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Impact of acute stress, sex, and childhood maltreatment on fear learning and fear generalization in a fear-potentiated startle paradigm

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Impact of Acute Stress, Sex, and Childhood Maltreatment on Fear Learning and Fear Generalization in a Fear-Potentiated Startle Paradigm

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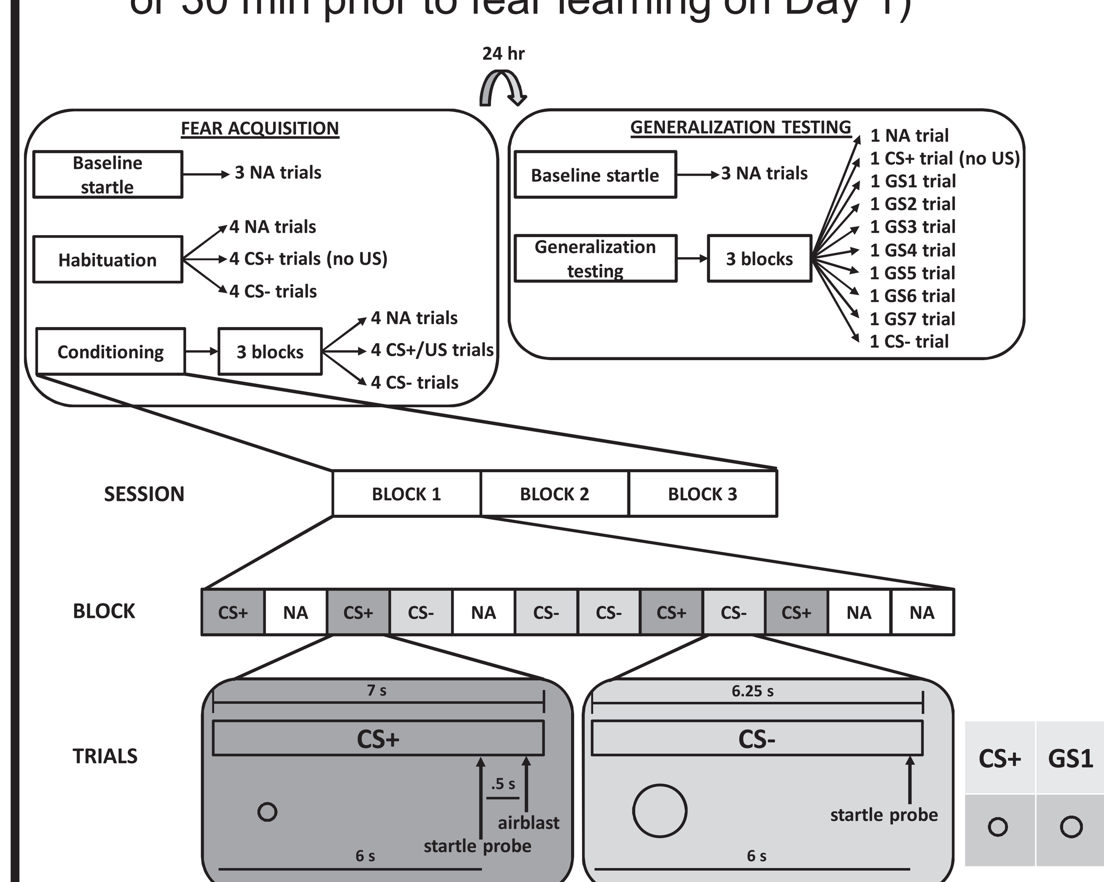
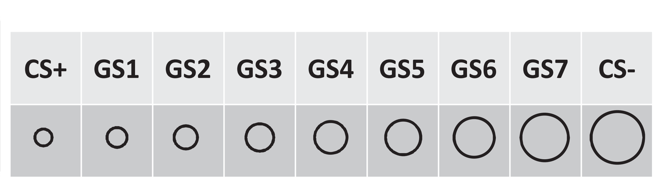
Introduction

The effects of pre-learning stress on long-term memory are relevant for our understanding of eyewitness and traumatic memories. Research has shown that when stress is administered shortly before learning, long-term memory is enhanced[1]; conversely, when stress is temporally separated from learning, long-term memory is impaired[2]. Previous work that has examined how the timing of stress impacts its influence on cognition suggested that participants' cortisol responses to the stressor mediated the impact of stress on fear learning[3-4]. In the present study, we aimed to extend previous work by examining the time-dependent effects of stress on fear generalization. We examined the impact of childhood maltreatment, sex, and stress administered immediately or 30 minutes before fear conditioning on fear acquisition and fear generalization.

