all food and beverages other than water for 4 hr prior to their experimental session. Participants were compensated $10/hour for their time. Descriptive information on participants' age, gender, drinking habits, and alcohol-related problems is provided in Table 1.

General Procedure

Consent and screening. On arrival at the lab, participants provided proof of age and signed a consent form approved by the institutional review board. All participants also completed a medical screening questionnaire to verify their report from the phone screening. Female participants were administered an in-stream urine pregnancy test, with a negative result required for participation. A preexperiment blood alcohol concentration (BAC) of 0.00% was verified via breathalyzer. Participants were first informed about the electric shock procedure during the consent procedure and were offered an opportunity to ask questions about it at this time. No participants withdrew from the experiment at this or any other point during the study.

Pretask startle reactivity assessment. Prior to consuming study beverages, participants completed a procedure to assess their overall startle response magnitude. This pretask startle reactivity was used as a covariate in the main analyses to reduce the impact of individual differences in startle response magnitude (e.g., Miller & Chapman, 2001). In this pretask assessment, participants viewed a series of eight colored squares presented on a computer monitor. Each square was presented for 6 s with a variable ITI (range = 5 s–12 s). Mean overall startle reactivity was based on six startle-eliciting noise probes presented during cues and ITI periods (see *Eyeblink Startle Response Measurement* section below).

Beverage manipulation. Equal numbers of male and female participants were randomly assigned to the alcohol and placebo beverage groups. All participants, regardless of beverage group assignment, were informed that they had been assigned to the alcohol group and would receive a moderately impairing dose of alcohol equivalent to 2–3 drinks in 1 hr for a 160-lb man. Participants assigned to the alcohol group received a beverage consisting of fruit juice mixed with 100-proof vodka (Smirnoff Blue Label) in a 3:1 juice-to-vodka ratio designed to produce a peak BAC of .08% approximately 30 min after consumption of the beverage. Participants assigned to the placebo group received a volume-matched beverage consisting of fruit juice mixed with water poured from a vodka bottle in their presence (see Curtin & Fairchild, 2003, for a description of the dosing formula and placebo-related procedures). The total beverage was evenly divided into two drinks, each consumed in 15 min, for a total drinking period of 30 min. The experimental session began after a 15-min postdrinking absorption period. Participants' BACs were measured at two points during the experiment: (a) just prior to the start of the main procedure and (b) immediately after the completion of the main procedure.

Shock sensitivity assessment. To control for individual differences in shock sensitivity, we calibrated the intensity of shocks received during the main procedure to each participant's individual tolerance threshold. This assessment was performed after completion of the drinking period to prevent beverage group differences in shock tolerance that might occur as a result of alcohol's possible analgesic effects.

Main procedure. The main procedure was a modified version of a task developed by Grillon et al. (2006) to manipulate

[1] These studies did provide support for a reduction in fear-potentiated startle in a divided attention condition that focused attention away from the threat cues. These observations are consistent with predictions from the attention allocation model. However, it may be that divided attention or distraction alter the nature of the emotional response from fear to something more like anxiety. We return to this idea in the discussion.

Table 1
Means and Standard Deviations for Individual Differences in Self-Reported Drinking Variables

	Placebo		Alcohol	
Measure	*M*	*SD*	*M*	*SD*
Age (years)	23.8	2.6	23.0	2.2
Gender				
Female	50% (n = 16)		50% (n = 16)	
Male	50% (n = 16)		50% (n = 16)	
Current alcohol use or problems				
Frequency (occasions/week)	2.9	3.0	2.6	1.7
Quantity (drinks/occasion)	4.0	2.9	3.8	2.1
Alcohol problems	4.9	2.0	4.5	2.0

Note. Nondemographic data for 1 male placebo participant are missing. Alcohol problems are measured with the Young Adult Alcohol Problems Scale (Hurlbut & Sher, 1992).

fear versus anxiety in the laboratory. Participants were instructed that they would complete seven blocks of trials. In each block, participants viewed a series of five colored square cues presented for 6 s each and separated by a variable ITI (range = 19–23s). These cues were presented in one of three block types: unpredictable shock blocks (U), predictable shock blocks (P), and no-shock blocks (N). Participants completed two blocks of unpredictable shocks, two blocks of predictable shocks, and three blocks of no shocks in one of two between-subject block orders: UNPNPNU or PNUNUNP. A message was presented on the monitor to indicate the onset of each block type. In addition, text indicating the block type remained on the screen in the upper left corner throughout the block and the color of the square cues varied across the three block types. Block duration was 140 s per block and the entire procedure required approximately 17 min to complete.

In unpredictable shock blocks, participants were instructed that electric shocks could be administered at any point during the block, both during the cues and in the ITI. A total of 5 shocks were administered across the two unpredictable shock blocks (2 during the cues and 3 during the ITI). In predictable shock blocks, participants were instructed that electric shocks would be administered only during the cues and that no shocks would ever be administered during the ITI. Five electric shocks were administered in each predictable shock block (i.e., during every cue; 10 total shocks) at 5.5 s post–cue onset. In no-shock blocks, participants were instructed that no shocks would be administered either during the cues or in the ITIs. The no-shock block was included as a nonaversive control condition from which to calculate startle potentiation during cues in predictable and unpredictable shock blocks.

Individual difference measures, debriefing, and release. After completing the main procedure, all participants answered two questions to assess the success of our placebo. First, they estimated the content of their total beverage in terms of standard alcoholic drinks and reported their level of intoxication on a 5-point Likert-type scale (anchors were 1 = *not at all intoxicated* and 5 = *extremely intoxicated*). After responding to these placebo check questions, all participants provided information on their drinking history (current frequency and quantity of alcohol use) and problems (Young Adult Alcohol Problems Screening Test; Hurlbut & Sher, 1992). After this, participants were debriefed and those in the placebo condition were paid and dismissed. Participants who had received alcohol remained at the study site until their BAC reached .02% or lower, at which point they were paid and dismissed.

