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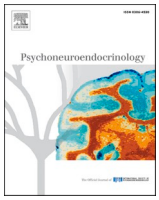

Threat exposure moderates associations between neural and physiological indices of emotion reactivity in adolescent females

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ABSTRACT

Early life adversity (ELA) characterized by threat (e.g., abuse, witnessing violence) impacts neural and physiologic systems involved in emotion reactivity; however, research on how threat exposure impacts the interplay between these systems is limited. This study investigates ELA characterized by threat as a potential moderator of the association between (a) neural activity during a negative image processing fMRI task and (b) cortisol production following a modified Trier Social Stress Test (TSST). The sample is comprised of 117 young adolescent females (M_{age} = 11.90 years, SD = 1.69) at elevated risk for internalizing problems. Whole-brain analyses revealed a positive association between cortisol production and increased right lateral orbitofrontal cortex activity during the emotion reactivity task. In moderation models, threat exposure interacted with bilateral amygdala activation (b = −3.34, p = 0.021) and bilateral hippocampal activation (b = −4.14, p = 0.047) to predict cortisol response to the TSST. Specifically, participants with low, but not high, levels of threat exposure demonstrated a positive association between cortisol production and neural activity in these regions, while no significant association emerged for participants with high threat exposure. Findings contribute to the growing field of research connecting physiological and neural emotion processing and response systems, suggesting that dimensions of ELA may uniquely disrupt associations between neural activation and cortisol production.

1. Introduction

Experiences of early life adversity (ELA), defined as stressful events occurring prior to age 18 that threaten a child's sense of safety or impact normative development, are associated with physical morbidity, mortality, and virtually all forms of psychopathology across the lifespan (Kessler et al., 2010). Identifying mechanisms of risk is necessary to ameliorate the impact of ELA on health and well-being. An individual's response to stressful or emotion-eliciting stimuli (i.e., emotion reactivity) stands out among candidate mechanisms, given its relation to both ELA and mental health problems (Kim and Cicchetti, 2010). Disruptions in emotion reactivity can manifest as increased negative affect, atypical (i.e., elevated or blunted) physiologic reactivity, difficulty regulating emotions, and increased salience of negative information (Gross and Jazaieri, 2014). The association between ELA characterized by *threat* (e.g., physical abuse, sexual abuse, witnessing domestic violence) and emotion reactivity is particularly robust (Sheridan and McLaughlin, 2014; McLaughlin et al., 2019), even after controlling for other forms of ELA such as deprivation (e.g., lack of cognitive stimulation in early childhood, neglect).

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The dimensional model of adversity and psychopathology (DMAP), a mechanistic theory of the impact of specific forms of adversity on neurodevelopment, delineates threat (e.g., abuse, exposure to violence) from deprivation (e.g., neglect, lack of cognitive stimulation). In the DMAP, the association between ELA and emotion reactivity is posited to result from exposure to adverse experiences that impact the developing neural networks supporting environmental processing, reactivity, and regulation (Sheridan and McLaughlin, 2014). Research has established that *threat* exposure is associated with altered development of the neuroendocrine systems that underlie these neural networks as well as atypical physiologic activation following perceived environmental stressors (Busso et al., 2016; Thompson et al., 2014). To date, most research investigating the impact of threat on these components of neurobiological development has been conducted in relatively separate literatures. However, neural and physiologic systems work together to facilitate emotion reactivity and regulation processes; therefore, understanding how threat exposure impacts the link between these systems represents a critical step in the accurate characterization of emotion reactivity following ELA.

One body of work has focused on the impact of ELA on the hypothalamic-pituitary-adrenal (HPA) axis, a vital neuroendocrine system that mediates the impact of stress by regulating the release of cortisol (steroid hormone) from the adrenal glands. Although a certain level of cortisol secretion in response to acute stress is necessary for energy mobilization (McEwen, 2007; Sapolsky et al., 2000a), long-term activation of the HPA axis can negatively contribute to allostatic load and, consequently, mental and physical health deterioration (Sapolsky et al., 2000a). Evidence suggests that exposure to threatening experiences in childhood, such as physical abuse, can disrupt the feedback pathways of the HPA axis due to early sustained periods of hyper-reactivity, altering the regulation of glucocorticoid receptors and resulting in blunted cortisol in response to stress (Bunea et al., 2017; Gunnar et al., 2015; Machlin et al., 2019; McEwen, 2007). Long-term blunted cortisol reactivity patterns, in turn, are linked to emotion dysregulation, health problems (e.g., obesity, cardiovascular disease), and the emergence of multiple psychiatric disorders across the life course (Zorn et al., 2017).

A second body of research has documented associations between ELA characterized by threat and neural processing of negative environmental stimuli. In typically developing individuals, regions that co-activate as a part of the salience network (e.g., insula, amygdala) and are recruited in emotion regulation tasks (e.g., ventromedial prefrontal cortex, hippocampus) tend to be recruited to a greater degree in response to negative stimuli (Jankord and Herman, 2008; Ochsner and Gross, 2014). In individuals exposed to ELA characterized by threat, activation of these regions is further enhanced. Studies have documented greater recruitment of regions in the salience network (i.e., amygdala, putamen, anterior insula) for those exposed to high levels of threat as compared to peers with little or no threat exposure (Jenness et al., 2021; McLaughlin et al., 2015), suggesting an increased detection and interpretation of negative stimuli as potentially dangerous. Threat exposure is also associated with reduced activation in regions involved in emotional control and memory when viewing negative stimuli, including the ventromedial prefrontal cortex (vmPFC) and hippocampus (Jenness et al., 2021; McLaughlin et al., 2015), which may indicate a compromised ability to engage in higher-order emotion regulation strategies that require individuals to identify a regulatory goal, hold this goal in working memory, and select and implement a corresponding regulatory strategy (e.g., cognitive reappraisal; Silvers, 2020).

