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Dissociable impact of childhood trauma and deployment trauma on affective modulation of startle

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ABSTRACT

Trauma disorders are often associated with alterations in aversive anticipation and disruptions in emotion/fear circuits. Heightened or blunted anticipatory responding to negative cues in adulthood may be due to differential trauma exposure during development, and previous trauma exposure in childhood may also modify effects of subsequent trauma in adulthood. The aim of the current investigation was to examine the contributions of childhood trauma on affective modulation of startle before and after trauma exposure in adulthood (a combat deployment). Adult male participants from the Marine Resilience Study with (n = 1145) and without (n = 1312) a history of reported childhood trauma completed an affective modulation of startle task to assess aversive anticipation. Affective startle response was operationalized by electromyography (EMG) recording of the orbicularis oculi muscle in response to acoustic stimuli when anticipating positive and negative affective images. Startle responses to affective images were also assessed. Testing occurred over three time-points; before going on a 7 month combat deployment and 3 and 6 months after returning from deployment. Startle response when anticipating negative images was greater compared to pleasant images across all three test periods. Across all 3 time points, childhood trauma was consistently associated with significantly blunted startle when anticipating negative images, suggesting reliable effects of childhood trauma on aversive anticipation. Conversely, deployment trauma was associated with increased startle reactivity post-deployment compared to pre-deployment, which was independent of childhood trauma and image valence. These results support the hypothesis that trauma exposure during development vs. adulthood may have dissociable effects on aversive anticipation and arousal mechanisms. Further study in women and across more refined age groups is needed to test generalizability and identify potential developmental windows for these differential effects.

1. Introduction

Experiences of childhood trauma are common and have substantial negative short- and long-term effects on psychological, social and physical well-being (Copeland et al., 2018; Curran et al., 2016; Giovanelli et al., 2016). Physical, sexual, and emotional abuse, as well as physical and emotional neglect are frequently linked to the early emergence and persistence of many neuropsychiatric disorders, particularly mood and anxiety disorders like post-traumatic stress disorder (PTSD) and major depressive disorder (Afifi et al., 2014; Berens et al., 2017; Hovens et al., 2010; McLaughlin et al., 2012; McLaughlin and Lambert, 2017; Taillieu et al., 2016). Understanding the mechanisms underlying childhood trauma effects on subsequent response to adult trauma may inform why some individuals with childhood trauma are at a greater risk of developing psychiatric disorders, as well as parse out the individual contributions of developmental trauma and adult trauma effects on risk for psychopathology.

Childhood trauma alters physiological systems that coordinate stress responding and modifies development of neural systems and circuits associated with negative valence and potential threat (McLaughlin et al.,

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2014; Teicher et al., 2016). Potential threat, e.g. anticipation of aversive stimuli, is a transdiagnostic research domain criteria (RDoC; Kozak and Cuthbert, 2016) that is disrupted in psychiatric disorders (Abend et al., 2020). Anticipating future threats is an adaptive response that effectively mobilizes defensive resources to manage dangers and risks. Exaggerated aversive anticipation produces a heightened state of anxiety and hypervigilance, and diminished anticipatory reactions may produce an undervaluation of risks and affective blunting to threats (Grupe and Nitschke, 2013). Aversive anticipation activates the threat circuit (anterior cingulate cortex, insula, amygdala) and can be objectively operationalized by physiological responses (e.g. startle reactivity, galvanic skin response) to cues associated with onset of negative stimuli (Bradley et al., 2018; Dichter et al., 2002; Hur et al., 2020; Nitschke et al., 2002; Sabatinelli et al., 2001; Sege et al., 2014). Understanding how childhood trauma affects this system, and how this system responds to trauma exposure over time, may allow us to understand how childhood trauma mediates increased risk for stress disorders.

Cross-sectional studies indicate that childhood trauma can be associated with both heightened and blunted aversive anticipatory responding in adulthood. There are studies reporting both increased (Jovanovic et al., 2009; Pole et al., 2007) and decreased acoustic startle reactivity and/or reactivity to aversive anticipation in individuals with a history of childhood trauma (Klauke et al., 2012; McTeague and Lang, 2012). The defensive acoustic startle response consists of a series of involuntary reflexes elicited by a sudden, intense auditory or tactile stimulus (de Haan et al., 2018; Kuhn et al., 2020). In all mammals, this response is heightened under conditions of threat, and hyperreactivity of startle under threat is consistently observed in trauma and anxiety-related disorders (Acheson et al., 2014; Grillon, 2008; Risbrough, 2010). However, the majority of studies often include subjects with both childhood trauma and adult psychiatric disorders such as PTSD and depression (Glenn et al., 2016; Taubitz et al., 2013; Taylor-Clift et al., 2011), which can make it challenging to know whether these findings are a result of childhood trauma, the effects from current psychiatric symptoms, or the effects of additional trauma exposure in adulthood. One way to address this question is to utilize a prospective study design of trauma exposure in adults with and without childhood adversity. Like the childhood trauma findings, the majority of prospective studies of adult trauma suggests that after recent trauma exposure, startle reactivity is most consistently increased in aversive or threat contexts (Griffin, 2008; Grillon et al., 2009; Guthrie and Bryant, 2005; Pole et al., 2009; Shalev et al., 2000), although there is also evidence of decreased startle reactivity in some populations (Glenn et al., 2016; Lis et al., 2020).