Eyeblink Startle Response Measurement

Electromyographic activity in the orbicularis oculi muscle was sampled at 2000 Hz with a bandpass filter (30–500 Hz) from electrodes placed under the right eye according to published guidelines (Van Boxtel, Boelhouwer, & Bos, 1998). Eyeblink startle response to startle-eliciting noise probes (50 ms of 102-dB white noise with near instantaneous rise time) was measured. Noise probes were presented at 5 s post-onset of square cues and either 13 s or 15 s post–cue offset during the ITIs. A minimum of 13 s separated each startle probe from any preceding startle eliciting events (i.e., another startle probe, electric shock). A total of 42 noise probes were presented across unpredictable (6 probes during cue, 6 during ITI), predictable (6 during cue, 6 during ITI), and no-shock blocks (9 during cue, 9 during ITI). Offline processing of eyeblink startle magnitude included epoching (−50 to 250 ms surrounding noise probe), smoothing (signal rectification followed by a 30-Hz low-pass filter), and baseline correction. Eyeblink startle magnitude was scored as the peak response between 20 and 120 ms post–probe onset.

Results

Manipulation Checks

BAC. The mean BAC of participants in the alcohol group was .071% (*SD* = .016%) immediately prior to the start of the main procedure and .076% (*SD* = .010%) immediately post-procedure. Mean peak BAC (i.e., highest BAC across the two measurements) was .079% (*SD* = .012%).

Placebo manipulation. To evaluate our placebo manipulation, we compared the alcohol and placebo groups on two placebo manipulation check questions that were completed at

the conclusion of the experiment.[2] Participants in the alcohol group reported that their beverage contained significantly more alcohol (M = 3.5 drinks, SD = 1.3, range = 0–5 drinks) than did placebo participants (M = 1.9 drinks, SD = 1.0, range = 2–6 drinks), $t(62) = 5.56$, $p < .001$. However, perceived alcohol content was significantly above 0 in both beverage groups (ps < .001 for one sample t test in each beverage group). Participants in the alcohol group also reported that they were significantly more intoxicated (M = 3.0, SD = 0.6, range = 2–4) than did placebo participants (M = 1.7, SD = 0.6, range = 1–3), $t(62) = 8.83$, $p < .001$. Nonetheless, perceived level of intoxication was significantly elevated above 0 in both beverage groups (ps < .001 for one sample t test in each beverage group).

Beverage Group Effects on Startle Response: Unpredictable Versus Predictable Shock

To test for predicted selective effects of alcohol during unpredictable versus predictable shock cues, we examined startle response in a general linear model (GLM) with beverage group (alcohol vs. placebo) as a categorical between-subject factor and block type (unpredictable shock vs. predictable shock vs. no shock) and cue (cue vs. ITI) as within-subject factors. Pretask startle reactivity (mean centered) was included as a quantitative covariate. See Table 2 for startle response means (and standard deviations) across beverage group, block type, and cue. Multivariate statistics are reported for all effects involving block type because the data did not meet the sphericity assumption necessary for univariate tests. Partial eta squared indices of effect size are reported for all significant effects. Raw score regression coefficient (B) effect size estimates from the GLM and regression analyses are also reported for significant 1degree of freedom effects.[3]

A significant main effect of beverage group was observed, $F(1, 61) = 62.57$, $p < .001$, $\eta_p^2 = .51$, $B = -96.6$, indicating that alcohol reduced overall startle response consistent with the well-replicated suppressive effect of alcohol on auditory processing and reflexive responding. A significant effect of the between-subject pretask startle reactivity covariate was also detected, $F(1, 61) = 165.38$, $p < .001$, $\eta_p^2 = .73$, $B = 79.1$, confirming the expected strong positive relationship between pretask and main session startle response that justified its inclusion as a covariate in these analyses.

As expected, a significant Block Type × Cue interaction was observed, indicating that the cue effects differed significantly across block types, $F(2, 60) = 34.05$, $p < .001$, $\eta_p^2 = .53$. More important, the predicted Beverage Group × Block Type × Cue interaction was significant, $F(2, 60) = 4.60$, $p = .014$, $\eta_p^2 = .13$, indicating that the pattern of cue effects across blocks was moderated by beverage group. This three-way interaction was decomposed into four separate simple interaction contrast analyses to clarify the response to predictable and unpredictable cues and the moderating effect of beverage group on response to these cues. Pretask startle reactivity was retained as a covariate in all follow-up analyses.

Predictable shock. A Beverage Group × Predictable Shock Cue Versus No-Shock Cue simple effect analysis was conducted to test for alcohol's effect on startle potentiation to predictable shock cues. Startle potentiation to predictable shock cues is best referenced to no-shock cues because the no-shock cues provide an important control for the attentional (visual) foreground across the contrast (i.e., both conditions involve visual cues). Figure 1A displays startle response during predictable shock cues (gray bars) and no-shock cues (white bars). Predictable shock cue versus no-shock cue difference scores (i.e., an index startle potentiation to predictable cues) are displayed with hatched bars. The predictable

Table 2
Means and Standard Deviations for Startle Response by Beverage Group, Block Type, and Cue

	Placebo group		Alcohol group	
Block type	*M*	*SD*	*M*	*SD*
No shock				
Cue	130.7	49.1	50.5	47.4
ITI	160.7	52.3	56.4	50.4
Predictable shock				
Cue	196.9	51.9	112.1	70.8
ITI	168.0	50.4	67.3	63.3
Unpredictable shock				
Cue	202.8	57.0	96.9	55.5
ITI	201.1	51.0	97.6	54.7

Note. Startle response means and standard deviations are covariate adjusted on the basis of pretask startle response reactivity. ITI = intertrial interval.

