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Neural circuitry involved in conditioned inhibition via safety signal learning is sensitive to trauma exposure

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ABSTRACT

Exposure to trauma throughout the lifespan is prevalent and increases the likelihood for the development of mental health conditions such as anxiety and post-traumatic stress disorder (PTSD). Safety signal learning (SSL)—a form of conditioned inhibition that involves reducing fear via conditioned safety—has been shown to effectively attenuate fear responses among individuals with trauma exposure, but the association between trauma exposure and the neural mechanisms of SSL remains unknown. Adults with varied prior exposure to trauma completed a conditioned inhibition task during functional MRI scanning and collection of skin conductance response (SCR). Conditioned safety signals reduced psychophysiological reactivity (i.e., SCR) in the overall sample. Although exposure to a higher number of traumatic events was associated with elevated SCR across all task conditions, SCR did not differ between threat in the presence of conditioned safety (i.e., SSL) relative to threat alone in a trauma-related manner. At the neural level, however, higher levels of trauma exposure were associated with lower hippocampal, amygdala, and dorsolateral prefrontal cortical activation during SSL. These findings suggest that while conditioned safety signals can reduce fear in the presence of threat even among individuals exposed to higher degrees of trauma, the neural circuitry involved in SSL is in fact sensitive to trauma exposure. Future research investigating neural processes during SSL among individuals with PTSD or anxiety can further elucidate the ways in which SSL and its neural correlates may reduce fear and link trauma exposure with later mental health conditions.

1. Introduction

Exposure to trauma throughout the lifespan is prevalent, with more than 65% of individuals experiencing at least one traumatic event by age 16 (Copeland et al., 2018) and nearly 70% of adults experiencing lifetime traumas (Kessler et al., 2017). There is vast heterogeneity in individual responses following trauma exposure. Often, responses to traumatic experiences function to help an individual navigate a society and world that harmed them (Cohen et al., 2016). These responses (e.g., heightened fear to innocuous trauma reminders), however, can also lead to significant distress and interfere with daily life, resulting in the development of mental health conditions such as anxiety and post-traumatic stress disorder (PTSD), with PTSD present among an estimated 5.6% of adults who experienced trauma (Koenen et al., 2017) and up to 30% of all mental health conditions in adulthood associated with exposure to childhood trauma (Green et al., 2010). Investigating approaches to fear reduction is therefore of critical importance for individuals living with anxiety and PTSD following traumatic life experiences.

Currently, exposure-based cognitive behavioral therapy (CBT) is the most prevalent evidence-based psychosocial approach to fear reduction (Rothbaum and Davis, 2003). Extinction of fear (i.e., repeated exposure to the threatening cue in the absence of the aversive outcome) is the core principle supporting exposure-based therapy and relies on competing threat and safety memories (Gershman et al., 2013; Rothbaum and Davis, 2003). Given that these threat and safety memories are

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competing, return of fear expression through reinstatement or spontaneous recovery can be common following the process of fear extinction, and could partially explain why CBT may not be sufficiently effective in nearly 50% of individuals with anxiety disorders (Hudson et al., 2015; James et al., 2015; Kar, 2011; Loerinc et al., 2015; Walkup et al., 2008) and does not lead to stable remission in more than 50% of adults (Springer et al., 2018). Indeed, this outcome could also be attributed to factors like barriers to care due to systemic inequities, co-occurring health conditions, and cultural factors (Kar, 2011), in addition to insufficient fear reduction strategies that are employed during therapy, underscoring the critical need to examine additional mechanisms of fear reduction.

The present study investigates associations between trauma exposure and safety signal learning (SSL), which is a mechanism of fear reduction and a form of conditioned inhibition (Rescorla, 1969). During conditioned inhibition via SSL, a cue is repeatedly trained to explicitly predict the non-occurrence of an aversive outcome (i.e., a safety cue) and reduces fear when presented with a separate threatening cue (Christianson et al., 2012; Myers and Davis, 2004; Odriozola and Gee, 2021). Given that SSL leverages a conditioned safety cue that is separate from the threatening cue, it is distinct from the process of extinction during which the previously threatening cue is conferred with competing threat and safety representations (Christianson et al., 2012; Gershman et al., 2013). Importantly, SSL has been shown to reduce fear across species (i.e., in humans and rodents) (Christianson et al., 2012; Jovanovic et al., 2009b) and to involve a hippocampal-prefrontal—specifically, a hippocampal-dorsal anterior cingulate cortex (dACC)—pathway (Meyer et al., 2019). Furthermore, several studies examining SSL in adults with and without trauma exposure and with fewer PTSD symptoms have shown significant reduction in threat reactivity in response to conditioned safety, which is diminished among individuals with higher PTSD symptoms (Jovanovic et al., 2009a, 2009b, 2010a). It remains unknown, however, whether the neural correlates of SSL are associated with trauma exposure. Taken together, SSL may be effective in reducing fear due to the type of safety that is learned and the process by which fear is being reduced, warranting investigation of the neural processes among individuals with trauma exposure.

