

ABSTRACT

The role of stress in alcohol use generally and relapse among alcoholics is clear. Recent preclinical research implicates stress neuroadaptation following chronic alcohol use as a key etiologic mechanism in alcoholism. However, stress is a broad and often ill-defined construct in human research. This may have slowed progress on translating research on stress neuroadaptation from animal models to humans.

Recent affective neuroscience research suggests that the negative affective response to stressors can be parsed into the components of *fear* vs. *anxiety* by manipulating time course of threat (phasic vs. sustained, respectively). Cues which reliably predict the occurrence of threat elicit fear, whereas cues that signal uncertain threat elicit anxiety. Previous research from our lab has established that alcohol intoxication selectively dampens anxiety to uncertain threat but not fear to certain threat. Based on extant theory about neuroadaptive responses to repeated heavy alcohol use, we hypothesized that recently detoxified alcoholics would demonstrate increased negative affective response to uncertain threat. We additionally predicted that this effect would interact with baseline startle, as previous work from our lab suggests that individuals with higher tonic levels of startle responsivity may be most susceptible to these effects.

We examined the negative affective response to certain and uncertain threat in recently (1-8 weeks) sober alcoholics vs. healthy controls. Using an instructed threat task adapted from preclinical research, participants viewed a series of cues that predicted shock administration. In certain threat blocks, all cues lasted 5 seconds resulting in imminent, certain threats. In uncertain threat blocks, participants were instructed that cue duration would vary unpredictably from 5 seconds to 3 minutes. Startle potentiation relative to no shock blocks provided the measure of negative affective response.

The interaction of Group X Condition was not significant, nor was the Main Effect of Group. However, descriptively, alcoholic participants demonstrated increased startle potentiation during uncertain vs. certain threat. We found a significant interaction of Group X Baseline startle response, such that the group difference was most substantial among those with higher levels of baseline startle response.

BACKGROUND & HYPOTHESES

- Negative affect is a commonly reported symptom of withdrawal from alcohol use among dependent users
- Stress exposure is a power precipitant for relapse to use among abstinent alcoholics
- Recent research suggests that alcohol (and other drug use, e.g., nicotine) produces acute and chronic changes in the **affective** features of the stress response:
 - We have found that acute doses of alcohol selectively reduce affective responses to uncertain threat (Moberg & Curtin, 2009; Hefner & Curtin, 2011)
 - Theoretical work from Koob and others suggests that repeated exposure to alcohol causes **neuroadaptations** that result in compensatory responses in brain stress systems

- Stressors that are certain vs. uncertain elicit the distinct emotional states of fear and anxiety, respectively

Parsing the Stress Response

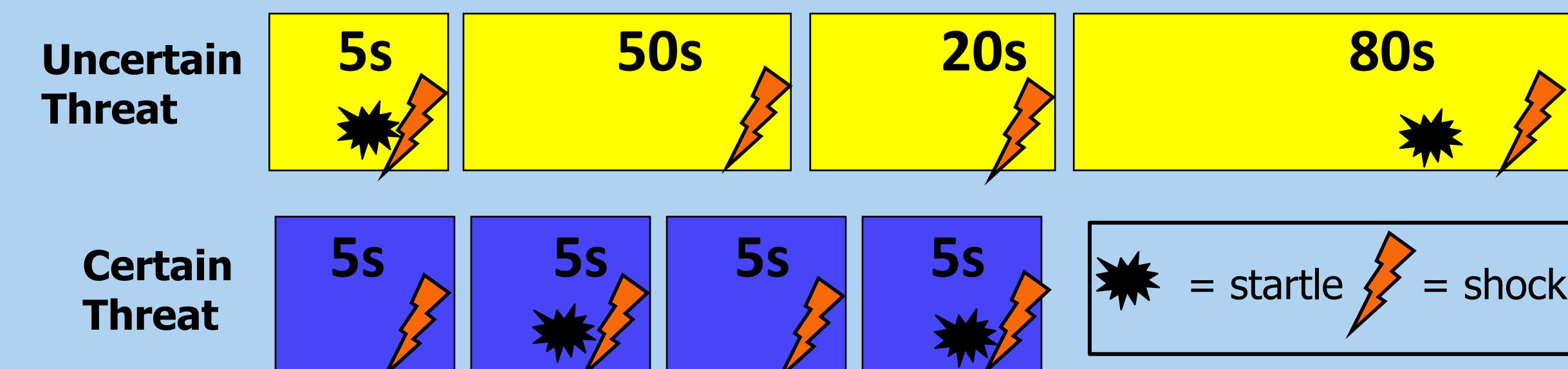
- Phasic (brief) startle potentiation (SP) is observed when threat is highly predictable, certain, and imminent. These manipulations have been used to model **fear** in the lab.
- Sustained SP is observed when threats are more distal, tonic, uncertain, or otherwise unpredictable. These manipulations have been used to model **anxiety** in the lab.