[2] The decision to use a placebo, as opposed to a true no-alcohol comparison group, was a reasoned one. First, as noted by Greeley and Oei (1999) in their review of the preceding decade of alcohol and stress response research, placebo effects are rarely observed in this area. They further concluded that the majority of stress-response-dampening effects, when present, appear to have a clearly pharmacological basis. Moreover, correlational analyses in the current study failed to detect any significant relationship between our placebo manipulation check questions and either overall startle response or startle potentiation associated with either predictable or unpredictable electric shock. Even though placebo effects are very unlikely for the reasons provided above, we believe that attempting to control for alcohol consumption expectancy as best possible (via use of a placebo comparison group) represents the most rigorous method to establish a pharmacological effect of alcohol. It is clear that participants in the alcohol group believed that they had consumed alcohol. Therefore, to allow us to unambiguously conclude that differences between beverage groups result from pharmacological effects of alcohol, it is important that the members of the comparison group also believed that they had consumed alcohol. Thus, possible subtle effects resulting from this belief (i.e., a reduction in stress on the basis of the belief that alcohol should reduce stress or, conversely, any compensatory response associated with attempt to combat the expected effects of alcohol) are held constant across our beverage groups, to the best of our ability. As indicated by manipulation check analyses, we were successful in establishing an expectation of alcohol consumption and related intoxication among participants in both the alcohol and the placebo groups. However, as is typical with these manipulations, we were not entirely successful in matching the level of expectancy across the beverage groups.

[3] All effects were mean centered such that the intercept, when reported, indicates the overall unweighted dependent variable mean. Dichotomous contrasts were unit weighted such that B can be interpreted as the mean difference between the two levels of the contrast (i.e., Level 1 M − Level 2 M). Quantitative effects were standardized such that Bs can be interpreted as the change in the dependent variable associated with a 1 standard deviation increase on the quantitative effect.

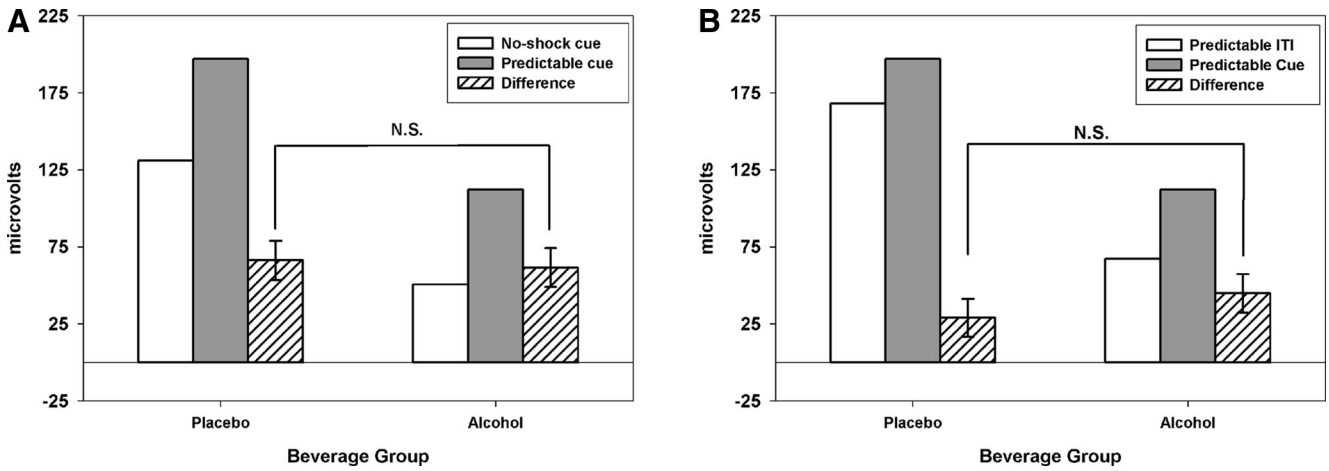

Figure 1. Startle response and startle potentiation during predictable shock cues. A: Raw startle response is displayed for predictable shock (gray) and no-shock (white) cues by beverage group. Startle potentiation difference scores (predictable shock cue – no-shock cue) are displayed (hatched) with standard errors for the beverage group effect. Predictable shock cues produced significant startle potentiation relative to no-shock cues (difference > 0; $p < .001$). The nonsignificant beverage group effect on startle potentiation indicates that alcohol does not reduce startle potentiation to predictable shock cues relative to no-shock cues. For all figures, the beverage group effect on startle potentiation difference scores is statistically equivalent to the Beverage Group $\times$ Cue Type interaction for raw startle response. B: Raw startle response is displayed for predictable shock cues (gray) and predictable shock intertrial intervals (ITIs; white) by beverage group. Startle potentiation difference scores (predictable cue – predictable ITI) are displayed (hatched) with standard errors for the beverage group effect. Predictable shock cues produced significant startle potentiation relative to the predictable shock ITI period (difference > 0; $p < .001$). The nonsignificant beverage group effect on startle potentiation indicates that alcohol does not reduce startle potentiation to predictable shock cues relative to the ITI period in the same predictable blocks.

shock cue versus no-shock cue contrast was significant, $F(1, 61) = 102.46$, $p < .001$, $\eta_p^2 = .63$, $B = 63.9$, confirming that startle response was potentiated during cues that were associated with predictable administration of electric shock. Beverage group did not significantly moderate this contrast, $F(1, 61) = 0.13$, $p = .716$, $\eta_p^2 = .00$, $B = -4.6$. In other words, alcohol did not reduce startle potentiation during predictable shock cues (vs. no-shock cues).

A Beverage Group $\times$ Predicable Shock Cue Versus Predicable Shock ITI analysis was also conducted. The predictable shock cue versus predictable shock ITI contrast provides an alternative method to index startle response potentiation to predictable cues. See Figure 1B for startle response during predictable shock cue and ITI in predictable shock blocks. The predictable shock cue versus ITI contrast difference scores are also displayed. The predictable shock cue versus ITI contrast was significant, $F(1, 61) = 35.36$, $p < .001$, $\eta_p^2 = .37$, $B = 36.8$. This confirms that predictable shock administration produced a phasic potentiation of startle response only during the cue (but not ITI) period in predictable shock blocks. As above, beverage group did not moderate this contrast, $F(1, 61) = 1.64$, $p = .206$, $\eta_p^2 = .03$, $B = 15.9$.

These two analyses confirm the following:

1. Startle response is potentiated during cues that are predictably paired with electric shock relative to both no-shock cues and the ITI period in the predictable shock blocks.

2. This startle potentiation during predictable shock cues is phasic. In other words, it is observed only during the cue but not during the ITI period, as expected.