The neural regions responsible for coordinating HPA axis activity overlap with the regions involved in the perception and modulation of emotion that are selectively impacted by threat exposure, including the vmPFC, amygdala, and hippocampus (Lupien et al., 2009; McEwen, 2007), underscoring the importance of examining brain-body connections. In the extant literature, increased amygdala activation in response to negative stimuli is associated with heightened endogenous cortisol production in response to psychological stressors, whereas engagement of prefrontal regions and the hippocampus in response to negative stimuli have each been related to decreased salivary cortisol (Harrewijn et al., 2020). These findings contribute to a paradoxical understanding of the impact of ELA on the biological underpinnings of emotion reactivity, such that threat exposure has been linked to patterns of neural activation consistent with *elevated* cortisol (e.g., amygdala hyperactivity), yet evidence increasingly links ELA to *blunted* cortisol production (Bunea et al., 2017). Therefore, it is possible that one consequence of childhood threat exposure is the de-coupling of typical physiologic stress responses (e.g., HPA axis activation) from expected neural activation patterns. An integrated, multi-system approach is needed to elucidate the impact of threat-based ELA on brain-body connections.

The present study 1) examined the association between HPA axis regulation in response to acute social stress and activation of neural circuitry involved in emotion reactivity and 2) investigated threat exposure as a potential moderator of this association. We focused on adolescent females to decrease heterogeneity in neurobiological reactivity markers related to biological sex and to capture a salient developmental context that includes still-maturing neurobiologic systems, increased exposure to interpersonal (e.g., peer) stress, and increased risk for emerging mental and physical health symptoms (Costello et al., 2011; Rose and Rudolph, 2006; Thompson et al., 2004). We first conducted a whole-brain analysis to examine the association between neural activation during the processing of negative emotional stimuli and cortisol production in response to an acute social stress task. No studies to our knowledge have examined this association in adolescent females; therefore, this analysis is largely exploratory. However, the few studies that have utilized similar paradigms in other populations suggest a positive association between cortisol production and amygdala activity and a negative association between cortisol and vmPFC and hippocampal activity (see Harrewijn et al., 2020 for a meta-analytic review), and we hypothesize that these associations will emerge in the present sample.

Next, we next investigated whether exposure to threat-based ELA moderates the association between neural substrates of emotion processing and cortisol in three predetermined regions of interest: the amygdala, the vmPFC, and the hippocampus. We hypothesized that threat-based ELA would disrupt the expected cross-system links between neural activation and cortisol reactivity. Specifically, we hypothesized that individuals with low/absent threat exposure would demonstrate associations between neural activation and cortisol, such that high cortisol production will be associated with heightened amygdala activation and decreased vmPFC and hippocampal activity, consistent with prior research, whereas these associations would be absent for individuals with a history of high threat exposure. We expected these associations to remain robust while controlling for other forms of ELA, specifically deprivation, as well as age, pubertal timing, medication use, time of day of cortisol sampling, time between study visits, and symptoms of psychopathology.

2. Method

2.1. Participants

Participants were 117 adolescents assigned female at birth who endorsed experiencing at least one mental health concern (e.g., depression, anxiety) in the two years prior to study recruitment. Participants provided data on ELA exposure, saliva samples, and completed scanning procedures. Of note, participants were recruited from a larger sample of 229 adolescents assigned female sex at birth, originally enrolled in a longitudinal investigation of biological and behavioral responses to stress as risk factors for internalizing symptoms and self-injurious thoughts and behaviors. Participants were initially recruited through local psychiatric inpatient units (approximately 40%) and community advertisements (e.g., flyers, e-mails, TV commercials).

Eligibility for the study included: (a) female sex; (b) 9–14 years old at baseline assessment; (c) caregiver (parent or guardian) available for study participation; and (d) a history of mental health concerns (e.g., affective disorders, anxiety, substance use, disruptive behavior disorders) within the past two years. Exclusion criteria included active psychosis, developmental disorder, and lack of ability to speak/read English. A preliminary phone interview with adolescents' caregivers was conducted to determine the presence of mental health concerns, including whether adolescents had received a prior diagnosis, prior treatment, or experienced prior symptomatology.

A subset of participants was invited to participate in a subsequent fMRI scan visit. Participants who declined being contacted for follow-up ($n = 1$), were left-handed ($n = 13$), had MRI contraindications ($n = 4$), or were unable to participate for other reasons (e.g., moved out of state, did not complete baseline assessment; $n = 13$) were not eligible, and 38 participants declined participation, yielding a sample of 138. Within the scanned subsample, participants with missing or unusable (i.e., data that did not meet imaging quality checks) emotion reactivity fMRI task data ($n = 21$) were excluded from the present analyses, yielding an analytic sample of 117. Excluded participants differed from the analytic sample on age ($t = -4.41$, $p < .001$), such that excluded participants were younger than included participants. There were no other significant group differences in demographic variables or adversity (threat or deprivation) exposure.

Eligible adolescents and their caregivers were invited to the laboratory to complete a series of tasks, including surveys collecting demographic information and data on ELA, a social stress task with accompanying saliva sampling to assess cortisol, and a functional MRI task to assess the neural correlates of emotion reactivity/processing. The average age of participants was 11.90 years old ($SD = 1.69$) at the time of the initial assessment and 12.81 ($SD = 1.92$) at the time of the scan visit. On average, participants completed their fMRI scan 3.99 months after their baseline assessment (range = 0–37 months; $SD = 6.77$ months). Participants self-reported as Black or African American ($n = 38$, 32.5%), Asian ($n = 3$, 2.6%), White/Caucasian ($n = 51$, 43.6%), Hispanic/Latina ($n = 7$, 6.0%), American Indian or Alaska Native ($n = 2$, 1.7%), or more than one race/other ($n = 16$, 13.7%).

2.2. Social stress task and cortisol

Participants completed a modified Trier Social Stress Test (TSST; Kirschbaum et al., 1993) to induce stress in the laboratory and activate the HPA axis approximately three hours after arrival at the laboratory during their initial (baseline) visit. Prior to the TSST, participants underwent a relaxation period consisting of watching an emotionally neutral movie clip to ensure that pre-task cortisol reflected resting HPA axis activity. Participants then received instructions to imagine that they were auditioning for a reality show about how teenagers make friends and interact with other teens (Calhoun et al., 2012). Participants were allotted a one-minute preparation period followed by a three-minute audition/speech. During the speech presentation period, participants were oriented towards a camera connected to a closed-circuit feedback screen displaying their own live image. Two young adult judges were present in the room with the adolescent female during the speech task to evaluate the participant's speech. The presence of adult judges was intended to increase the social-evaluative nature of the task, given that laboratory tasks that elicit social evaluation and threaten an individual's social self are known to specifically activate HPA axis stress responses. The judges did not provide feedback during the speech and prompted participants to continue their speech if they stopped before the end of the allotted three-minute period. Self-reported affect was measured at baseline (approximately 2 h after arrival to the lab, 50 min prior to the stress task) and immediately post-stress task with a modified version of the Positive and Negative Affect Schedule for Children (Laurent et al., 1999). Participants were fully debriefed following this task.