The aim of the current investigation was to leverage the Marine Resilience Study (MRS; Baker et al., 2012) dataset to examine first, whether a history of childhood trauma is associated with elevated or blunted anticipatory responding, and second, if threat anticipation is changed after trauma exposure in adulthood. The MRS is a large prospective evaluation of active duty Marines and accompanying Navy personnel with the aim of identifying neurocognitive predictors and biomarkers of risk and resilience for postcombat stress symptoms (Baker et al., 2012; Glenn et al., 2016). A benefit of the MRS study is that both childhood trauma and deployment-trauma is assayed — allowing us to test how a relatively recent adult trauma modulates the effect of childhood trauma on affective startle modulation. Here we focused on a self-reported measure of childhood trauma (i.e., The childhood trauma questionnaire, CTQ) (Bernstein et al., 2003), that was completed by participants prior to combat deployment. Study participants also completed a well-validated measure of aversive anticipation that probes the threat-detection circuit (e.g., insula and amygdala) (Acheson et al., 2012; Simmons et al., 2011; Simmons et al., 2006) that was given at three time points, pre-deployment, 3 months post-deployment, and 6 months post-deployment. The task was designed to assay the affective modulation of the acoustic startle response during aversive anticipation and image viewing, permitting assessment of anticipatory responses as well as responses to the emotional images. To assess deployment trauma, we utilized a self-report measure of both combat and post-battle experiences that are consistently associated with increased risk for PTSD symptoms (Baker et al., 2012; Vogt et al., 2013).

We hypothesized that startle response during aversive anticipation is increased in individuals with a history of childhood trauma compared to individuals without a history of trauma. Deployment trauma often leads to an increase in threat detection and startle reactivity (DiGangi et al., 2018; van Wingen et al., 2012). Therefore, we hypothesized that recent trauma experienced during deployment would moderate the amplification of aversive anticipation in individuals with a history of childhood trauma. We also conducted secondary analyses to examine whether particular childhood trauma types modulate aversive anticipation because of recent reports of differential influences of abuse versus neglect on emotion regulation and threat reactivity (McLaughlin et al., 2014; Puetz et al., 2020).

2. Methods and materials

2.1. Study design and participants

Participants (N = 2593) were recruited from First Marine Division infantry battalions preparing to deploy from bases in southern California to either Iraq (battalions 1 and 2, 2008) or Afghanistan (battalions 3 and 4, 2009–2010) (Baker et al., 2012). See Table 1 for demographic information. All active-duty members (Marines and accompanying Navy personnel) of these operational units were eligible. Participants attended three study visits during this study (1-month predeployment, 3-months postdeployment, and 6-months postdeployment). At each study visit, participants completed a battery of biological, psychophysiological, psychosocial, and neurocognitive assessments (Acheson et al., 2015b; Baker et al., 2012; Glenn et al., 2016). For the current study, we focused on one psychophysiological task and psychosocial measures associated with childhood and adult trauma and psychiatric symptoms. There were no exclusion criteria. Women were not included because female Marines were not part of infantry battalions at the time of testing. Study procedures were approved by the institutional review boards of the Veterans Affairs San Diego Healthcare System; the University of California San Diego; and the Naval Health Research Center. All participants provided voluntary written informed consent.

2.2. Self-report measures

Out of the 2593 participants consented, 2485 completed a 34-item modified version (Agorastos et al., 2014) of the original childhood trauma questionnaire (CTQ) (Bernstein et al., 1994) at the study visit. The CTQ is a retrospective measure assessing the presence or absence and frequency of childhood trauma events covering emotional abuse, physical abuse, sexual abuse, emotional neglect, and physical neglect. Presence or absence of specific trauma types (yes/no) was determined by meeting a threshold of moderate trauma severity as indicated by existing guidelines and prior research (cutoff scores: emotional abuse: $\geq$13; physical abuse: $\geq$10; sexual abuse: $\geq$8; emotional neglect: $\geq$15; physical neglect: $\geq$10) (Agorastos et al., 2014; Scher et al., 2001). We categorized our population according to the presence of early childhood trauma (at least one trauma subcategory experienced) and the absence of early childhood trauma (experienced none of the trauma subcategories).