3. There was no evidence that alcohol reduced startle potentiation to these predictable shock cues in either analysis. In fact, although not significant, the beverage group effect on startle potentiation was in the opposite direction in the second analysis (i.e., startle response potentiation was approximately 16 μV greater in the alcohol group than the placebo group).

Unpredictable shock. As with predictable cues, startle potentiation to unpredictable shock cues is best referenced to no-shock cues to control for visual attention foreground. Therefore, a Beverage Group $\times$ Unpredictable Shock Cue Versus No-Shock Cue simple effect analysis was conducted to test for alcohol's effect on startle potentiation to unpredictable shock cues. See Figure 2A for startle response during unpredictable shock cues and no-shock cues and the startle potentiation contrast difference scores. The unpredictable shock cue versus no-shock cue contrast was significant, $F(1, 61) = 120.55$, $p < .001$, $\eta_p^2 = .66$, $B = 59.2$, confirming that startle response was potentiated during cues that were associated with unpredictable administration of electric shock. However, in contrast to earlier analysis of predictable shock cues, beverage group did significantly moderate this contrast, $F(1, 61) = 5.65$, $p = .021$, $\eta_p^2 = .09$, $B = -25.7$. In other words, alcohol significantly reduced the potentiation of the startle response observed during unpredictable cues (relative to no-shock cues; see hatched bars on Figure 2A).

To determine if the significant alcohol effect on unpredictable shock cues was also observed during the ITI period of the unpre-

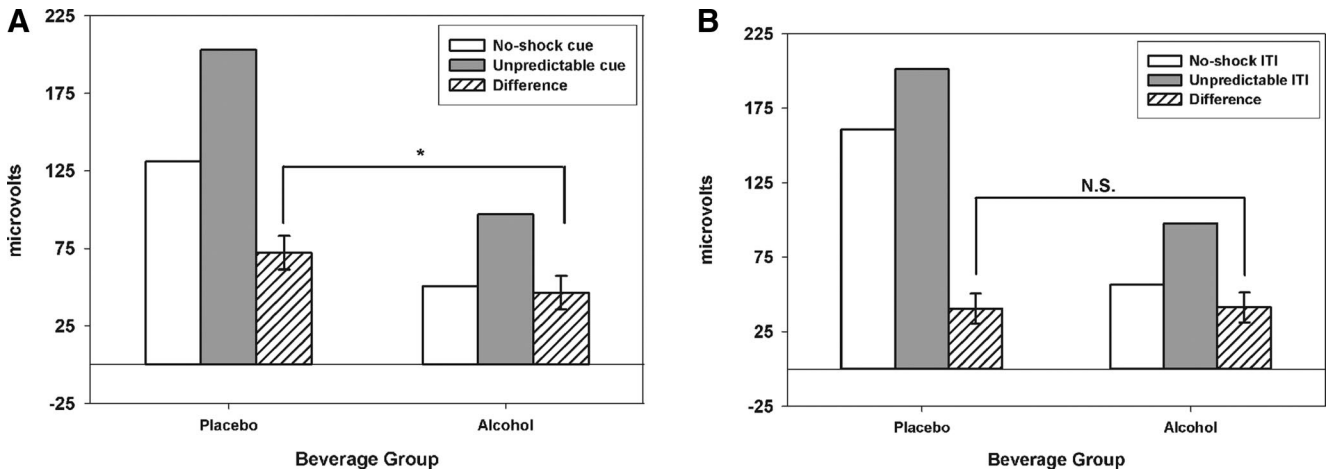

Figure 2. Startle response and startle potentiation during unpredictable shock cues and ITI. A: Raw startle response is displayed for unpredictable shock (gray) and no-shock (white) cues by beverage group. Startle potentiation difference scores (unpredictable cue – no-shock cue) are displayed (hatched) with standard errors for the beverage group effect. Unpredictable shock cues produced significant startle potentiation relative to no-shock cues (difference > 0; $p < .001$). The significant beverage group effect ($^{*}p = .021$) on startle potentiation indicates that alcohol selectively reduces startle potentiation to unpredictable shock cues relative to no-shock cues. B: Raw startle response is displayed for the unpredictable intertrial interval (ITI) period (gray) and no-shock ITI period (white) by beverage group. Startle potentiation difference scores (unpredictable ITI – no-shock ITI) are displayed (hatched) with standard errors for the beverage group effect. Unpredictable ITIs produced significant startle potentiation relative to the no-shock ITI period (difference > 0; $p < .001$). The test nonsignificant beverage group effect on startle potentiation indicates that alcohol does not reduce startle potentiation during the unpredictable ITI period relative to the comparable ITI period in the no-shock blocks.

dictable shock blocks, we conducted a Beverage Group × Unpredictable Shock ITI Versus No-Shock ITI analysis. As predicted, the unpredictable shock ITI versus no-shock ITI contrast was significant, $F(1, 61) = 65.84$, $p < .001$, $\eta_p^2 = .52$, $B = 40.8$, indicating that the startle response potentiation that was observed during unpredictable shock cues was maintained into the ITI period of unpredictable shock blocks. However, beverage group did not significantly moderate this contrast, $F(1, 61) = 0.01$, $p = .934$, $\eta_p^2 = .09$, $B = 0.8$.

These two analyses confirm the following:

1. Similar to results for predictable shock cues, startle response is also potentiated during cues that are unpredictably paired with electric shock relative to cues during the no-shock blocks.

2. In contrast to predictable shock cues, startle response potentiation during unpredictable shock cues is sustained throughout the unpredictable shock block (i.e., observed during both cue and ITI periods).[4]

3. Most important, startle potentiation during unpredictable cues was significantly reduced by alcohol. This is in contrast to the absence of any effect of alcohol on startle potentiation predictable shock cues. Furthermore, this alcohol effect is confined to the cue period in the unpredictable shock blocks. Alcohol did not reduce startle potentiation during the ITI period in unpredictable shock blocks.