Hypotheses:

- Abstinent alcoholics will demonstrate increased affective response to stressors
- The increased affective response demonstrated by abstinent alcoholics will be greatest under conditions of *uncertain* threat
- Previous work in our lab suggests that individuals who exhibit higher baseline startle reactivity (i.e. startle response in the absence of threat) may be more likely to exhibit the neuroadaptations described above

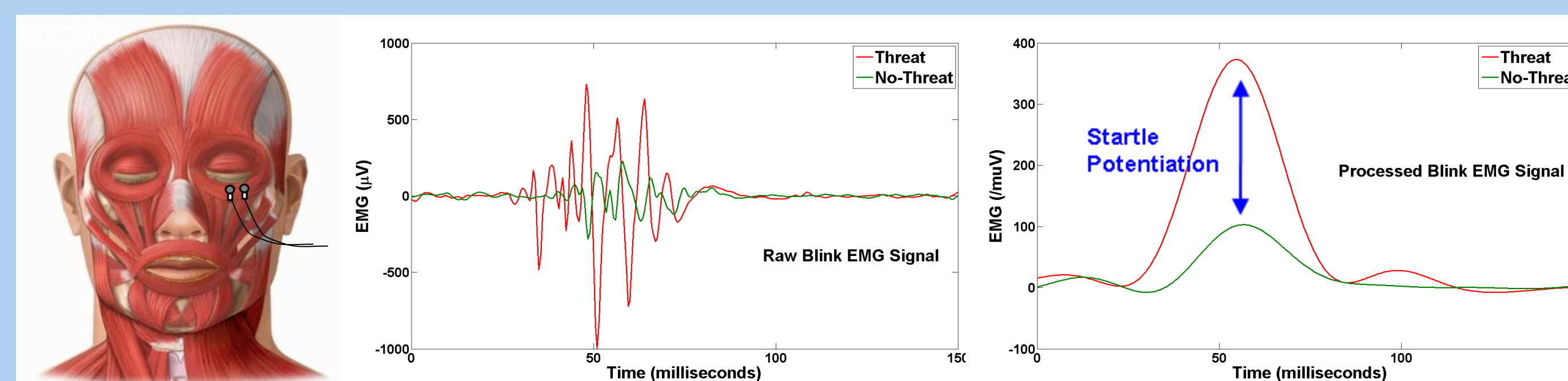
INSTRUCTED THREAT TASK AND MEASURES

- Participants viewed blocks of colored square threat cues
- Cue duration varied by block, such that threat timing was either Certain or Uncertain