Participants provided saliva using the Sarstedt Salivette Synthetic Swab (Sarstedt, Newton, NC 28658, USA) at five time points: (1) upon arrival, (2) pre-TSST baseline (i.e., immediately before TSST instructions), (3) 20 min after the TSST, (4) 30 min after the TSST, and (5) 40 min after the TSST. No stressful procedures were administered for 30 min before the baseline sample or for 40 min after the speech. Salivary samples were frozen and stored at − 25 °C and shipped on dry ice to Pennsylvania State University's Behavioral Endocrinology Laboratory for assay (Salimetrics, PA) for assay using EIA. EIA kits have excellent lower limit sensitivity, ranging from 0.007 μg/dL to 1.2 μg/mL. Samples were assayed in duplicate and the mean levels for each sample were utilized for analysis. The inter-assay coefficient of variation (CV) for each sample ranged from 5.62% to 6.54%.

To index cortisol, we plotted a reactivity curve for each participant, calculating the area under the curve (AUC) with respect to ground (AUCg), following methods set forth by Pruessner et al. (2003). AUCg was chosen as a measure of cortisol response because it captures the intensity and sensitivity of the HPA axis response, including both baseline cortisol levels and the cortisol response to the stressor, therefore providing a comprehensive measure of overall cortisol output (Fekedulegn et al., 2007; Pruessner et al., 2003). Further, AUCg is less influenced by cortisol fluctuations that are not related to the stressor, such as circadian variations, whereas AUC with respect to increase (AUCi) is sensitive to cortisol increases that are not related to the stressor and may not reflect the individual's overall cortisol output (Pruessner et al., 2003). Importantly, because saliva sample 1 (arrival) was collected over 60 min prior to the TSST, AUCg was calculated using samples 2–5, as sample 1 may not reflect the individual's true baseline cortisol level and may lead to an overestimation of the cortisol response to the TSST (Pruessner et al., 2003).

2.3. Emotion reactivity task (in-scanner)

During the second laboratory visit, participants completed a simple task to assess neural markers of emotion reactivity based on a task widely used in adults (Ochsner et al., 2004) that has been successfully adapted for adolescent and pediatric samples (Jenness et al., 2021; McLaughlin et al., 2015; Silvers et al., 2012, 2017). In this task, participants viewed images from the International Affective Picture System (Lang et al., 2008) and from a normed sample of images for youth (available here: https://osf.io/43hfq/) that were either neutral (e.g., a leaf) or negative (e.g., a child in a medical gown crying; Jenness et al., 2021). Pictures were preceded by a "look" cue, during which participants were instructed to simply look at the image and allow emotions to unfold naturally without altering their emotional reaction. An additional cue of "decrease" was given before a subset of negative images to prompt participants to engage in previously reviewed emotion regulation strategies; however, decrease trials were not included in the current analyses, given our focus on emotion reactivity.

After each stimulus, participants rated the strength of their emotional reaction on a 5-point scale that they received extensive training on prior to the task. During training, participants were given explicit anchors for the emotion ratings ranging from a minimum of 0, "I experienced almost no emotion," to a maximum of 4, "It would be hard for me to imagine feeling this emotion more strongly." Verbal descriptors of "Low (0,1)," "Medium (2)," and "Strong (3,4)" were also included on the rating screen to remind participants of the anchors. A constant of "1" was added to all responses for analyses to translate the rating scale range to 1–5. Negative and neutral pictures were randomized within each run.

In total, adolescents participated in 6 runs lasting 6 min and 37 s each. The task proceeded as follows: An instructional cue appeared for 2 s, the emotional stimulus appeared for 4, 6, or 8 s, the rating screen appeared for 4 s, and the inter-trial interval (ITI) lasted from 0.5 to 7.5 s (see Fig. 1). A pseudo-exponential distribution was used to select ITI and stimulus lengths, following accepted guidelines (Ollinger et al., 2001), and the data were analyzed using an event-related design. Specifically,

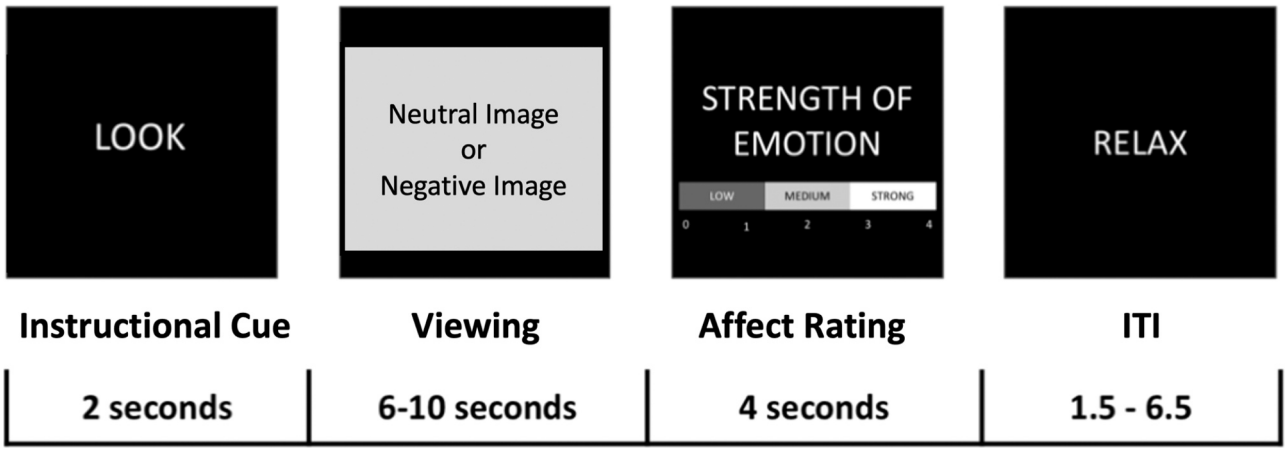


Fig. 1. Emotion reactivity fMRI task.

we used approximately 50% of the fastest possible duration, 25% of the middle duration, and 25% of the longest duration for both the emotional stimulus and ITI. Stimuli were presented in one of 2 series (Series A/Series B, counterbalanced across participants to reduce the effects of single pictures on neural activation), each consisting of 3 runs. The task included 48 trials of each type distributed evenly across runs such that a given run contained eight neutral stimuli with the "look" instruction, eight negative stimuli with the "look" instruction, and eight negative stimuli with the "decrease" instruction. Importantly, because a social evaluation and rejection paradigm was introduced after the third run, only the first three runs were used in analyses. The main effects of the emotion reactivity condition, including self-reported affect, the neural correlates of look versus decrease, neural cues across all respondents, and the impact of rejection on the neural correlates of emotion regulation, are reported elsewhere (see Miller et al., 2018).