Method

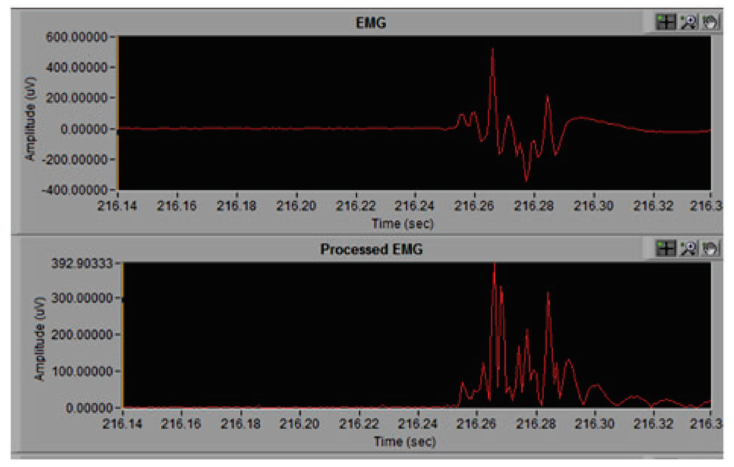
- 478 participants (170 males, 308 females; M_{age} = 19.10 years)
- Fear-potentiated startle paradigm
  - CS+, CS- = two geometric shapes (small circle, large circle); counterbalanced
  - US = 250-ms, 140-p.s.i. airblast to the larynx (paired w/CS+, 100% reinforcement rate during conditioning phase)
  - Startle probe = 40-ms, 108-dB noise burst
  - Startle response = peak EMG eyeblink 20-200 ms after startle probe
  - US expectancy ratings [-1 (no air), 0 (unsure), +1 (air)]
- Timeline
  - Day 1 = fear acquisition; Day 2 = generalization testing
- Between-subject IVs
  - Childhood stress [based on responses on the Childhood Trauma Questionnaire (CTQ)[5]]
  - Acute stress (socially evaluated cold pressor test, administered immediately or 30 min prior to fear learning on Day 1)