Next, we examined whether deployment trauma moderated the effect of childhood trauma on anticipatory responding across time (see analytic approach section). Deployment trauma was assessed using a composite score comprised of the post-battle experiences and combat experience subscales from the Deployment Risk and Resilience Inventory-2 (DRRI-2) (Vogt et al., 2013). To determine whether childhood and deployment trauma associations with startle are independent of psychiatric symptoms, we ran secondary analyses where we entered

Table 1
Sample characteristics.

Variable	No Childhood Trauma (n = 1312)	Childhood Trauma (n = 1145)
Age	22.84 (3.56)	22.66 (3.31)
Race		
African American	4.1%	5.2%
American Indian/Alaskan Native	0.9%	2.1%
Asian	2.2%	3.4%
Native Hawaiian/Pacific Islander	1.4%	1.6%
White	85.4%%	81.3%
Other	6%	6.4%
Ethnicity		
Not Hispanic or Latino	79.3%	72.3%
Cuban	0.4%	0.3%
Mexican	11.9%	14.8%
Puerto Rican	1.8%	2.5%
South/Central American	2.4%	4.4%
Other	4.2%	5.7%
CTQ	31.42 (4.93)	50.34 (13.67)
Emotional Abuse		24.01%
Physical Abuse		69.26%
Sexual Abuse		14.59%
Emotional Neglect		41.48%
Physical Neglect		50.48%
CAPS-IV		
Pre-deployment	11.65 (13.12)	18.40 (16.83)
3-month post-deployment	12.26 (15.39)	19.26 (18.94)
6-month post-deployment	13.62 (15.81)	21.92 (19.48)
BAI		
Pre-deployment	5.81 (6.93)	7.94 (8.73)
3-month post-deployment	3.62 (6.18)	6.24 (8.52)
6-month post-deployment	3.32 (6.18)	5.42 (8.48)
BDI-II		
Pre-deployment	5.23 (6.38)	8.02 (8.47)
3-month post-deployment	5.21 (6.37)	8.00 (8.48)
6-month post-deployment	3.83 (6.04)	6.04 (7.67)
Deployment trauma		
Post-battle experiences	5.38 (4.70)	6.16 (4.89)
Combat-experiences	13.11 (10.93)	14.57 (12.06)

Note. CTQ=Childhood Trauma Questionnaire; CAPS-IV= Clinician-Administered PTSD Scale for DSM-IV; BAI=Beck Anxiety Inventory; BDI-II=Beck Depression Inventory II. For CTQ abuse type, the percent reported reflects the percent of participants meeting criteria for the specific trauma type (see Section 2.2 for details of criteria) and is calculated within the childhood trauma group only (i.e., percent is not based on full sample that includes no childhood trauma).

PTSD, depression, and anxiety as covariates in our models. Current PTSD symptoms were assessed at all three time points with the Clinician-Administered PTSD Scale (CAPS), a structured diagnostic interview designed to assess DSM-IV PTSD symptoms (Blake et al., 1995). Interrater reliability was high between CAPS interviewers and trained observers (intraclass correlation coefficient = 0.99, n = 261). Depressive symptoms were measured through self-report using the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996) and measured at all three time points. Anxiety symptoms were also measured through self-report using the Beck Anxiety Inventory (BAI) (Beck and Steer, 1993) and assessed at all three time points.

2.3. Anticipation task

The aversive anticipation startle task was similar to the one described in Acheson et al. (2012) and by others (Bannbers et al., 2011; Hellgren et al., 2012), and is modeled on a well validated neuroimaging task to assess brain circuit response to threat anticipation (Simmons et al., 2004; Simmons et al., 2006). During the anticipation task, participants were instructed that visual blue circle cues would signal the presentation of a pleasant image and yellow circle cues an unpleasant image. They were instructed to anticipate the type of scene they were about to see, pleasant or unpleasant, during the cue period, and that each image would be a new image. As shown in Fig. 1, participants were presented with a series of colored circle cues (8 s) followed by positive or negative images (2 s). Startle pulses (105 dB 40-ms broad-band pulses) were presented 2–6 s following the circle cue onset on 5 positive trials and 5 negative trials to assess anticipatory-potentiated startle. Startle pulses were also presented 1.5 s following image onset on 5 positive and 5 negative trials to assess fear potentiated startle. Images of both positive and negative valence were taken from both the International Affective Pictures Scale (IAPS) (Lang et al., 1999); and from a set of Iraq/Afghanistan war-related images that were scored for arousal and valence by a subset of Marine participants after MRS testing (See Supplementary Table S1). Images were counterbalanced across the 3 time points and balanced for levels of arousal across negative and positive images. Each image was shown only once during the procedure to enhance the unpredictability and potential aversiveness of the procedure, and trials were presented in pseudo-random order to control for startle habituation. All participants completed 10 trials of each valence (positive & negative). A total of 2457 participants completed the task at pre-deployment.