2.4. Image acquisition and processing

Scanning was performed on a 3.0-T Siemens Prisma Scanner using a 32-channel head coil. T1-weighted multiecho MPRAGE volumes were acquired for coregistration with fMRI images (repetition time= 2530 ms, echo time = 1670–7250 ms, flip angle = 7°, field of view = 192 × 192 mm, 176 slices, 1 ×1×1 mm voxels). BOLD signal during functional runs was acquired using a gradient-echo T2-weighted EPI sequence. An online prospective motion correction algorithm was used to reduce motion artifacts during functional scans. Standard fMRI scanning acquisition parameters were followed (repetition time = 2500 ms, echo time = 28 ms, flip angle = 90°, 44 slices, 2.4 ×2.4 ×2.4 mm voxels). Before each scan, three images were acquired and discarded.

Preprocessing of functional MRI data was implemented using fMRIPrep (Esteban et al., 2019), including slice-timing correction, motion correction, intensity correction, skull-stripping, spatial normalization, segmentation, and co-registration. Framewise displacement exceeding 0.9 mm in any direction was identified via the fsl_motion_outliers program in FSL (Jenkinson et al., 2012), and a four-dimensional registration algorithm simultaneously corrected for motion and slice-timing using NiPy (Roche, 2011). Advanced Normalization Tools software (Avants et al., 2011) was used to register images to the Montreal Neurologic Institutes (MNI) standards space. Preprocessed data were analyzed using FSL, including spatial smoothing (5-mm full width at half maximum) and high-pass temporal filtering. Participants were excluded due to motion if 40% of the time points exceeded 0.9 mm relative motion ($N = 5$ participants were excluded for this reason).

Select regions of interest (ROIs) were extracted using FSLutils (Jenkinson et al., 2012) from the preprocessed and nuisance-corrected images. ROIs were selected based on existing models of the neural underpinnings of HPA axis activity and emotion perception and modulation processes, including the vmPFC, amygdala, and hippocampus (Dedovic et al., 2009; Lupien et al., 2009; McEwen, 2007). The present analyses focused on regions selected from the Harvard–Oxford atlas (Harvard-Center for Morphometric Analysis). Functional regions of interest for the look negative > look neutral contrast were extracted from the peak of activation in the amygdala, vmPFC, and hippocampus with a 10 mm sphere and averaged bilaterally.

2.5. Early life adversity

Exposure to ELA characterized by threat was assessed using select items from the Childhood Trauma Questionnaire (CTQ; Bernstein et al., 2003), Stress and Adversity Inventory for Adolescents (STRAIN; Slavich et al., 2019), Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998), Peer Victimization Questionnaire (PVQ; Prinstein et al., 2001), and Parenting Styles and Dimensions Questionnaire (PSDQ; Robinson et al., 2001). Exposure to ELA characterized by deprivation was assessed using select items from the Child Chronic Strain Questionnaire (CCSQ; Rudolph et al., 2001), CTQ, and STRAIN.

The threat and deprivation composites used in analyses were created by first categorizing items by exposure type to avoid duplicate endorsements (e.g., positive endorsement of sexual abuse on the CTQ, STRAIN, and MINI). Threat exposures were categorized as: (1) sexual abuse or trauma ($\alpha = 0.92$), (2) physical abuse or harsh discipline ($\alpha = 0.69$), (3) emotional abuse ($\alpha = 0.81$), and (4) physical danger outside of the home ($\alpha = 0.69$). Deprivation exposures were categorized as (1) neglect/lack of parental availability ($\alpha = 0.76$) and (2) material deprivation ($\alpha = 0.81$). A list of items in each category is provided in Supplementary Table 1. Participants received a score of 1 in a given category if any item contributing to that category was endorsed. Participants received a score of 0 in a given category if no endorsements were present. Binary scores in each category were summed to create the final threat exposure variable (range: 0–4) and deprivation exposure variable (range: 0–2).

2.6. Pubertal timing

Pubertal timing was assessed to account for variation in puberty status among participants and the possible impact of puberty on neurobiological functioning (Ferri et al., 2014) via the Pubertal Development Scale (PDS; Petersen et al., 1988). The PDS, which was completed by caregivers and participants, consists of five items on a 4-point rating scale (1 = no development to 4 = development seems complete) that assess aspects of participants' physical development, including body hair, skin changes, growth spurt, breast development, and menarche (binary item; 1 = no, 4 = yes). Mean scores computed for

self-report (Cronbach's $\alpha = .86$) and caregiver-report (Cronbach's $\alpha = .86$) were strongly correlated ($r = .81$, $p < .001$). To incorporate multiple informants and create a more robust index, a cross-rater mean score was computed across self- and caregiver-report items (Cronbach's $\alpha = .93$).

2.7. Psychopathology symptoms

In line with past work (Rodriguez-Thompson et al., 2023), psychopathology was operationalized using a higher-order p factor model. The following questionnaires were used to compute p factor: the Youth-Self Report Aggressive Behavior subscale (Achenbach and Rescorla, 2001), the Conners-3 Parent Report Attention-Deficit Hyperactivity Disorder (ADHD) index (Conners, 2001), the parent and self-report of the Mood and Feelings Questionnaire (depression symptoms) (Angold et al., 1995), and the parent and self-report of the Screen for Child Anxiety Related Disorder (anxiety symptoms) (Birmaher et al., 1997). The Mini Neuropsychiatric Interview for Children and Adolescents (Sheehan et al., 2010), a semi-structured clinical interview, was administered to caregivers and youth separately to obtain a total symptom count for Conduct Disorder, Oppositional Defiant Disorder, Major Depression, Generalized Anxiety Disorder, and Post-Traumatic Stress Disorder.