Beverage Group Effects on Potentiated Startle: Unpredictable Versus Predictable Shock Cues

An analysis was conducted on potentiated startle scores for predictable and unpredictable shock cues. Specifically, a Beverage Group (alcohol vs. placebo) × Block Type (unpredictable vs. predictable) GLM was conducted on startle potentiation scores (i.e., startle response for predictable or unpredictable shock cue vs. no-shock cue). As with all earlier analyses, pretask startle reactivity (mean centered) was included as a covariate. Figure 3 displays startle potentiation scores by beverage group and block type. This analysis addresses two questions. First, it provides a comparison of the magnitude of startle potentiation produced across predictable versus unpredictable shock cues via the test of the block type main effect. Selective deficits are most clearly established when tasks and stimuli are matched with respect to the magnitude of response they generate (Chapman & Chapman, 1973). Second, the analysis provides an explicit test of whether beverage group effects are significantly greater for unpredictable versus predictable shock cues (i.e., a Beverage Group × Block Type interaction).

[4] In addition to being significantly potentiated relative to no-shock ITI, focused contrasts confirm that startle response during unpredictable ITI is significantly higher than during predictable ITI, $F(1, 61) = 42.77$, $p < .001$, $\eta_p^2 = .41$, $B = 31.7$. Moreover, startle response is comparable during unpredictable ITI and unpredictable cues, $F(1, 61) = 0.02$, $p = .904$, $\eta_p^2 = .00$, $B = -0.5$.

The main effect of block type was not significant, $F(1, 61) = 0.95$, $p = .333$, $\eta_p^2 = .00$, $B = 4.7$, indicating that unpredictable and predictable cues produced comparable potentiation of the startle response (59.2 vs. 63.9 μV, respectively).[5] The Beverage Group × Block Type interaction was significant, $F(1, 61) = 4.82$, $p = .032$, $\eta_p^2 = .07$, $B = 21.1$, indicating that the beverage group effect on unpredictable cue startle potentiation was significantly greater (reduction of 25.7 μV; $p = .021$) than the beverage group effect on predictable cue startle potentiation (reduction of 4.6 μV; $p = .716$).

Mediation of Beverage Group Effect by Attention

The startle response to acoustic probes is generally inhibited when participants direct attention toward other sensory modalities (e.g., attention to the visual cues reduces startle response to auditory probes; Anthony, 1985). As such, the startle inhibition that was observed during no-shock cues relative to the ITI period in no-shock blocks served as an index of participants' attention to the visual cues during the experiment. To test for an alcohol effect on attention to the visual cues, we conducted a Beverage Group × Cue (cue vs. ITI) GLM on startle response in the no-shock blocks (see Figure 4). Pretask startle reactivity (mean centered) was included as a quantitative covariate. As expected, a significant main effect of cue was observed with startle response to acoustic probes significantly reduced during the no-shock cues relative to the ITI period, $F(1, 61) = 37.74$ $p < .001$, $\eta_p^2 = .38$, $B = -17.9$. More important, the Beverage Group × Cue interaction was significant, $F(1, 61) = 16.99$, $p < .001$, $\eta_p^2 = .22$, $B = 24.1$, indicating that the magnitude of the attentional inhibition of startle was reduced by alcohol. Intoxicated participants directed less attention toward the visual no-shock cues.

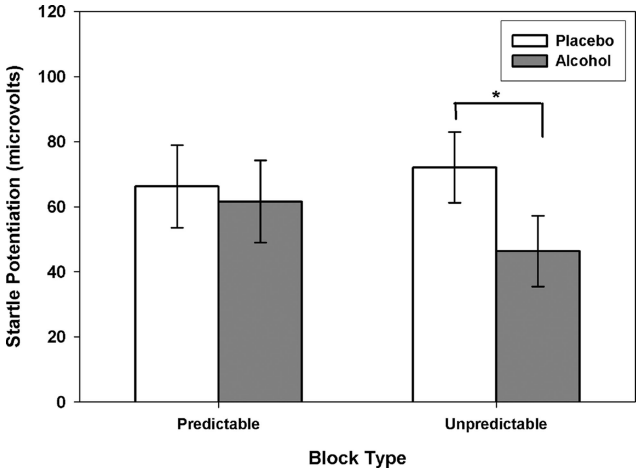

Figure 3. Startle potentiation to predictable and unpredictable shock cues by beverage group. Startle potentiation difference scores are displayed for predictable (predictable cue – no-shock cue) and unpredictable (unpredictable cue – no-shock cue) shock conditions. These startle potentiation differences scores were displayed separately in Figures 1A and 2A. These data are presented here together to facilitate direct comparison of startle potentiation magnitude across the two manipulations. Error bars represent standard errors of the beverage group effects. The significant Beverage Group × Block Type interaction ($p = .032$) indicates that alcohol has a larger effect on unpredictable versus predictable shock cue startle potentiation. The simple effect of beverage group is significant for unpredictable shock cues ($^{*}p = .021$) but not for predictable shock cues ($p = .716$).

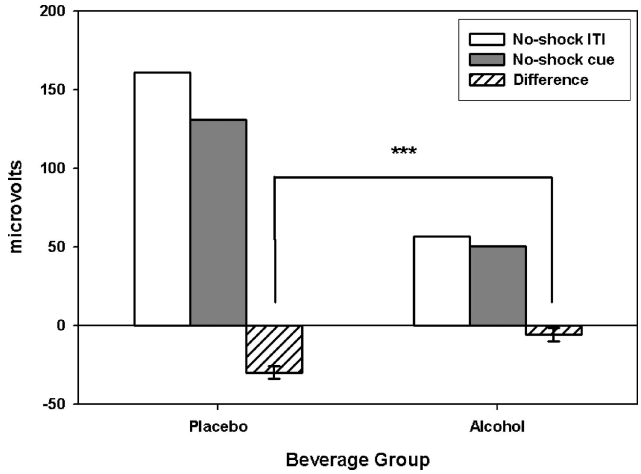

Figure 4. Startle response and startle inhibition during no-shock blocks. Raw startle response is displayed for no-shock cues (gray) and the no-shock ITI period (white) by beverage group. Startle inhibition difference scores (no-shock cue – no-shock ITI) are displayed (hatched) with standard errors for the beverage group effect. No-shock cues produced significant startle inhibition relative to the no-shock ITI period (difference scores < 0; $p < .001$). The significant beverage group effect ($^{***}p < .001$) on startle inhibition difference scores indicates that alcohol reduced startle inhibition associated with attention to the visual no-shock cues.