2.4. Startle acquisition and analysis

Prior to startle testing, hearing threshold was assessed using, 500, 1,000, 3,000, and 6000 Hz tones at 35 dB [A] via a Grason–Stadler Audiometer (Eden Prairie, MN, USA) at each study visit. Possible range of correct responses was 0–8 (4 frequencies, each ear). Startle pulses (white noise; 105 dB, 40 ms) were delivered using a San Diego Instruments (SDI, San Diego, CA, USA) SR-HLAB Electromyography (EMG) system. Stimuli were presented via E-Prime software (Psychology Software Tools, Inc., Sharpsburg, PA, USA) run on a desktop computer with a 48 cm monitor positioned directly in front of the participant. Eyeblink EMG responses to the acoustic pulses were recorded via two Ag/AgCl electrodes placed lateral to and below the *orbicularis oculi* muscles at the left eye and connected to the SDI SR-HLAB EMG system (Acheson et al., 2012, 2015a). A reference electrode was placed at the mastoid bone behind the left ear. Before electrode placement, skin was cleaned with alcohol and exfoliated with 3 M electrode prep tape. All electrode resistances were <10 kΩ. EMG data were recorded at a sampling rate of 1 KHz, amplified (0.5 mV electrode input was amplified to 2500 mV signal output) and band-pass filtered (100–1000 Hz).

EMG responses were rectified, smoothed (across 5 ms intervals) and visually examined across each trial by a trained technician to identify and remove artifact (e.g. voluntary blinks) that were not associated with the pulse onset (e.g. a response was not counted unless it was within 100 ms of pulse onset). To correct for baseline noise, the average response across the first 20 ms of the trial (i.e. no-stimulus response level before pulse initiation) was subtracted from the peak response of each trial (Acheson et al., 2012). Data points considered as non-responses (no increase above pre-probe baseline) and noise were removed from further analysis (<2% of trials). After pre-processing, 2446 participants remained at pre-deployment (No trauma group = 1307; Trauma group = 1139), 1789 participants at 3-month post-deployment (No trauma group = 968; Trauma group = 821), and 1554 participants at the 6-month post-deployment appointment (No trauma group = 849; Trauma group = 705).

2.5. Analytic approach

2.5.1. Contribution of childhood trauma to affective startle responses across time

We computed a Group × valence × time linear mixed-effects models (LME) using *lmer* from the *lme4* package in *R* (Bates et al., 2014; Brauer and Curtin, 2018). Models were computed for raw startle responses (after baseline correction) during the anticipation and image viewing separately. For both analyses, group (no trauma versus trauma) was