Within the overall sample with complete psychopathology data, we employed a confirmatory factor analysis using a higher-order model with p factor as a second-order factor and internalizing and externalizing as first-order factors (see Rodriguez-Thompson et al., 2023). A maximum likelihood estimation with robust (Huber-White) standard errors was used to estimate models. In the higher-order model, the loading of the second-order factor (p factor) to the first-order factors (internalizing and externalizing) was set to 1. Participants with greater than 20% of items missing on a questionnaire or subscale were excluded from the p factor computation ($n = 4$). In all other cases, missing items were imputed with the mean of remaining items. In the instances where both parent and self-report data were available, the highest score was included in the analysis.

2.8. Additional covariates

Given the diurnal rhythm of cortisol, all analyses controlled for the timing of saliva sampling to account for individual differences. Upon the arrival in the laboratory, which ranged approximately from 11:00 a.m. to 1:00 p.m., participants were asked to report at what time they woke up that morning. A cortisol timing variable was computed by subtracting adolescents' awakening time from the time of the first saliva sample. The cortisol timing variable ranged between 4 and 14.25 h ($M = 7.00$, $SD = 1.68$).

Adolescents and their caregivers also reported participants' current medication usage. A dichotomous variable was created distinguishing between adolescents who were currently taking medications that may impact cortisol levels, including birth control or corticosteroids, and those who did not. Approximately 13% of participants ($n = 18$) reported using oral contraceptives, and 8% of participants ($n = 11$) reported using corticosteroids. Medication was coded as 1 (present) or 0 (absent).

2.9. Statistical analyses

Whole-brain analyses were conducted in FSL in FEAT version 6.0.3 using FLAME1 (Eklund et al., 2016). To investigate the study hypotheses, we first conducted a single whole-brain multiple regression analysis using FSL FEAT, with AUCg cortisol as the continuous independent variable and neural activation to negative vs. neutral images as the outcome variable. Whole-brain analyses were conducted within a gray matter mask created by segmenting the MNI 152 2 mm voxel template image using FSL FAST. Cluster thresholding was determined using AFNI's 3dClustSim (Cox et al., 2017), which generates Monte Carlo simulations (10,000) to determine appropriate cluster sizes, and AFNI's 3dFWHMx, which accounts for the number of voxels and the intrinsic spatial autocorrelation in the data residuals. These corrections address prior work indicating that failure to account for this autocorrelation in cluster correction can inflate type 1 error (Eklund et al., 2016). We used a conservative voxel-wise threshold of $p < 0.005$ and a cluster-level threshold of $p < 0.05$.

The PROCESS package (Hayes, 2013) in IBM SPSS was used to test the hypothesized moderation of threat exposure on the association between cortisol reactivity and neural activation. Threat exposure served as the moderator of the association between each ROI and cortisol (AUCg), and conditional effects were probed to test simple slopes at low (the mean - 1 SD), moderate (the mean), and high (the mean + 1 SD) levels of the moderator. Confidence intervals that do not include zero indicate a significant simple slope. All analyses controlled for participant age, pubertal timing, timing of saliva sampling, medication usage, time between study visits, psychopathology symptoms (*p* factor), and deprivation exposure. Although the present study focused only on the impact of threat, we also controlled for the effects of the other hypothesized dimension of adversity, deprivation, to demonstrate the specific effects of threat on outcomes, consistent with past research and conceptual models (Sheridan & McLaughlin, 2014).

3. Results

3.1. Preliminary analyses

Approximately 89.9% of participants reported experiencing at least one threat-based adversity exposure, with 30.8% endorsing one category, 20.5% reporting two categories, 17.9% reporting three categories, and 19.7% reporting four categories.

Participants reported a large and statistically significant negative affective response to the TSST, including a significant increase in self-reported nervousness ($t = 22.46$, $p < .001$). Mean levels of cortisol in response to the TSST are presented in Fig. 2. A repeated measures ANOVA with cortisol at the four assessments as within-subject factors was performed to examine mean changes in cortisol levels from pre- to 40 min post-task. A significant effect of time was observed, $F(3, 114) = 36.48$, $p < 0.001$. Polynomial contrasts revealed a significant quadratic trend, $F(1, 116) = 66.51$, $p < 0.001$, indicating that cortisol levels increased from pre- to 20 min post-task and subsequently decreased approximately to pre-task levels at 40 min post-task. A significant cubic effect also was observed, $F(1, 116) = 66.75$, $p < 0.001$, suggesting an asymmetric cortisol trend characterized by an initial sharp increase and a subsequent more gradual decline.

Because participants in this sample reported experiencing at least one mental health concern in the two years prior to study recruitment, associations between p factor and key study variables were assessed. Correlation analyses indicate that p factor was positively associated with both threat ($r = .612$, $p < .001$) and deprivation ($r = .31$, $p < .001$) in this sample. P factor was negatively associated with cortisol output, such that higher symptomatology was related to lower cortisol output (AUCg) when controlling for age, pubertal status, saliva sample timing, and medication usage in a regression ($\beta = -0.26$, $p = .015$). P factor was not significantly associated with neural reactivity in the amygdala, hippocampus, or vmPFC in this sample ($ps > .10$) in regression analyses controlling for age and pubertal timing.

3.2. Whole-brain analysis

Results of the whole-brain analysis are provided in Fig. 3. Results indicate a positive association between cortisol (AUCg) during the TSST and activation in the right lateral orbitofrontal cortex (OFC) during the emotion reactivity task.