Subsequent analyses demonstrated that the magnitude of startle inhibition during visual cues in the no-shock blocks was significantly correlated with startle potentiation during unpredictable shock cues, partial $r = -.42$, $p < .001$. Participants who directed more attention toward the no-shock cues also displayed increased startle potentiation during unpredictable shock cues. To a lesser degree, the same relationship was observed between startle inhibition during no-shock cues and startle potentiation during predictable cues, partial $r = -.27$, $p = .032$.

These results raised the possibility that the significant beverage group effect on startle potentiation during unpredictable shock cues may be mediated by attention. To formally test this, we conducted the three regression analyses described by Baron and Kenny (1986) to establish mediation (see Table 3 for results of regression analyses). Consistent with all previous analyses, we included pretask startle reactivity as a covariate in these mediation analyses and mean centered all predictors. First, we regressed startle inhibition during no-shock cues (i.e., the putative attention mediator) on beverage group. Significant overall inhibition was observed during no-shock cues (i.e., intercept in this regression), $B = -17.9$, $SE = 2.9$, $t(61) = 6.14$, $p < .001$. As confirmed above, alcohol significantly reduced startle inhibition to no-shock cues, $B = 24.1$, $SE = 5.9$, $t(61) = 4.12$, $p < .001$. Second, we

[5] A more conservative test of the block type effect conducted in the control (placebo) group also failed to detect any significant difference between startle potentiation produced by predictable versus unpredictable cues, $F(1, 30) = 1.22$, $p = .279$, $\eta_p^2 = .04$, $B = 6.4$.

Table 3
Mediation of Alcohol Effect on Anxiety via Vigilance

Predictor	*B*	*SE*	*t*	*p*
Mediation Regression Analysis Step 1: Dependent variable is no-shock cue startle inhibition (mediator)				
Intercept	−17.9	2.9	6.14	.000
Pretask baseline	−9.1	3.0	3.08	.003
Beverage group	24.1	5.9	4.12	**.000**
Mediation Regression Analysis Step 2: Dependent variable is unpredictable shock cue startle potentiation				
Intercept	59.2	5.4	10.99	.000
Pretask baseline	24.1	5.5	4.41	.000
Beverage group	−25.7	10.8	−2.39	**.021**
Mediation Regression Analysis Step 3: Dependent variable is unpredictable shock cue startle potentiation				
Intercept	59.2	5.1	11.55	.000
Pretask baseline	18.5	5.6	3.31	.002
Beverage group	−10.9	11.6	0.93	**.354**
No-shock cue startle inhibition	−16.7	6.1	2.74	**.008**

Note. Outcomes of critical statistical tests to support mediation appear in bold.

regressed startle potentiation during unpredictable shock cues (i.e., our dependent measure of anxiety) on beverage group. Significant startle potentiation was observed during unpredictable shock cues (i.e., intercept in this regression), $B = 59.2$, $SE = 5.4$, $t(61) = 10.99$, $p < .001$. As confirmed earlier, alcohol significantly reduced startle potentiation to these unpredictable shock cues, $B = -25.7$, $SE = 10.8$, $t(61) = 2.38$, $p < .021$. The critical mediation test was provided in the third and final regression analysis, in which startle potentiation to unpredictable shock cues was regressed simultaneously on both beverage group and attentional startle inhibition during no-shock cues. In this analysis, startle inhibition remained as a significant predictor of startle potentiation during unpredictable shock cues, $B = -16.7$, $SE = 6.1$, $t(60) = 2.74$, $p = .008$. However, the beverage group effect was reduced and not significant, $B = -10.9$, $SE = 1.6$, $t(60) = 0.93$, $p = .354$. These results confirm that the beverage group effect on startle potentiation to unpredictable shock cues was mediated by alcohol's effect on attentional startle inhibition. A similar conclusion is supported by the Sobel test (Sobel, 1982), which directly tests the indirect (mediated) effect. The Sobel test confirms that the mediated pathway is significant, $z = 2.28$, $p = .023$.

Discussion

In this experiment, we examined the effect of alcohol on affective response in two distinct conditions involving either predictable or unpredictable administration of electric shock. Previous research with both animals and humans has suggested that predictable versus unpredictable threat exposure can serve as valid laboratory models for fear versus anxiety response, respectively (Grillon, 2008; Walker & Davis, 2008; Walker et al., 2003). In this experiment, predictable shock cues indicated a high probability of imminent threat and produced robust phasic potentiation of the startle response only during these cues. In contrast, both threat probability and imminence were lower during unpredictable shock cues. Despite this, these unpredictable shock cues also produced robust startle potentiation, which was sustained throughout the unpredictable shock block. In fact, these two manipulations produced comparable magnitude of startle response potentiation during cue presentation (see Figure 3 and related analyses). The comparable strength of these manipulations provided an opportunity to examine predicted differential effects of alcohol on startle response potentiation during unpredictable versus predictable shock cues with confidence that such effects would not be the spurious result of unmatched manipulations of anxiety versus fear (Chapman & Chapman, 1973).

In this experiment, alcohol selectively reduced startle potentiation associated with anxiety response during unpredictable shock cues but not fear response during predictable shock cues. To our knowledge, this is the first experiment to demonstrate such a dissociation for alcohol in humans. In addition, we demonstrated that alcohol reduced vigilance, as measured by attention to the threat-irrelevant no-shock cues in no-shock blocks. Moreover, this putative vigilance effect mediated alcohol's anxiolytic effect during unpredictable shock cues (see also Sher, Bartholow, Peuser, Erickson, & Wood, 2007). In the sections that follow, we elaborate on the theoretical and clinical implications of these results, as well as limitations and important future directions for research.