Here, in a group of adults with a range of trauma exposure and without mental health conditions, we first examined whether trauma exposure is associated with fear reduction via SSL using psychophysiology (i.e., skin conductance response; SCR). We expected that higher levels of trauma exposure (i.e., exposure to a greater number of traumatic events) would be associated with less effective fear reduction via SSL. We then tested whether trauma exposure is associated with the putative neural correlates of SSL, specifically hippocampal activation and hippocampal-dACC functional connectivity, building on recent work highlighting the role of these neural targets in SSL (Meyer et al., 2019). Given that this hippocampal pathway is part of a broader neural circuit that includes the amygdala (Odriozola and Gee, 2021) and the central role of the amygdala in threat and safety learning (Phelps and LeDoux, 2005), we also examined associations between trauma exposure and amygdala activation during SSL. We hypothesized that both hippocampal activation and hippocampal-dACC functional connectivity would be diminished, and that amygdala activation would be elevated, during SSL among adults with a greater degree of trauma exposure relative to those with less trauma exposure. Finally, given that various other neural regions have been implicated in SSL (Christianson et al., 2012; Odriozola and Gee, 2021), we investigated the association between trauma exposure and functional activation during SSL at the whole-brain level in order to identify additional neural processes involved in SSL in a trauma-dependent manner.

2. Methods

2.1. Participants and study procedures

Participants were 64 adults between the ages of 18 and 30 (Table S1). Participants did not have current or past psychiatric diagnoses or use of psychotropic medications. Participants completed a general assessment of handedness (Oldfield, 1971), a clinical interview (Anxiety and Related Disorders Interview Schedule for DSM-5; Brown TA and Barlow DH, 2014), and a trauma assessment using the UCLA PTSD Reaction Index (RI; Steinberg et al., 2004). Eligible participants were invited to complete a conditioned inhibition task in the MRI scanner. Study procedures were approved by the institutional review board at Yale University, and all participants provided written informed consent. See Supplemental Information (SI) for details about participants and study procedures.

2.2. Assessment of trauma exposure

The UCLA PTSD RI (Steinberg et al., 2004) includes screening questions for different types of traumatic stress (e.g., physical abuse, domestic violence, disasters) at three levels of exposure (i.e., directly experienced, witnessed, or learned about happening to someone close). For each type of event that was endorsed, participants reported on the cumulative list of ages at which they experienced this particular type of event. All analyses for the present study examined the degree of trauma using the total number of traumatic events endorsed by the participant across all ages, termed "total number of traumatic events" (Fig. S1). For example, if an individual experienced physical abuse at age 8, a natural disaster at age 9, and forced displacement at age 10, the total number of events was coded as three. If a participant experienced a chronic traumatic event across multiple ages (e.g., serious medical illness at ages 15, 16, and 17), the total number of events was coded as three. Events for which age was not reported were not included in the count of total events. The average age at which traumatic events were experienced (i.e., weighted average across all events) was 16.38 (SD = 5.55 years; Fig. S1B). Hereafter, reference to the "level" or "degree" of trauma exposure pertains to the total number of traumatic events experienced by an individual.

2.3. Conditioned inhibition task design

Participants completed a conditioned inhibition task (Fig. 1) in the scanner while fMRI and SCR data were acquired. This task paradigm (Meyer et al., 2019) was adapted from the AX+/BX-task of conditioned inhibition (Jovanovic et al., 2005, 2009b) for use during fMRI data collection and specifically with children and adolescents in related studies. All conditioned stimuli used in the task were geometric shapes of different colors, and the unconditioned stimulus (US) was an aversive metallic noise delivered at 95–100 dB through MRI-safe noise-cancelling headphones (Fig. 1). Participants were presented with US expectancy questions between trials and at the end of the task.