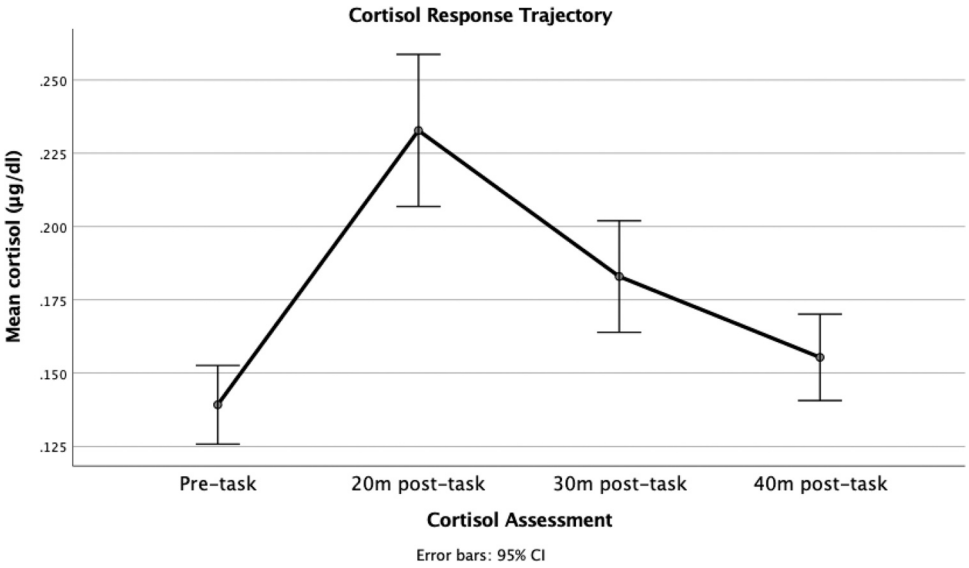
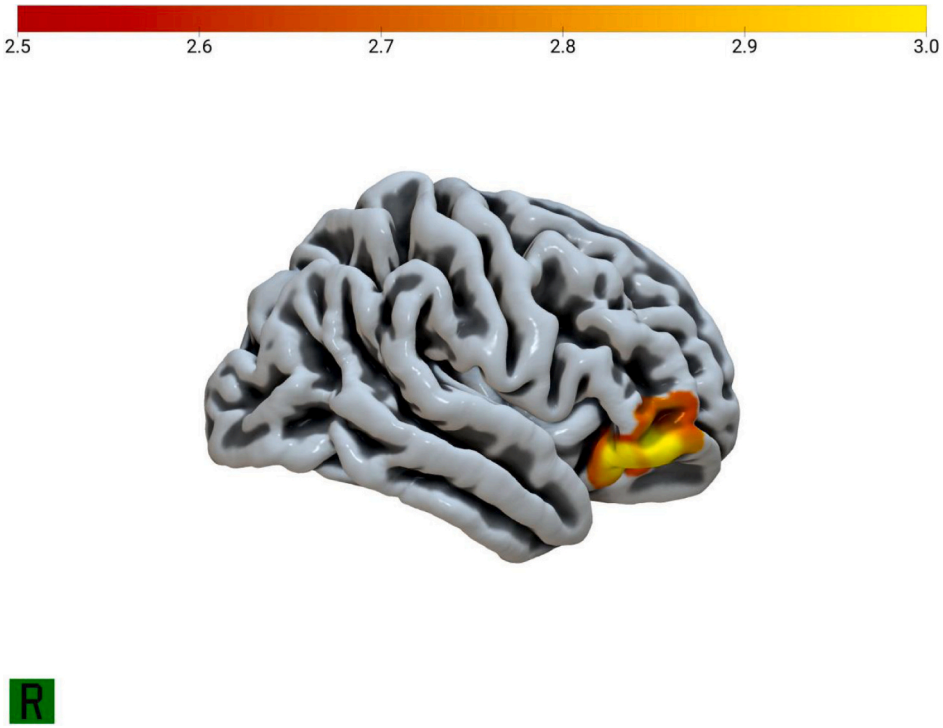


Fig. 2. Mean cortisol level in response to TSST.



Local Maxima Coordinates

Cluster	Size	x	y	z	Z-score	Region
1	498	44	36	-20	4.23	4.23

Note. Positive x coordinate corresponds to the right hemisphere.

Fig. 3. Whole-brain analysis.

3.3. Moderation analyses

Models assessing the interaction between neural activation and threat exposure in relation to TSST cortisol (AUCg) are presented in Table 1. The model testing threat as a moderator in the amygdala-AUCg association [$F(10,102) = 2.17$, $p = 0.026$] demonstrated that mean bilateral amygdala activation interacted with threat exposure to predict cortisol response to the TSST ($b = -3.34$, $p = 0.021$) after controlling for deprivation exposure, participant age, pubertal timing, timing of saliva sampling, medication usage, time between study visits, and p factor.

Table 1
Models of threat as a moderator of neural activation (look negative > look neutral) and cortisol (AUCg).

	b (SE)	95% CI	*p*
Amygdala			
Age	0.17 (0.35)	(−0.52, 0.85)	0.634
Pubertal timing	0.06 (0.76)	(−1.44, 1.56)	0.940
Saliva sample timing	0.12 (0.22)	(−0.31, 0.55)	0.576
Medication	-0.40 (1.30)	(−2.99, 2.18)	0.758
Time between visits	-0.41 (0.78)	(−1.95, 1.13)	0.601
Psychopathology (*p* factor)	-0.46 (0.66)	(−1.77, 0.85)	0.491
Deprivation	-0.73 (0.50)	(−1.72, 0.27)	0.150
Threat	-0.09 (0.41)	(−0.89, 0.72)	0.833
Amygdala activation (AMYG)	9.64 (3.27)	(3.17, 16.12)	0.004
Threat x AMYG	-3.34 (1.43)	(−6.17, −0.51)	0.021
Hippocampus			
Age	0.23 (0.35)	(−0.47, 0.94)	0.516
Pubertal timing	0.08 (0.77)	(−1.45, 1.60)	0.919
Saliva sample timing	0.17 (0.22)	(−0.27, 0.61)	0.438
Medication	-0.49 (1.33)	(−3.12, 2.14)	0.713
Time between visits	-0.35 (0.79)	(−1.91, 1.21)	0.656
Psychopathology (*p* factor)	-0.59 (0.67)	(−1.92, 0.74)	0.382
Deprivation	-0.77 (0.51)	(−1.79, 0.24)	0.133
Threat	-0.38 (0.37)	(−1.11, 0.34)	0.297
Hippocampal activation (HIPP)	8.19 (3.54)	(1.16, 15.21)	0.023
Threat x HIPP	-4.14 (2.06)	(−8.22, −0.06)	0.047
vmPFC			
Age	0.09 (0.36)	(−0.62, 0.79)	0.811
Pubertal timing	0.50 (0.78)	(−1.04, 2.04)	0.524
Saliva sample timing	0.20 (0.22)	(−0.24, 0.64)	0.379
Medication	-0.67 (1.34)	(−3.33, 1.99)	0.620
Time between visits	-0.62 (0.79)	(−2.18, 0.94)	0.433
Psychopathology (*p* factor)	-0.45 (0.68)	(−1.79, 0.89)	0.505
Deprivation	-0.72 (0.51)	(−1.74, 0.30)	0.162
Threat	-0.73 (0.42)	(−1.57, 0.11)	0.086
vmPFC activation	0.37 (1.48)	(−2.56, 3.31)	0.802
Threat x vmPFC	0.75 (0.64)	(−0.52, 2.02)	0.244

Note. AUCg is the dependent variable in all models

Probing of the interaction effect revealed that participants with low threat exposure (mean - 1 SD) demonstrated a significant positive association between cortisol production and amygdala activity ($b = 7.03$, $p = 0.005$), whereas no significant association between amygdala and cortisol production was observed for participants with high (mean + 1 SD) levels of threat exposure ($b = -1.70$, $p = 0.572$) (Fig. 4). The Johnson-Neyman significance region, calculated via the PROCESS macro for SPSS, was determined to be a threat score of 1.70 (% below: 40.71; % above: 59.29).