Previous research that specifically examined alcohol's effect on fear response has failed to observe direct robust effects of alcohol on fear when threat cues were presented in the focus of attention (Curtin et al., 1998, 2001). The results associated with predictable shock cues in this experiment are consistent with this previous research. Alcohol did not reduce startle potentiation during simple visual cues that unambiguously predicted imminent administration of electric shock. In contrast, recent research has demonstrated selective effects of anxiolytic drugs on anxiety but not fear response (Baas et al., 2002; Grillon et al., 2006). In this experiment, we confirmed that a moderate dose of alcohol appears to have a similar selective effect on anxiety using comparable laboratory procedures (i.e., unpredictable shock administration).

The selective anxiolytic effect of alcohol observed in this experiment only during unpredictable shock cues may provide an explanation for the heterogeneous stress-response-dampening effects of alcohol observed in earlier research. As reviewed earlier,

it is clear that drinkers believe that alcohol reduces stress, broadly defined, but consistent confirmation of this effect in the laboratory has been elusive (Curtin & Lang, 2007; Greeley & Oei, 1999). However, laboratory methods used to elicit stress responses have been quite varied in this literature. The implicit assumption that alcohol should have comparable effects regardless of the affect eliciting stimuli and nature of the associated negative affective response may be untenable. Evidence is rapidly accruing from multiple sources that fear and anxiety are distinct processes with dissociable neural substrates (Grillon, 2008; Walker & Davis, 2008; Walker et al., 2003). Thus, it should not be surprising that alcohol has different effects on fear versus anxiety, as suggested by the results of this experiment. Unfortunately, researchers often aggregate alcohol challenge results across experiments with varied procedures to attempt to reach broad conclusions about stress-response-dampening effects. This may have slowed efforts to understand when and how alcohol affects negative emotions.

Consideration of this distinction between fear and anxiety may also clarify the mechanism proposed by important cognitive models of the alcohol–emotion nexus (Sayette, 1993; Steele & Josephs, 1990). Steele and Josephs (1990) proposed that alcohol's effect on emotional response is mediated via impairment in attention when intoxicated, such that intoxicated individuals display reduced response to threats that are presented in the periphery of salient distracters (see Curtin et al., 1998, 2001, for empirical support using fear-potentiated startle). Similarly, Sayette (1993) suggested that alcohol reduces negative emotional response in situations where stressors would not be adequately appraised because of the nature and timing of the threats. The observed dissociation between alcohol's effect on fear versus anxiety in the context of predictable and unpredictable threats may offer a novel perspective on the mechanism(s) proposed by these cognitive models. Salient distracters and other manipulations that degrade threat cue appraisal may make aversive events less predictable, producing an ongoing anxious state in these environments. These environments also place higher demands on vigilance processes because of the absence of clear predictive information about threat onset, imminence, and/or probability. Alcohol appears to reduce anxiety in these environments. In contrast, when explicit threats are presented in the focus of attention, the onset and nature of the threat are more predictable, and phasic fear response is more tightly coupled with threat onset. Attentional demands are reduced in these environments because the threat is salient, well-defined, and easily appraised. Alcohol appears to be ineffective at reducing fear response in these environments.

Of course, further research clarifying the critical parameters that distinguish fear from anxiety is necessary. Davis (2006) has proposed that fear and anxiety result from "two phenomenologically and anatomically dissociable response systems" (p. 750). As reviewed earlier, the CeA appears to be critically involved in a rapid response system that mediates brief, phasic fear response to explicit, simple cues that predict imminent, highly probable threat. Fear is linked to action tendency and immediate defensive behavior. In contrast, Davis (2006) argued that the BNST mediates a slower onset but more sustained anxiety response that occurs in complex multimodal environments where threats are more ambiguous, abstract, or otherwise ill-defined and temporal precision regarding threat onset and/or probability is reduced. Activity in this anxiety response system may persist even after termination of a specific threat. Generally, anxiety is future oriented, involves more complex cognitive processing of symbolic representations of danger, and is not associated with well-coordinated, organized behavioral response. Moreover, vigilance is heightened, but attention is less focused on specific stimuli during anxiety than fear (Cornwell, Echiverri, Covington, & Grillon, 2008; Hasler et al., 2007).

It is clear that the neurobiological substrates of fear and anxiety, including both the CeA and the BNST, play an important role in attention as well as affective response (Davis & Whalen, 2001). However, the attentional changes that covary with fear versus anxiety may be different in nature. Cornwell et al. (2008) demonstrated that fear-relevant, high probability, imminent threat of electric shock was associated with narrowly focused attention on stimuli in the threat-related sensory modality (in this case, tactile). Others have proposed that when potential threats exist but are not imminent, vigilance is increased and the individual will be broadly attentive to stimuli across modalities that may be at all threat relevant (Blanchard & Blanchard, 1989; Fanselow, 1994).

Startle inhibition during no-shock cues in this experiment appeared to index processes associated with this more diffuse vigilance state. Inhibition of acoustic startle response indicated participants' tendency to attend to the visual cues that were not themselves threat relevant nor in the same modality as the threatening electric shocks. However, these no-shock cues resembled stimuli that did predict threat at other times (i.e., predictable shock visual cues). Inhibition of startle during ambiguous no-shock cues was more strongly correlated with unpredictable shock cue startle potentiation. Alcohol reduced both this vigilance-relevant startle inhibition and anxiety-relevant unpredictable shock cue startle potentiation. In fact, alcohol's effect on anxiety was mediated via its effects on vigilance. This pattern of results provides additional support for the expected coupling of cognitive and affective changes when the neurobiological substrates associated with anxiety-relevant unpredictable threat are activated. Moreover, the results provide preliminary evidence that these processes are particularly sensitive to alcohol administration.

The contrast of alcohol's effect on startle potentiation during unpredictable shock cues versus the unpredictable shock ITI period provides further support that attentional processes associated with vigilance and threat cue processing may be involved in the anxiolytic effects of alcohol. Alcohol administration significantly reduced startle potentiation during unpredictable shock cue presentation. However, alcohol was ineffective at reducing startle potentiation that was sustained into the ITI period after unpredictable shock cue termination. In combination with mediation analyses, this pattern of results suggests that intoxicated participants may have failed to attend and respond to unpredictable shock cues because the threat associated with these cues was not clear given the lower probability of shock administration during these cues.

