Alcohol intoxication: Selective reduction of anxiety in the face of uncertain threat

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ABSTRACT

Recent research indicates that fear and anxiety are distinct processes with separable neurobiological substrates. Experimental procedures using predictable vs. unpredictable shock administration have been used to elicit fear vs. anxiety, respectively (Grillon et al, 2004). Using these procedures, our lab has demonstrated that alcohol reduces anxiety to unpredictable shock but not fear to predictable shock (Moberg & Curtin, 2009). However, this manipulation of predictability varied both the probability and temporal precision of shock threat, raising crucial questions as to which stimulus characteristics are central to both the elicitation of anxiety and the anxiolytic effects of alcohol. To disentangle these two characteristics, we developed a novel paradigm to systematically vary threat probability, holding the temporal precision of threat constant. Intoxicated (0.08% BAC) and placebo participants viewed a series of 5s visual cues. The probability of shock administration (at 4.5s post cue onset) varied across blocks (20% vs. 60% vs. 100%). High probability shock cues (100%) were equivalent to predictable shock cues that elicited fear in earlier research. Lower probability shock cues (20% & 60%) were designed to elicit anxiety due to the unpredictable nature of the threat during any individual cue. The inter-trial interval (ITI) modeled anxiety in anticipation of temporally uncertain, distal (during future cues) shock. Startle potentiation (SP) relative to matched cue and ITI periods in no-shock blocks provided the primary measure of affective response.

Two key findings were observed. First, all shock cues produced robust SP. Alcohol reduced SP during shock cues monotonically as a function of shock probability, with a substantial significant effect observed during low probability (20%) shock cues and no detectable alcohol effect during cues with high shock probability (100%). Second, sustained SP was observed during ITIs in shock blocks despite no imminent threat in this period. Alcohol significantly reduced SP during ITIs in all shock blocks.

These results build on evidence suggesting that fear and anxiety are distinct, separable affective responses, and suggest that anxiety can be elicited by altering either threat probability or temporal predictability. Underscoring previous findings that alcohol selectively reduces anxiety but not fear, this work has important implications for high rates of comorbidity between anxiety disorders and alcoholism.

BACKGROUND

The Startle Reflex

- The startle reflex is used to assess affective response to threat (e.g., electric shock, unpleasant images; Davis, 1989; Grillon & Baas, 2004).
- Startle potentiation (SP) is defined as the increase in startle response (to an acoustic "startle probe") during threat vs. no-threat conditions.
- SP is objective, non-invasive, and can be assessed reliably across species.

Fear vs. Anxiety

- Phasic (brief) SP is observed during ***certain*** (punctate, highly predictable, imminent) threats. These manipulations have been used to model *FEAR* in the lab.
- In contrast, sustained SP is observed during more distal, tonic, temporally unpredictable, or otherwise ***uncertain*** threats. These manipulation have been used to model *ANXIETY* in the lab.
- Research in rats has implicated the central nucleus of the amygdala (CeA) in SP during *fear* versus the bed nucleus of the stria terminalis (BNST) during *anxiety* (see Walker et al., 2003 for a review).

Alcohol Effects on Fear vs. Anxiety

- Moberg & Curtin (2009) demonstrated that alcohol selectively reduced SP during uncertain but not certain threat cues using a manipulation of unpredictability.
- This unpredictability manipulation confounded threat *probability* with threat *imminence*. In addition, the alcohol effect was limited to the cue period in unpredictable shock blocks.
- The current experiment uses a novel manipulation of *threat probability* to dissociate these two discrete factors that may potentially contribute to anxiety. This allows for more precise conclusions regarding the nature of alcohol's effect on affective response.

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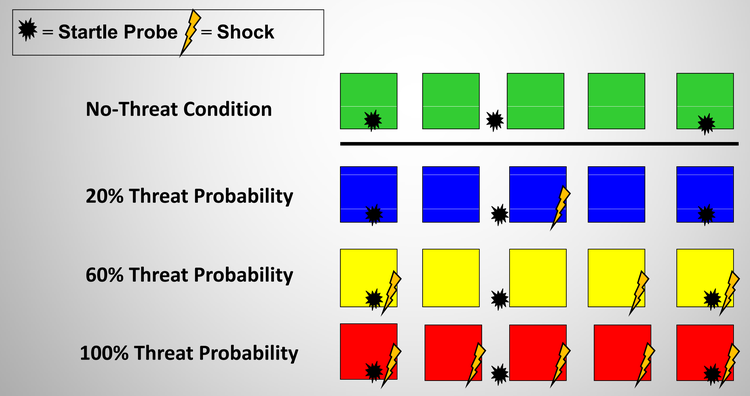
METHOD