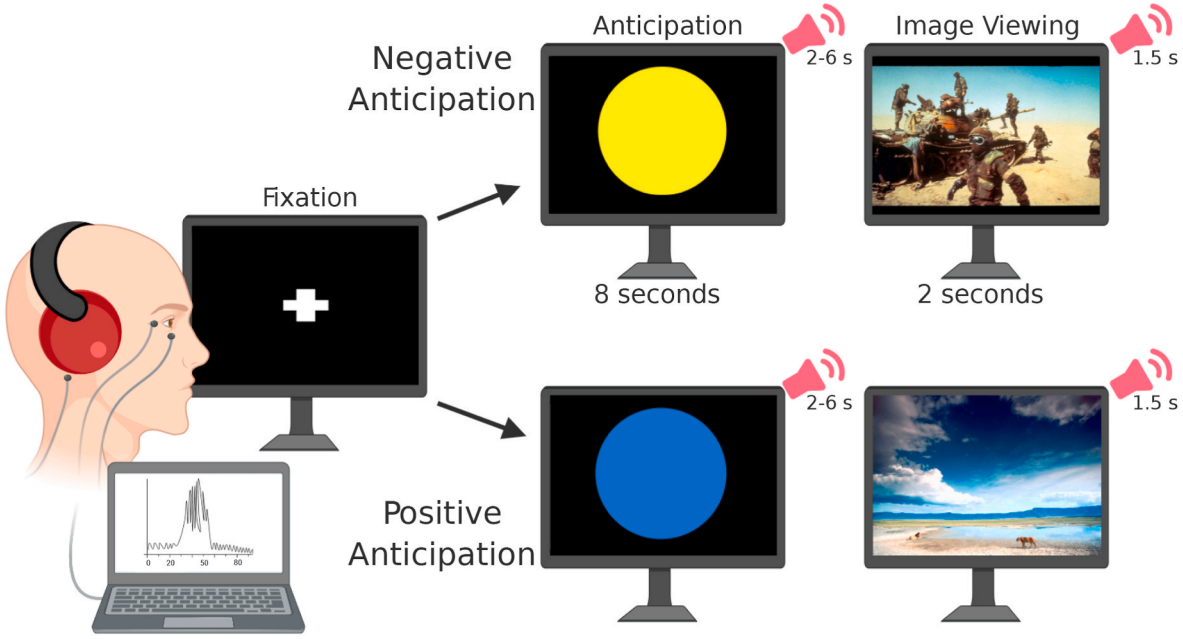

Fig. 1. Anticipation task. The trial sequences began with a fixation cross. Next, a yellow (top row) or blue circle (bottom row) was presented for 8 s. The color of the circle predicted whether a combat-related/negative picture would be presented (top row) or a pleasant/positive image would be presented (bottom row). After the anticipation period, an image appeared for 2 s. To measure startle response, acoustic startle probes (105 dB 40-ms) were presented 2–6 s during the anticipation period and 1.5 s into the image viewing. Portions of this figure was created using BioRender.com (San Francisco, CA). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

entered as a between-subject fixed effect, valence (positive versus negative) was entered as a within-subject categorical fixed effect, time was mean centered and entered as a fixed effect. The critical three way and lower order two-way interactions were additionally modeled as fixed effects. The random effect of time was also modeled to allow the effect of time to vary between participants. We ran a separate model to control for the effects of PTSD, depression, and anxiety symptoms by adding CAPS, BDI-II, and BAI as covariates to the model. To determine effects of hearing ability, we computed a separate model adding the number of correct responses on the hearing threshold test as a covariate to account for hearing differences potentially affecting startle reactivity. Finally, age and battalion cohort were added as nuisance covariates to our models to control for the effect that these variables may have on our primary analyses.

We performed three secondary analyses to further examine the findings from the primary model. First, we examined whether childhood trauma severity, defined as CTQ total score, was driving the childhood trauma × valence interaction. To test this, we replaced the categorical childhood trauma group with CTQ total scores (mean-centered) as a continuous variable. Second, following the approach by Agorastos et al. (2014), we examined the effect of "trauma load" on anticipatory startle by categorizing participants into three groups: no-trauma ($n = 1312$), one-trauma ($n = 530$), and two-or-more traumas ($n = 615$) and entered 3-level group as a fixed effect into the primary model. Third, the type of trauma experienced (e.g., abuse versus neglect) may also be an important factor in determining the long-term consequences on psychophysiological markers of aversive anticipation (McLaughlin et al., 2014). Therefore, we examined whether there was a specific form of childhood trauma (Emotional Abuse, Physical Abuse, Sexual Abuse, Emotional Neglect, and Physical Neglect) that underlies the findings from the primary model. For each of the five childhood trauma group types, we categorized participants into groups on the presence of a childhood trauma or no trauma. We then computed an LME to test the main effect of childhood trauma and the childhood trauma type group × valence interaction. A model was computed for each childhood trauma type (Jovanovic et al., 2009) and p-values were Bonferroni adjusted ($0.05 \div 5 = 0.01$) to control for Type I errors, where 5 is the number of models computed.

2.5.2. Contribution of deployment trauma and symptom development

We sought to answer the question of whether deployment trauma might moderate the influence of childhood trauma on anticipatory responding. To test this hypothesis, first we computed a model that included a composite score using the post-battle experiences and combat experience subscales from DRRI-2 (mean-centered) as a moderator to our primary model that included group, valence, and time and their interactions as fixed effects and time as a random effect.

3. Results

3.1. Anticipation

Across all groups and time points, startle was significantly greater when anticipating a negative image as compared to a positive image, valence: $\beta = 20.39$ ($SE = 1.19$, 95% CI = 18.05–22.72), t (6707.85) = 17.08, $p = 2.0 \times 10^{-16}$; valence × time interaction, $\beta = -2.16$ ($SE = 0.49$, 95% CI = −3.10 to −1.22), t (6713.14) = −4.51, $p = 6.57 \times 10^{-6}$; positive versus negative startle difference at each time point, $ps < .001$, see Fig. 2a). However, anticipatory startle reactivity, specifically during negative images, diminished across time, $negative_{slope} = -2.14$ ($SE = 0.49$), $t = -4.37$, $p < .01$; $positive_{slope} = 0.01$ ($SE = 0.49$), $t = 0.03$, $p = .98$. There was also a significant group × valence interaction, $\beta = -2.45$ ($SE = 1.19$, 95% CI = −4.79 to −0.11), t (6707.85) = −2.05, $p = .04$ (See Supplementary Table S2). As shown in Fig. 2b, post-hoc analyses show that there were no group differences in startle response when anticipating a positive image, $p = .98$. However, individuals with a history of childhood trauma had a lower startle response when anticipating a negative image compared to individuals without a history of childhood trauma, $p = .04$ (Tukey corrected). The significant CTQ × valence interaction remained significant after entering PTSD, depression, and anxiety symptoms as covariates ($p = .034$) and when controlling for age and battalion cohort as covariates into the model, $ps < .048$. No other