The model testing threat as a moderator in the hippocampus-AUCg association was also significant [$F(10,102) = 1.80$, $p = 0.070$]. A significant, negative interaction between mean bilateral hippocampal activity and threat exposure emerged ($b = -4.14$, $p = 0.047$) when controlling for deprivation exposure and other covariates. Probing of the interaction effect indicated that participants with low threat exposure (mean - 1 SD) demonstrated a significant positive association between cortisol production and hippocampal activity ($b = 4.95$, $p = 0.048$), whereas no significant association between hippocampal activation and cortisol production was observed for participants with high levels of threat exposure ($b = -5.86$, $p = 0.215$) (Fig. 5). Results of the Johnson-Neyman significance test indicate that threat exposure significantly influenced the relationship between hippocampal activation and AUCg at the value of 0.80 (9.73% below, 90.27% above). No significant interaction emerged in moderation analyses testing vmPFC and threat exposure in relation to TSST cortisol production [$F(10, 102) = 1.66$, $p = 0.100$].

4. Discussion

This study is the first to investigate how ELA characterized by threat (e.g., physical abuse, sexual abuse, witnessing domestic violence, neighborhood violence) moderates the association between patterns of neural activation and cortisol production. At separate time points, we measured cortisol production throughout an experimental exposure to acute social stress and neural responses to static negative images. We first demonstrated that cortisol, indexed via AUCg, was negatively correlated with threat exposure, consistent with past research showing a blunting effect of threat on the HPA axis response to social stress (Bunea et al., 2017), and was positively associated with activation in the right orbitofrontal region. In tests of moderation, associations between amygdala activation and AUCg and between hippocampal activation and AUCg were each significantly moderated by threat exposure.

The positive association between cortisol production in the TSST and orbitofrontal activity is in line with past work linking HPA axis activity with prefrontal activation (Harrewijn et al., 2020). Research suggests that the OFC plays a role in emotional, cognitive, and behavioral flexibility (Britton et al., 2010; Li et al., 2019; Robbins et al., 2012; Schoenbaum et al., 2011), as well as in reward processing, including anticipation, the evaluation of expected outcomes, and value-guided decision-making (Arana et al., 2003; O'Doherty et al., 2002). The association between lateral OFC activation in this emotion reactivity task and cortisol (AUCg) in another setting may support the importance of OFC recruitment in the service of naturally experiencing and regulating negative emotions, including those associated with HPA axis activation.

In tests of moderation, threat significantly moderated the association between amygdala activation (fMRI emotion reactivity task) and cortisol

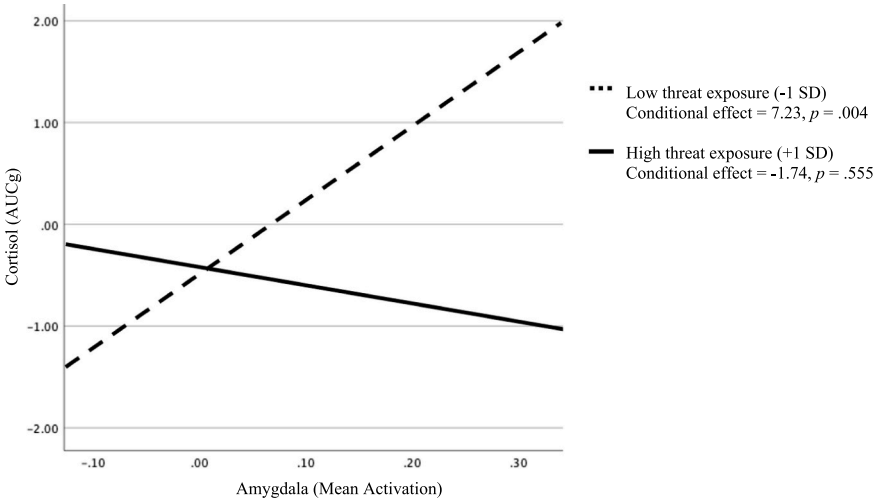


Fig. 4. Threat as a moderator between amygdala activation and cortisol.

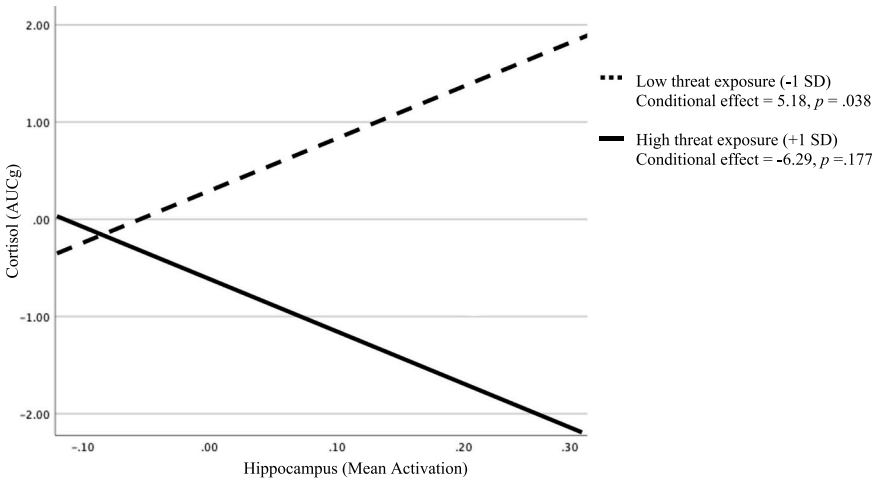


Fig. 5. Threat as a moderator between hippocampal activation and cortisol.