Davis, Walker, and their colleagues (Walker & Davis, 2008; see also Grillon, 2008) have indicated that threat probability, threat imminence, and the time course of the response (phasic vs. sustained) are all important dimensions along which fear and anxiety response and their neurobiological substrates can be dissociated. However, the initial tasks that have used predictable versus unpredictable shock have confounded these three dimensions, making it difficult to determine which, if any, are key causes rather than correlates. For example, we have recently demonstrated that se-

lective manipulation of threat probability, while holding threat imminence constant, can affect the time course of startle potentiation (Hefner & Curtin, 2008). In this experiment, shocks are always presented during cue presentation only (similar to predictable shock blocks). However, the percentage of cues that are paired with shock varied from 20% to 100%. High probability (100%) shock cues produced phasic startle potentiation only during cue presentation. However, cues that are infrequently paired with shock elicited startle potentiation that is sustained into the ITI period even though shocks are never administered during the ITIs. This suggests that threat probability may be the critical moderator that determines if threat exposure elicits phasic fear versus more sustained anxiety response. Clearly, further careful experimental research is needed to clarify the role these various factors play in the elicitation and characterization of fear and anxiety.

Clinical Implications

These results also may have important implications for understanding drug use motivational processes in addiction itself. Many classic and contemporary models of addiction identify adaptations in stress systems as a critical mechanism in the development of addiction across many classes of drugs (Baker, Piper, McCarthy, Majeskie, & Fiore, 2004; Koob & LeMoal, 2001; Solomon & Corbit, 1974). In short, repeated homeostatic adjustments in stress systems during periods of acute intoxication eventually lead to chronic compensatory adaptations in the structures involved in emotional response and its regulation. These adaptations persist beyond periods of acute use and result in dysregulated negative affect (e.g., increased anxiety) on cessation of drug use. Reliable reports of increased negative affect during withdrawal from most common addictive drugs (e.g., alcohol, nicotine, opiates; for a review, see Baker et al., 2004) support this assertion. We propose that systematic laboratory acute drug challenge (e.g., alcohol administration) and drug withdrawal studies in humans using varied addictive drugs can provide an important method to identify these stress-related adaptations that support addictive drug use. Specifically, paradigms that reveal antagonistic or compensatory effects during drug challenge versus drug withdrawal are ideal candidates to advance this effort. Similar acute anxiolytic effects have been demonstrated for benzodiazepines in this paradigm (Baas et al., 2002; Grillon et al., 2006). Conversely, withdrawal from nicotine produces a compensatory increase in anxiety in this paradigm (Grillon, Avenevoli, Daurignac & Merikangas, 2007; Hogle, Kaye, & Curtin, 2008; see also Hogle & Curtin, 2006). Pronounced activation of the BNST has been observed during withdrawal from opiates (Aston-Jones, Delfs, Druhan, & Zhu, 1999; Delfs, Zhu, Druhan, & Aston-Jones, 2000). We believe this body of research provides preliminary support that adaptations in anxiety and its neurobiological substrates may represent one cross-drug mechanism that contributes to the motivation to use drugs among addicts.

Limitations and Additional Future Directions

This experiment used a well-studied laboratory task for independently manipulating fear and anxiety. However, confidence in this selective alcohol effect will be increased by replication with other methods used to manipulate anxiety in the laboratory (e.g., darkness, Grillon, Duncko, Covington, Kopperman, & Kling, 2007; CO_2 challenge, Zvolensky, Eifert, Lejuez, & McNeil, 1999). Moreover, future research must clarify the eliciting conditions and cognitive and behavioral consequences that distinguish anxiety from other negative emotions (e.g., fear, depression). As noted earlier, threat predictability appears to be important to distinguish between fear and anxiety. However, predictability itself may be a function of the complexity of the cuing stimuli, the probability of threat occurrence, and the duration of the threat, among other parameters (see also Zvolensky, Lejuez, & Eifert, 2000). These parameters are an active topic of study in basic affective science (e.g., Mol, Baas, Grillon, van Ooijen, & Kenemans, 2007). More precise measurement of vigilance using event-related brain potentials (e.g., Curtin et al., 2001) can extend the preliminary findings associated with startle inhibition to no-shock cues and help to explicate differences in the cognitive consequences of fear versus anxiety manipulations.

In this experiment, we only administered one dose of alcohol designed to produce a moderate blood alcohol level (.08%). A next important step will be to investigate possible dose–response effects on anxiety versus fear. Other recent research has examined alcohol dose–response effects using emotionally valent images to elicit affective response (Donohue, Curtin, Patrick, & Lang, 2007). In this research, alcohol selectively reduced startle potentiation to unpleasant images without any concurrent effect on positive emotional response to pleasant images. However, this selective effect on negative emotional response was only observed at higher blood alcohol levels. Unfortunately, slide viewing tasks do not provide the necessary precision to parse fear versus anxiety. Therefore, future research with the current methods can confirm if the alcohol dose–response effect observed by Donohue et al. is limited to anxious negative affect or occurs more broadly (i.e., includes fear and other negative affective response; see also Sher & Walitzer, 1986). Future research could also use both placebo and true no-alcohol comparison groups to more precisely tease apart pharmacological and expectancy (and compensatory) effects.

In this article, we reviewed recent evidence that fear and anxiety can be distinguished both phenomenologically and anatomically. Basic research in affective science has validated laboratory procedures that selectively manipulate fear versus anxiety, using potentiated startle to measure affective response. On this theoretical and methodological foundation, we demonstrated that a moderate acute dose of alcohol selectively reduced anxiety but not fear response. This selective effect may help to explain inconsistency in the literature on the stress-response-dampening effects of alcohol. Moreover, these results provide clear direction for future research on the cognitive and neural mechanisms of alcohol's actions. Clinically, acknowledgement of a selective effect of alcohol on anxiety may provide insight into patterns of alcohol use disorder comorbidity with anxiety disorders and, possibly, the nature of addiction itself. More broadly, this program of research highlights the potential to advance psychologists' understanding of the motivation to use drugs and the etiology of human addiction by attending to basic research in affective neuroscience.

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