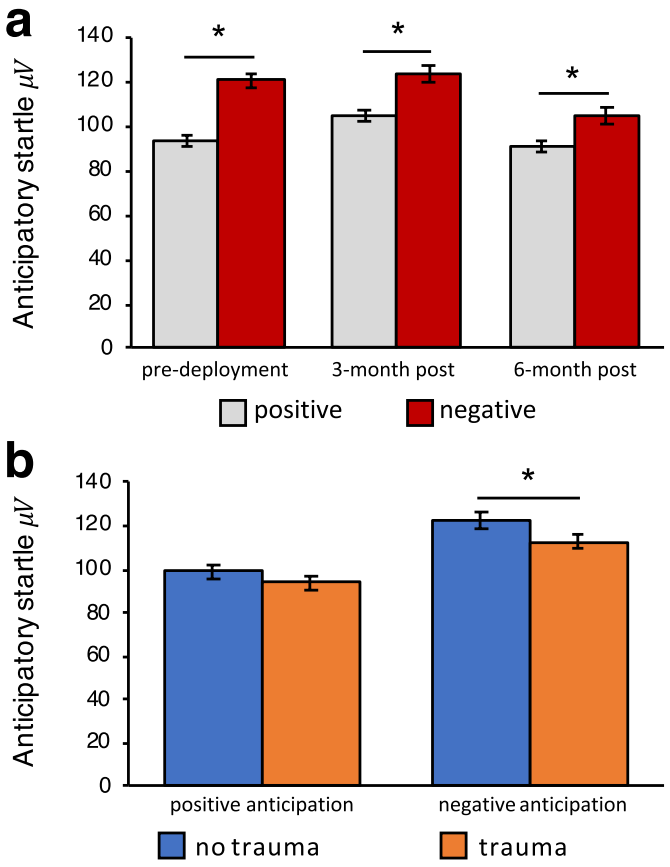

Fig. 2. Bar plot depicts the estimated marginal means reported from (a) the significant valence × time interaction. Anticipatory startle response was significantly higher for negative than positive images at all three time points. (b) Bar plot depicts the estimated marginal means reported from the significant group × valence interaction. Anticipatory startle was lower for individuals with a history of childhood trauma than those without for negative but not positive anticipation.

main effects or interactions were significant, *ts* < 1.35, *ps* > .18.

We next examined whether the severity of trauma was associated with aversive anticipation responses by examining either CTQ total score (range of 25–106) or ordinal score (0, 1, 2+ subcategories of trauma). CTQ total score was not associated with differences in anticipatory startle responding: CTQ main effect: $\beta = -0.22$ (*SE* = 0.18, 95% CI = −0.62 – 0.10), t (2674.69) = −1.21, p = .23; CTQ interactions: *ps* > .08 (see Supplementary Table S3). When participants were categorized into three groups, the group × valence interaction was not significant (p = .064).

Next, we examined if exposure to a particular trauma type was driving the results of differential startle response between negative and positive anticipation. We examined each trauma type in five separate LMEs where abuse and stimulus valence were modeled as fixed effects and time was modeled as both a fixed and random effect (Emotional Abuse, Physical Abuse, Sexual Abuse, Emotional Neglect, and Physical Neglect). However, no abuse type was significant after controlling for multiple comparisons (Bonferroni corrected p-values > .01).

We next conducted analyses to determine if the effect of childhood trauma is moderated by deployment trauma. Deployment-related trauma (DRRI-2) was significantly associated with increased startle (see Supplementary Table S4). Startle increased post-deployment when individuals reported higher deployment trauma, and this effect was independent of image valence (time × deployment trauma interaction, p = .02; see Fig. 3). The group × valence interaction was reduced (p = .056) and the valence × time interaction remained significant (p = .003).