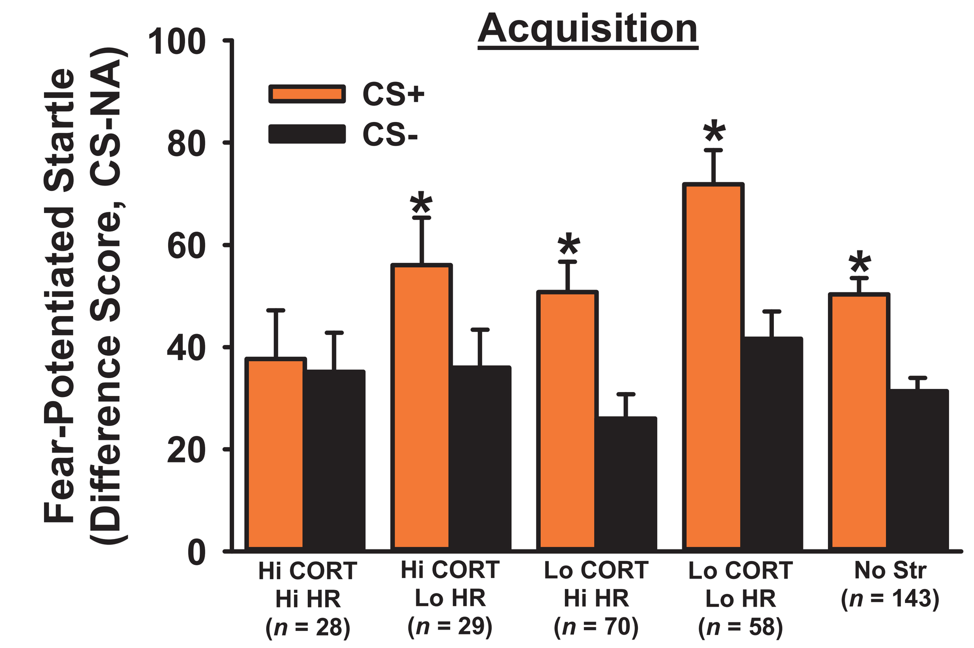


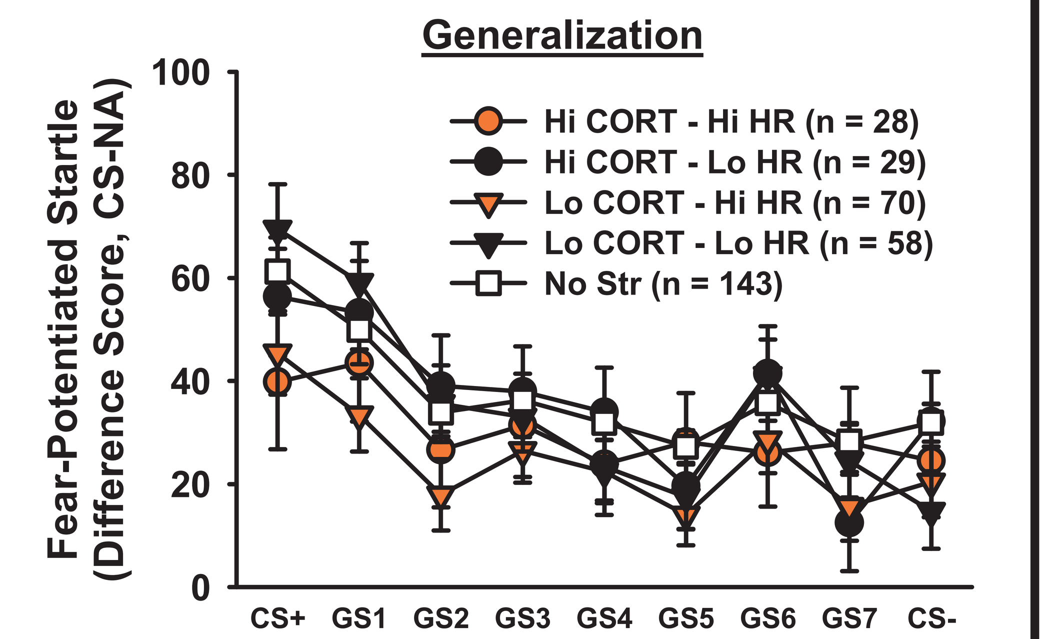


Results (all data are means ± SEM)

EMG signal processing: EMG signals were filtered with MindWare EMG analysis program (MindWare Technologies, Ltd., Gahanna, OH). Fear-potentiated startle was quantified by computing difference scores for the EMG recordings [(startle magnitude to the CS+, GS, or CS- in each block) – (startle magnitude to the NA trials in each block)].







Figures 1 and 2: Conditioned fear during acquisition and generalization was examined across both time points based on participants' physiological responses to the stressor on Day 1. Stressed participants who exhibited an increase of at least 1.5 nmol/l of salivary cortisol (CORT) were categorized as "Hi CORT" participants; a median split for change in heart rate (HR) from baseline was used to categorize participants into "Hi HR" and "Lo HR" groups. During the conditioning phase of acquisition, stressed participants who exhibited Hi CORT *and* Hi HR exhibited impaired fear learning [Group x CS interaction: $F(4,383) = 2.634$, $p = 0.034$]. During generalization testing, the generalization gradient for stressed participants who exhibited Hi CORT *and* Hi HR was flatter than that of other groups [linear component of Group x CS interaction: $F(4,398) = 2.77$, $p = 0.027$]. * $p < 0.01$ relative to CS-.