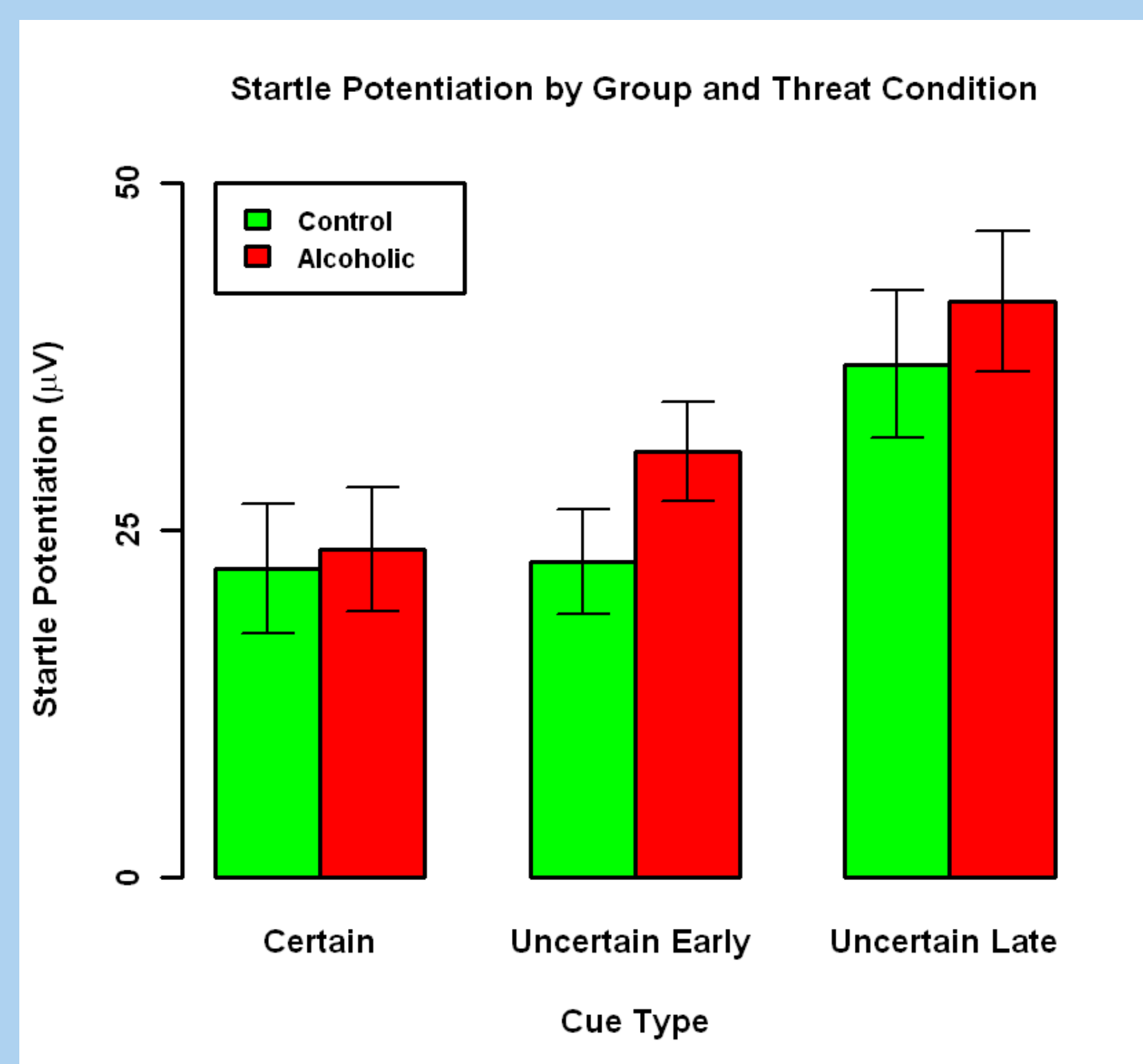


Measures

- EMG eyeblink startle response to noise probes scored as peak response in 20-120ms post-probe onset
- Potentiation scores are calculated as the startle response to a given probe during a shock block minus startle response to the corresponding probe during a no shock block with matched cue timing