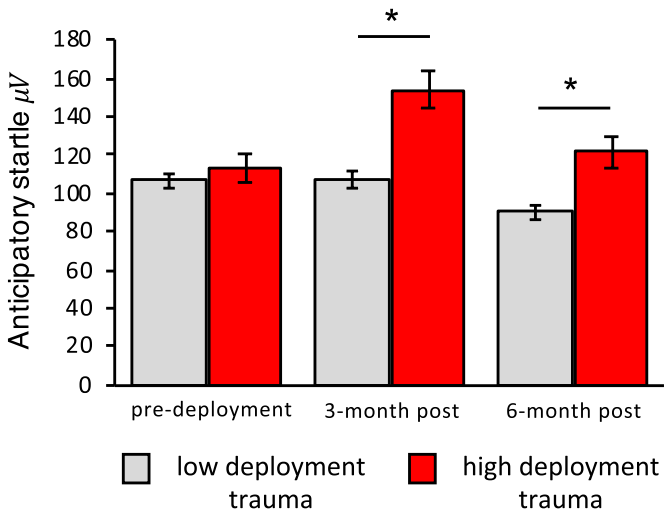

Fig. 3. Bar plot depicts the estimated marginal means from the significant deployment trauma × time interaction. Anticipatory startle response was significantly higher at 3-month and 6-month post deployment for high levels of deployment trauma regardless of valence. High and low levels of pre-deployment trauma were categorized for visual purposes. Error bars denote standard error of the mean. *p < .05 Tukey corrected.

3.2. Image viewing

Startle was increased during negative images compared to positive images ($\beta = 6.92$ (*SE* = 1.54, 95% CI = 3.9–9.94), t (6921.26) = 4.49, $p = 7.33 \times 10^{-6}$), however this effect was relatively small and inconsistent across time-points with increases predominating post-deployment but not pre-deployment (valence × time interaction, $\beta = 1.42$, *SE* = 0.65, 95% CI = 0.21–2.63, t (6921.55) = 2.29, p = .022; pre = deployment, p = .75, 3-month, p < .0001, 6-mo post-deployment;, p <. 0001) (see Supplementary Figure 1a). Unlike aversive anticipation, there were no main effects or interactions with childhood trauma group when directly viewing affective images ($\beta = -9.59$ (*SE* = 5.24, 95% CI = −19.85 – 0.67), t (2601.78) = −1.83, p = .07; group × valence, p = .54, other main effects and interactions *ts* < 1.46, *ps* > .15) (See Supplementary Table S5). Deployment trauma was associated with increased startle across time (time × deployment trauma interaction, p = .003; Supplementary Figure 1b). Increases in levels of deployment trauma were associated with a greater startle response to negative images compared to positive images (valence × deployment trauma interaction, p = .049; see Supplementary Table S6).

4. Discussion

This is the first large (N > 2500) study to examine how early life adversity modifies threat response before and after trauma exposure in adulthood. Individuals who reported a history of childhood trauma, compared to those who did not, consistently showed significant albeit modest decreases in startle response when anticipating negative stimuli but not when anticipating positive stimuli. This blunted anticipatory response was stable across 3 different visits over a 1.5 year long time span and was significant even after controlling for PTSD, depression, and anxiety psychiatric symptoms, suggesting that although the effect size was modest, the association was robust and thus likely reliable. In contrast to childhood trauma, deployment trauma was associated with robust *increases* in startle reactivity after deployment regardless of valence when anticipating emotional images and specifically increased when viewing negative images. Deployment trauma associations were independent from childhood trauma exposure. We interpreted this finding as evidence for a modulatory effect of recent combat trauma on defensive startle reactivity. Collectively, these results demonstrate that

childhood trauma has long-term consequences during states of negative anticipation and that deployment-related stress has an independent role in the modulation of defensive responses to threats.

A primary finding that we observed was the opposite pattern of results between childhood trauma and deployment trauma on startle reactivity. Whereas childhood trauma was associated with a blunted anticipatory response, recent deployment trauma was associated with an increase in both affective anticipation and startle to negative images. The deployment trauma-related increase in startle is consistent with the extant literature showing that deployment trauma is consistently associated with enhanced threat detection and startle reactivity (DiGangi et al., 2018; Glenn et al., 2017; van Wingen et al., 2012). The effects of childhood trauma are also in line with a recent study showing childhood trauma in women is associated with blunted startle reactivity to conditioned fear cues (Lis et al., 2020). This similar finding in women suggests that childhood trauma associations with blunted defensive startle is not unique to men. One parsimonious explanation for this differential pattern of trauma associations with startle is the ages at which these traumas were experienced (Gee, 2019). Trauma experienced in early life, a critical period of brain development, results in developmental abnormalities resulting in blunting of the stress response via the salience network (Zhu et al., 2019), through the hypothalamic-pituitary-adrenal (HPA) axis (Nemeroff, 2016; Young et al., 2020) or its neuroendocrine modulators (Kaczmarczyk et al., 2019; Wiedemann et al., 2000). This pattern of differential effects of trauma across age is also observed on the HPA axis, with adults reporting a history of childhood trauma showing decreased cortisol reactivity to stressors (Bunea et al., 2017; MacMillan et al., 2009), while stress in adulthood is linked to excitation of these systems (Herman et al., 2005; van Oort et al., 2017). The age that childhood trauma is experienced can also lead to dissociable outcomes in threat-response circuits. Youth who experience trauma in early childhood show a decrease in threat-reactivity as measured by amygdala activity, while youth who experienced trauma in adolescence display increased threat reactivity (Zhu et al., 2019).