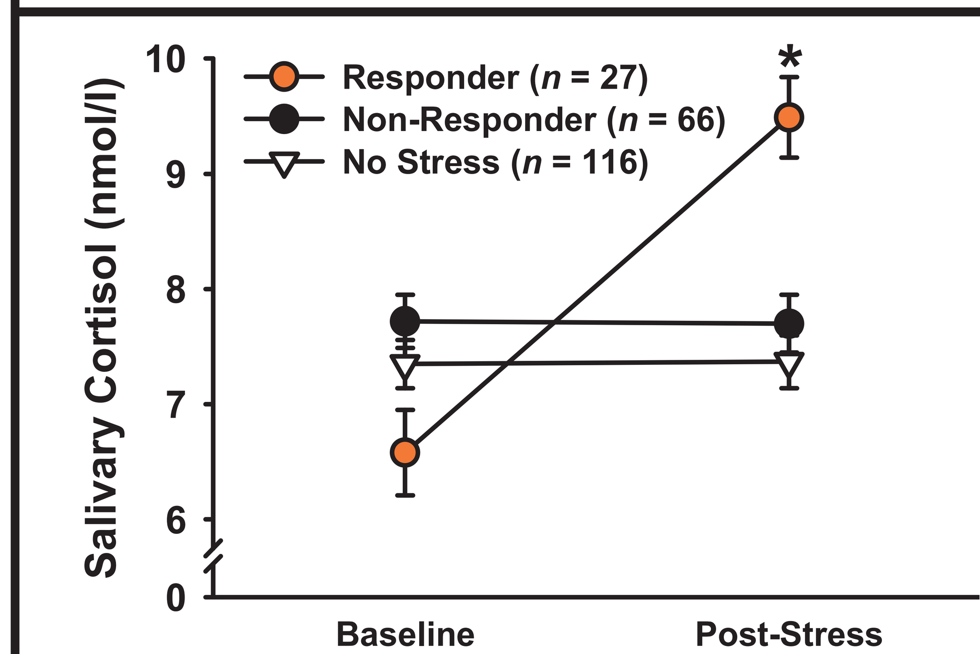


Figure 3: Participants who were stressed 30 min prior to fear learning and exhibited an increase of at least 1.5 nmol/l of CORT were categorized as CORT responders. These participants displayed greater CORT than non-responders and non-stressed participants following the water bath manipulation [Group x Time Point interaction: $F(2,203) = 36.11$, $p < 0.001$]. * $p < 0.001$ relative to all other groups.

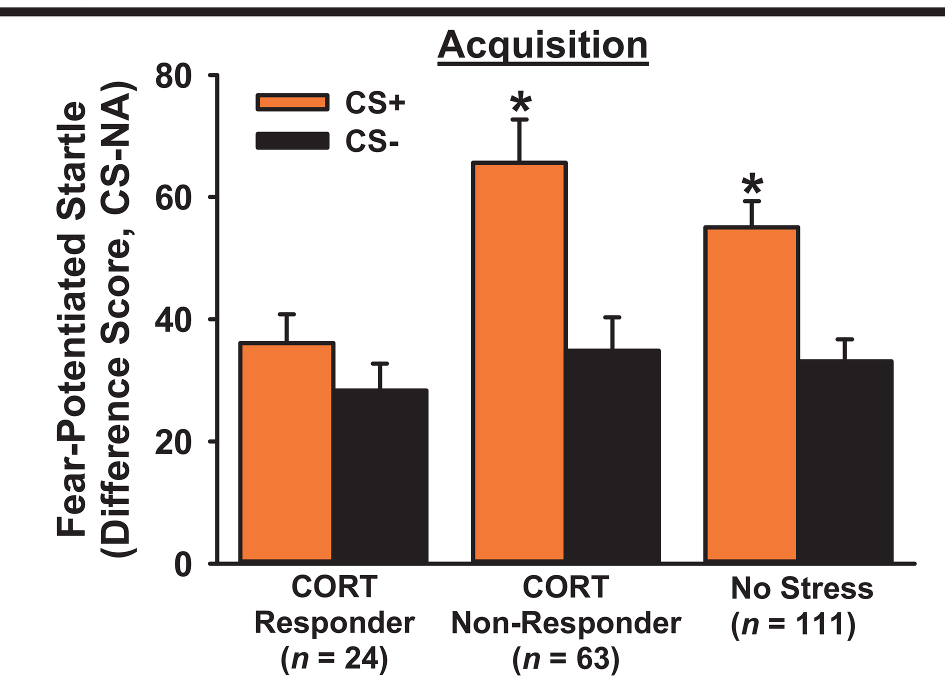


Figure 4: Participants who were stressed 30 min prior to fear learning and exhibited an increase of at least 1.5 nmol/l of CORT exhibited impaired fear acquisition [Group x CS interaction: $F(2,384) = 3.053$, $p = 0.05$]. * $p < 0.001$ relative to CS-.