(TSST). Specifically, individuals with low threat exposure (i.e., mean threat score below 1.84) demonstrated a positive association between amygdala activation and cortisol. This finding is consistent with literature indicating that the amygdala is an important component of the neural circuitry that contributes to HPA axis activity (Segal, 2016; Sullivan et al., 2004) and past research noting positive associations between amygdala activation and physiological stress reactivity (Root et al., 2009). In individuals with high threat exposure in our sample, amygdala activation and cortisol production were not significantly associated, suggesting that cross-system organization may be disrupted in adolescents with a history of threat exposure. It is possible that exposure to severe threat during early periods of neuroendocrine development disrupts the excitatory inputs from the amygdala that promote HPA axis activation (Jankord and Herman, 2008). As such, we might observe more typical amygdala-HPA axis coordination in young children with threat exposure, with the divergence of cross-system coordination occurring later in development.

A similar moderation effect emerged when examining hippocampal activation, such that threat significantly moderated the association between hippocampal activation and cortisol production. Individuals with low threat exposure in our sample, specifically an average threat exposure score of 0.88 or less, demonstrated a positive association between hippocampal activation and cortisol production. This finding is surprising considering the negative feedback inhibitory influence of the hippocampus on the HPA axis (Herman and Mueller, 2006) and past studies yielding a negative association between hippocampal activity and cortisol production (Harrewijn et al., 2020). However, studies of this association in humans have generally focused on the effects of cortisol on hippocampal activation during working memory or recall tasks (e.g., Kukolja et al., 2011; Fleischer et al., 2019). Our findings may be attributable to task differences, given that our study focused on neural activation in response to negative images. The positive association between hippocampal engagement when viewing negative images and cortisol production following stress for individuals with low threat exposure may suggest that, in the absence of traumatic threat exposure, individuals who engage in greater memory-based cognitive functions when processing negative environmental stimuli tend to exhibit a higher physiological response to stress. For example, individuals who build strong associative memories when encoding environmental cues may be more likely to associate the TSST with prior negative public speaking experiences, prompting a stronger stress response. In line with this theory, Khalili-Mahini and colleagues (2010) found that individuals classified as "high-responders" based on their cortisol response to stress showed higher hippocampal activity during a picture encoding task compared to "low-responders" (Khalili-Mahani et al., 2010).

Similar to the pattern observed when probing the association between amygdala activation and cortisol, the association between hippocampal activation and cortisol was nonsignificant for individuals with high levels of threat exposure. It is possible that threat exposure has profound but *separate* effects on the hippocampus and the HPA axis during development. The neurotoxicity hypothesis suggests that stress-induced prolonged exposure to glucocorticoids (e.g., cortisol) can lead to a reduction in hippocampal cell complexity and eventual cell death (e.g., Sapolsky et al., 2000b), and studies of youth with histories of trauma have demonstrated reduced hippocampal activity during memory tasks (e.g., Carrion et al., 2010). Moreover, the blunting of the HPA axis, arising from continued overexposure to threatening stimuli early in development, results in long-term patterns of low cortisol following acute stress (Bunea et al., 2017). Therefore, consistent with the neurotoxicity hypothesis, experiences of traumatic threat may initially prompt high levels of cortisol that are related to reduced hippocampal volume and activation. However, if cortisol levels become blunted over time, reflected in the negative correlation between cortisol during the TSST and threat exposure observed in this study, the inverse association between hippocampal activity and cortisol may dissipate.

Of note, threat exposure did not emerge as a moderator of vmPFC activity and cortisol reactivity. We did, however, observe activation in lateral prefrontal regions in the whole-brain analysis in relation to greater cortisol production for the full sample. The vmPFC is an important component of the neural circuitry mediating emotional responses to environmental stimuli and is thought to support regulatory processes through projections to the amygdala (Ochsner et al., 2004; Phelps et al., 2004). However, it may be that the particular nature of the negative image task used in the scanner is more related to the function of lateral versus medial ventral prefrontal regions (Johnstone et al., 2007; Ochsner et al., 2004). It is possible that threat would act as a significant moderator of the vmPFC-cortisol association when assessing neural activity in emotion regulation tasks that elicit greater prefrontal recruitment.

4.1. Limitations and future directions

Findings from this study should be considered in light of a few limitations. First, the sample size, although substantial in the field of neuroimaging and physiological data collection, may have limited the power to identify interaction effects between predictors. Second, we control for p factor in moderation models to account for the impact of psychopathology symptoms in this sample. However, we did not examine whether various forms of psychopathology (e.g., depression, anxiety, conduct disorder) differentially impact neural or physiological emotion reactivity processes. Additionally, because symptoms of psychopathology were not re-assessed during the fMRI visit, we were

unable to account for possible changes in psychiatric status in our models. Third, we utilize AUCg as the index of cortisol in this study; thus, results only reflect overall cortisol output in the TSST and conclusions about the specific dynamics or patterns of cortisol secretion in relation to neural markers of emotion reactivity cannot be drawn. Fourth, the fMRI task used in this study is specific to negative images whereas the TSST represents a live social evaluative threat. It is possible that, if our two tasks were more similar, we may have observed stronger cross-system links. Finally, neural and physiological indices of emotion reactivity were not collected simultaneously. As such, conclusions about the real-time coordination of these emotion reactivity systems cannot be made. Research replicating this study design in different samples, as well as research using a single stress-induction paradigm, is necessary to draw conclusions about cross-system coordination within and across stressful contexts, respectively.

4.2. Conclusion

ELA characterized by threat has profound effects on the developing brain and physiologic stress response systems, which can exacerbate risk for a wide range of physical and mental health problems. Investigating the impact of threat on the links between the neurobiological systems underlying the stress response is crucial to understanding the etiology of stress-related disorders and shedding light on the potential neurodevelopmental mechanisms underlying specific types of early adversity. In the present study, we observed that higher production of cortisol during a social-evaluative stressor was linked to greater activation in the OFC. Furthermore, higher amygdala and hippocampal activation when viewing negative stimuli were related to higher cortisol production only for individuals with low levels of previous threat exposure. These associations were not present for individuals with high levels of prior threat exposure, raising the possibility that threat exposure may have a "de-coupling" effect on neural and physiological systems, eliminating the presence of cross-system associations that are observed in the general population. Findings are consistent with the idea that disruptions in associations between the amygdala and hippocampus and the HPA axis could contribute to the atypical patterns of emotion reactivity that are observed following threat-related ELA.

Declaration of Competing Interest

None.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.psyneuen.2023.106405.

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