Presence of neuropsychiatric symptoms also modify trauma associations with affective modulation of startle; individuals with a history of childhood trauma with significant anxiety and depressive comorbidity exhibit decreased startle (McTeague and Lang, 2012). Yet, our results indicate that blunted startle during aversive anticipation in individuals with childhood trauma remains significant even after controlling for psychiatric symptoms of PTSD, depression, and anxiety — suggesting a durable impact regardless of psychiatric comorbidity. Another potential reason for the dissociable effect between childhood and deployment trauma on affective modulation of startle could be due to the differences in the types of trauma experienced (McLaughlin et al., 2020). Childhood trauma and deployment trauma likely reflect different levels of threat chronicity, predictability, and severity — which may lead to differential coordination of biological mechanisms required to regulate responses to these differential trauma types (Ellis et al., 2009; McLaughlin and Sheridan, 2016). Collectively, these results indicate that early life trauma and later adult trauma during deployment have a multifaceted impact on systems underlying defensive threat responding including aversive anticipation (Gee, 2021; McLaughlin et al., 2014; Nemeroff, 2016).

Strengths of the study include a very large sample size in a relatively homogenous group (sex, age, adult trauma type, occupation) and the prospective and longitudinal design to assess reliability of findings and effects of trauma exposure. Limitations are that because the group was relatively homogenous it is not clear how well these findings generalize to other populations (e.g. women). Given the clear evidence for sex modifying the effects of stress during development on anxiety phenotypes and trauma risk (Bale and Epperson, 2015) and increased prevalence of depressive, anxiety, and fear related disorders in female civilian and military populations (Levine and Land, 2014; Perrin et al., 2014), it will be important to investigate whether the results of the current investigation generalize to women and civilian populations. Second, our task contained elements of both certainty (an aversive image is imminent) and predictability (colored circle always predicted the aversive image) (Bennett et al., 2018; Hur et al., 2020). However, many forms of psychopathology are characterized by exaggerated responses to unpredictable and uncertain threats compared to when the threat is certain and predictable (Grillon et al., 2017; Grupe and Nitschke, 2013). Therefore, future work will be necessary to determine whether childhood trauma is characterized by a blunted or heightened startle response to uncertain threats. Third, we relied on a retrospective self-report of childhood trauma, which can be limited in accuracy due to the time between the trauma and the self-report (Shaffer et al., 2008; Tajima et al., 2004) and did not allow for more refined assessments of when and for how long the trauma occurred (instruction in the CTQ is limited to "when I was growing up."). Finally, in human studies such as the current study it is difficult to control for time between trauma and assessment (i.e., differential effects may be due to differential passage of time after the trauma exposure rather than age effects). However, animal studies support that age of stress exposure has differential effects on startle and other threat-response traits even when controlling for time after trauma (Toth et al., 2014; Yohn and Blendy, 2017).

5. Conclusion

These results provide evidence that a history of childhood trauma is associated with a reduced startle response when anticipating negative images while deployment trauma in adulthood is associated with an overall increase in startle reactivity independent of stimulus valence. Our findings set the stage for a more detailed understanding of how early life trauma and recent deployment-related stressors in adulthood have a dissociable impact on psychophysiological indices of anticipating and responding to threats, key mechanisms implicated in the development of neuropsychiatric disorders.

6. Data availability

Data will be available under institutional approved data use agreement.

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Author contribution

Daniel M. Stout: Paper conceptualization, Formal analysis, Visualization, Writing-wrote the manuscript. Susan Powell: Methodology, Writing – review & editing. Aileen Kangavary: Writing – review & editing. Dean T. Acheson: Methodology, Data curation, Formal analysis, Writing – review & editing. Caroline M. Nievergelt: Conceptualization, Data curation, Supervision Investigation, Writing – review & editing. Taylor Kash: Data curation, Data collection. Writing-review & editing. Alan. N. Simmons: Methodology, Writing – review & editing. Dewleen G. Baker: Methodology, Conceptualization, Investigation, Supervision,

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Declaration of competing interest

All authors declare no conflicts of interest.

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Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ynstr.2021.100362.

APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at.

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