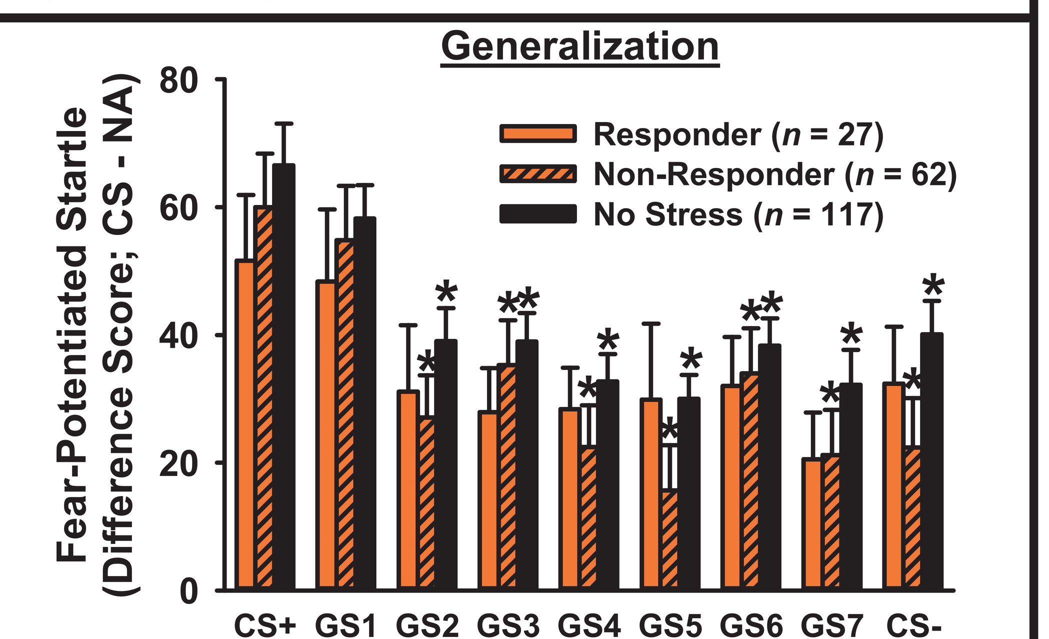
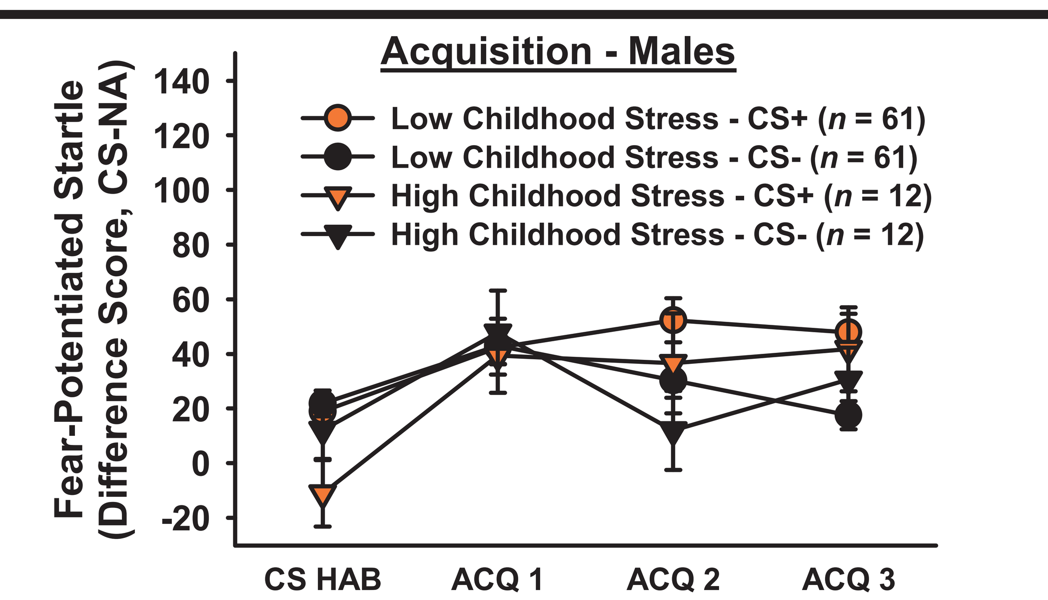
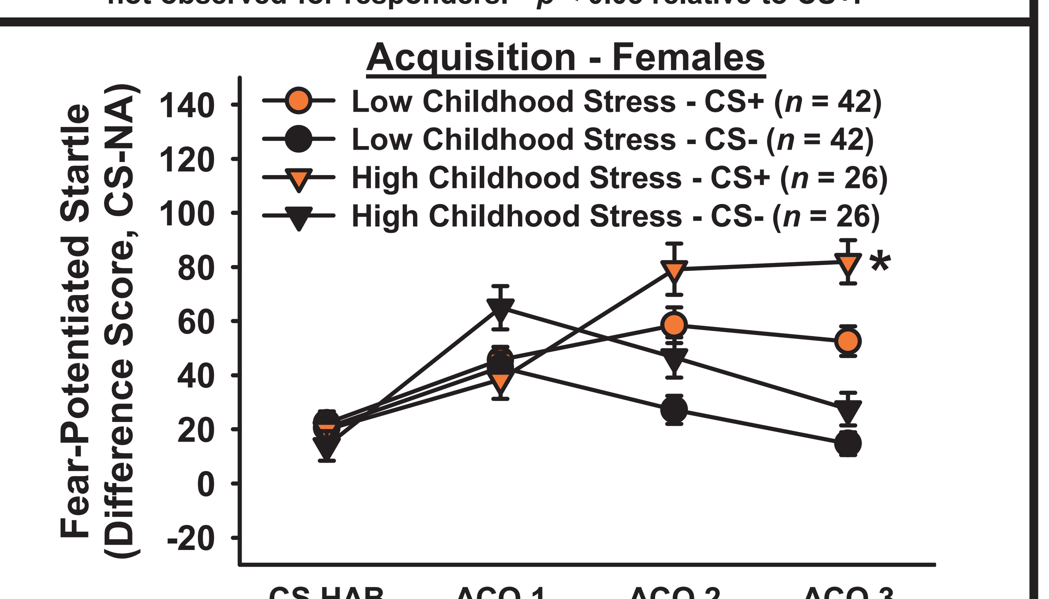