RESULTS

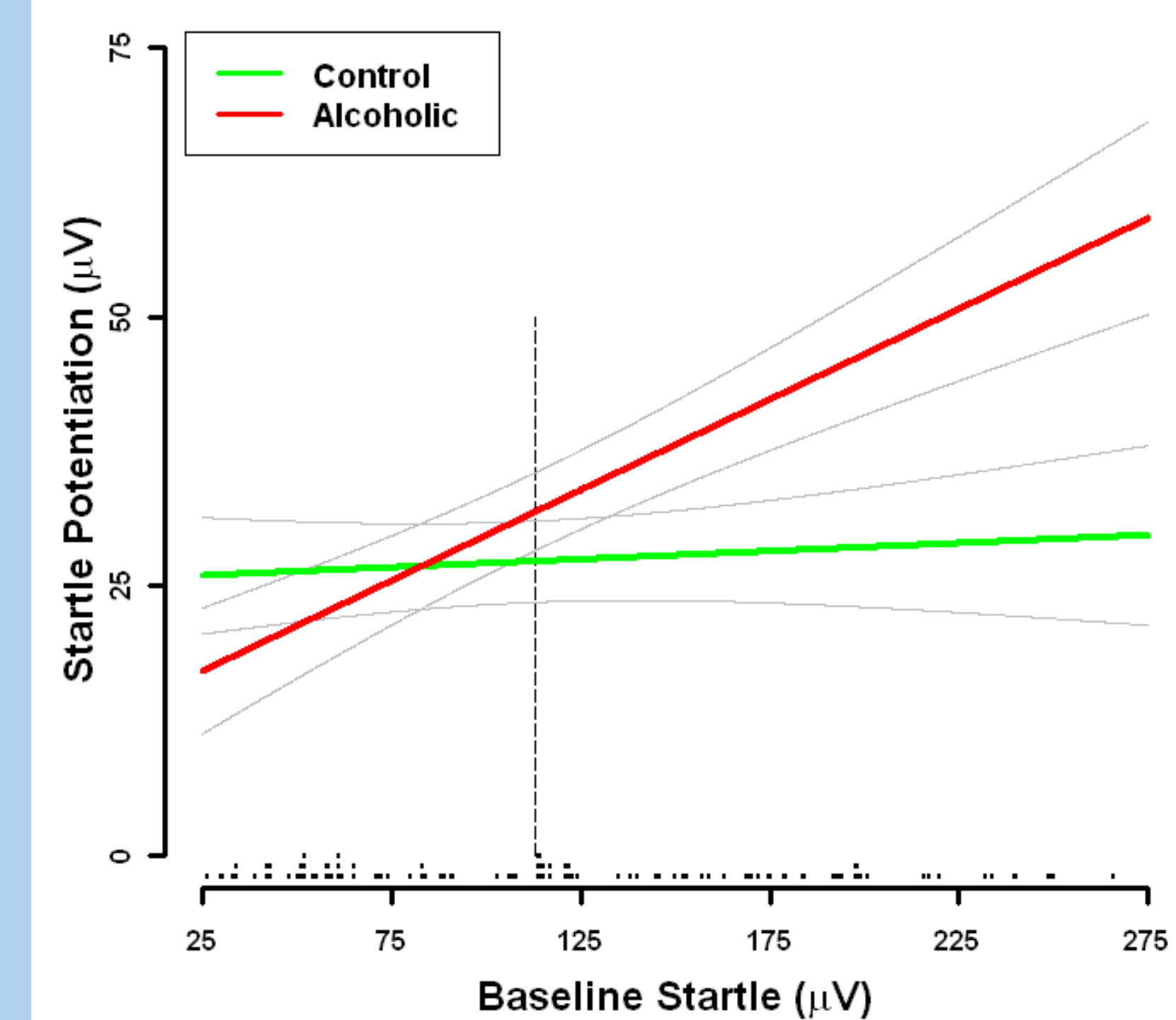


- Startle potentiation was analyzed in a fully interactive General Linear Model with regressors for Group (Alcoholic vs. Control), Threat Condition (Certain vs. Uncertain Early vs. Uncertain Late), and baseline startle response

- For those of average baseline startle, the alcoholic group demonstrated an average of 4.6 μV greater startle potentiation across all three conditions. However, this main effect of Group was not significant, $p=0.38$.

- At average baseline startle, the Group effect was descriptively greater during Uncertain threat (6.22 μV) than Certain threat (1.4 μV). However, this interaction contrast was also not significant, $p=0.42$.

Group Main Effect by Baseline Startle Interaction



- Based on previous work from our lab suggesting that baseline startle is an important moderator of threat effects, we examined the interaction between baseline startle and Group

- The interaction of the Main effect of Group X Baseline Startle is significant ($p = 0.03$)

- As Baseline startle increases, the Group effect increases: for each 1 μV increase in Baseline startle, the Group effect increases by 0.2 μV

- The simple effect of Baseline startle is significant in the Alcoholic group ($p < 0.01$) but not significant in the Control group ($p = 0.74$)

INTERPRETATIONS

- In the aggregate, the Abstinent Alcoholic group demonstrated descriptively greater startle potentiation. This effect was largest during conditions of uncertain threat. However, both the main effect of Group and interaction of Group X Condition failed to reach significance.

- We found a significant interaction between Group and Baseline startle response, such that the group effect is largest among those individuals with higher baseline startle response.

- Further examination of this effect indicates that Control participants did not demonstrate increased startle potentiation at greater levels of baseline startle; Alcoholic individuals did, such that those at higher levels of baseline startle evidenced greater startle potentiation.

- In other preliminary work from our laboratory, we have found baseline startle reactivity to be anxiety-relevant; individuals with higher baseline startle responses demonstrate greater defensive responding even under neutral, but novel, conditions (i.e. in the absence of threat of shock).

- We have found a similar Baseline startle response X Group effect in work with abstinent marijuana smokers and abstinent cigarette smokers, consistent with the possibility that individuals with higher baseline startle reactivity may be more likely to evidence the hypothesized *stress neuroadaptations*.

FUTURE DIRECTIONS

- The Alcoholic group was quite heterogeneous, so it will be important to consider potential individual differences moderators of these effects, such as trauma history or premorbid affective functioning.