Participants

- 121 healthy social drinkers (60 females)
- Two beverage groups: Alcohol (target BAC: 0.08%) and Placebo

General Procedure

- All participants completed a pre-drink baseline startle assessment and a post-drink shock tolerance assessment
- Participants viewed blocks of 5s colored square "cue" presentations separated by an inter-trial interval (ITI; mean 17.5s, range 15-20s)
- Threat probability was manipulated within subjects across block types
- Shocks were administered at 4.5s during cues in three block types that varied threat probability
  - **20% Threat Probability**: Shocks administered during one out of every five cues
  - **60% Threat Probability**: Shocks administered during three out of every five cues
  - **100% Threat Probability**: Shocks administered during every cue (five out of five cues)



Measurement of Startle Potentiation

- Startle response to acoustic startle probes was measured via EMG in cue and ITI periods
- Startle probes during cues occurred at 4s post-cue onset.
- Startle response was scored as peak response in 20-120ms post-probe onset.
- Startle potentiation (SP) scores were computed for each threat probability (vs. startle during the no-shock control condition).

HYPOTHESES

A moderate dose of alcohol will reduce SP in the face of uncertain threat (an elicitor of anxiety) but not in the face of certain threat (an elicitor of fear).

During Cues:

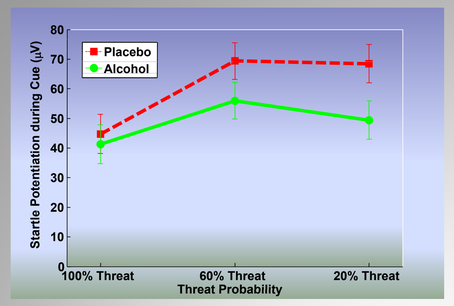
- Threat probability will moderate the effect of alcohol on SP during cues.
- The effect of alcohol on SP will be greater as the probability of threat decreases. Support for this hypothesis would be offered by an interaction between beverage group and threat probability, with larger beverage effects as the probability of threat decreases.

During ITIs:

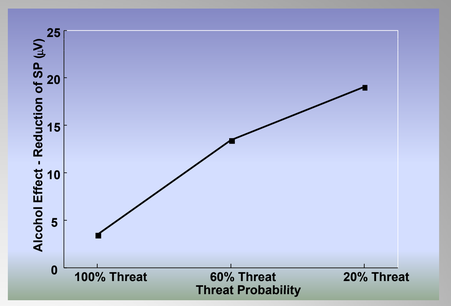
- Sustained SP is expected during ITI periods in all threat probability conditions. Alcohol will attenuate this SP in the absence of imminent threat.
- Support for these hypotheses would be offered by a main effect of beverage group on SP in the ITI periods (observed across all threat probability conditions)

STARTLE POTENTIATION RESULTS

CUE PERIOD



- As predicted, the **interaction** between **Beverage Group** and **Threat Probability** on SP during the cues was significant (p=.033)
- This indicates that the magnitude of alcohol's effect on SP varies according to threat probability.



- This figure displays the magnitude of the Alcohol effect (Placebo – Alcohol difference for SP)
- As Threat Probability decreases, Alcohol's effect on SP increases, with the greatest reduction in SP during 20% Threat Probability

ITI PERIOD

- Sustained potentiation of startle was observed during the ITI period of all threat blocks.
- As predicted, Alcohol significantly reduced sustained SP during the ITI period, evidenced by a **main effect** of **Beverage Group**, (p<.001)
- Threat Probability **did not interact** with Beverage Group, which indicates that the magnitude of the Beverage Group effect on SP during the ITI was comparable across threat probability conditions. This result stands in contrast to the effect of Beverage Group during the cue period.

CONCLUSIONS & CLINICAL IMPLICATIONS

- Attenuation of the sustained startle potentiation response in the face of uncertain threat appears to be the signature effect of a moderately intoxicating alcohol dose.
- It appears that both factors believed to elicit anxiety (low probability threat, distal threat) are sensitive to moderate alcohol intoxication.
- This experiment provided a conceptual replication of past work in our laboratory (Moberg & Curtin, 2009) with an important extension: parsing the previous manipulation of unpredictability into discrete components (i.e. threat probability vs. threat imminence).
- Specifically, the observation of a significant effect of alcohol on sustained SP during the ITI period resolves concerns that were raised by Moberg and Curtin's (2009) cue vs. ITI results.
- These findings may inform high rates of co-morbidity between alcohol use disorders and anxiety disorders.
- Alcohol's effects on the neurobiological substrates of anxiety may be one target for neuroadaptive changes supporting alcohol (and other drug) dependence and addiction.