Figure 5: The Group x CS interaction was not significant, but we performed Bonferroni-corrected planned comparisons to assess the difference between participants' responses to the CS+, relative to all other stimuli. These comparisons revealed that non-responders and non-stressed participants displayed greater fear-potentiated startle to the CS+ than to the GS2, GS3, GS4, GS5, GS6, GS7, and CS+. Such differences were not observed for responders. * $p < 0.05$ relative to CS+.

Figures 6 and 7: A subset of participants completed the Childhood Trauma Questionnaire[7] and were categorized into high and low childhood stress based on their responses on the CTQ. Females, but not males, reporting high levels of childhood stress demonstrated enhanced fear learning during late acquisition [Group x Sex x CS x Trial interaction: $F(3,411) = 3.394$, $p = 0.018$]. * $p < 0.01$ relative to all other groups.





Conclusions

Stressed participants with greater HR and cortisol responses to the stressor displayed impaired fear acquisition and a flatter generalization gradient. This effect is consistent with previous research suggesting that high levels of cortisol must be coupled with emotional arousal to exert a significant impact on cognition[6,7]. Our results also support previous studies demonstrating that, when pre-learning stress is temporally separated from fear conditioning, participants' cortisol responses negatively correlate with their fear memory[3,8]. We also found that females, but not males, reporting high levels of childhood stress demonstrated stronger fear learning than participants reporting low levels of childhood stress. This finding aligns well with previous work reporting reduced frontal cortex-amygdala connectivity in maltreated females, but not maltreated males, which the investigators hypothesized could result in more unregulated fear responses in maltreated females and stronger fear learning[9].

References

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