During the acquisition phase (Fig. 1A), participants viewed 20 trials of the threat cue (CS+), 10 of which were paired with an unconditioned stimulus (US), an aversive metallic white noise (Neumann et al., 2008). During the acquisition phase, participants also viewed 10 trials of the safety cue (CS-), which was never paired with the US. During the testing phase (Fig. 1B), which was conducted across two functional runs, participants viewed four different conditions: the threat cue (24 total trials across both functional runs, 12 of which were paired with the US), safety cue (12 total trials across both functional runs), compound stimulus in which the threat and safety cues were co-presented adjacent to one another to test for the transfer of safety and assess fear inhibition (12 total trials across both functional runs, never paired with the US), and control condition in which the threat cue and a novel stimulus were co-presented to control for the compound nature of the stimulus and rule

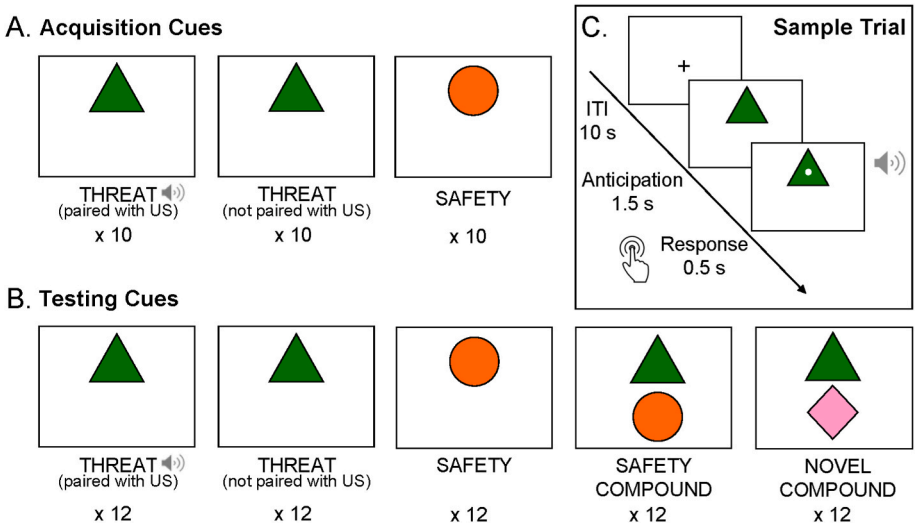

Fig. 1. Conditioned inhibition task design (Meyer et al., 2019). **(A)** The acquisition phase of the task included 10 threat cues paired with the unconditioned stimulus (US; i.e., a 95-dB metallic noise), 10 threat cues that were not paired with the US, and 10 trials of the safety cue. **(B)** Each of the two testing phases of the task included 6 threat trials paired with the US, 6 threat trials not paired with the US, 6 trials of the safety cue, 6 trials of the safety compound (i.e., the combination of the threat and safety cues into a single compound stimulus), and 6 trials of the novel compound (i.e., the threat cue combined with a novel cue into a single stimulus). Thus, there were a total of 12 trials for each condition. **(C)** The sample trial demonstrates task timing: a fixation cross was presented for 10 s (i.e., the intertrial interval; ITI), followed by 1.5 s of the cue presentation (i.e., anticipatory period), followed by 0.5 s in which a white dot appeared at the center of the shape and participants were instructed to make a button press (i.e., response period).

out the reduction of fear via novelty (i.e., external inhibition; 12 total trials across both functional runs). In both the acquisition and testing phases of the task, a 50% reinforcement rate was employed in order to enable assessment of the physiological and blood-oxygen-level dependent (BOLD) signal to the learned CS alone, without a potentially confounding influence of the response to the US (Büchel et al., 1998; Lonsdorf et al., 2017).

The task was an event-related design with three parts to each trial: the intertrial interval, anticipatory period, and response period (Fig. 1C; sample trial). A fixed intertrial interval (ITI) of 10 s separated each trial to allow for stabilization of the BOLD and SCR signals. During the anticipatory period of each trial, each stimulus was presented for 1.5 s, which was followed by the response period in which a white dot appeared in the center of the shape (presented for 0.5 s). For reinforced trials of the threat cue, the US onset at the same time as the dot in the center of the shape, lasted 5 s, and co-terminated with the threat cue. To maintain participant engagement, participants were instructed to press a button when the dot appeared in the center of the shape on each trial. Participants were explicitly informed that their button press did not do anything and that it was simply to ensure that they were paying attention. The assignment of the three shapes to the three stimulus types (threat, safety, or novel cue) was counterbalanced across participants.

For additional details regarding the task, see SI.

2.4. Acquisition and analysis of physiological data

To measure physiological responses associated with fear during the conditioned inhibition task, we assessed SCR using a Biopac MRI-compatible skin conductance recording system (https://www.biopac.com/) together with AcqKnowledge software (https://www.biopac.com/product/acqknowledge-software/) to amplify and record the SCR. SCR data from the acquisition and testing phases of the task were analyzed using a general linear model (GLM) with the PsychoPhysiological Modeling (PsPM) toolbox in MATLAB (http://pspm.sourceforge.net/). The reconstructed values from PsPM processing were then entered into a repeated-measures analysis of covariance (ANCOVA) in SPSS. Due to missing data, lack of robust response throughout the task, and lack of sustained learning during the acquisition phase of the task, the final subsample for the SCR analyses included 27 participants. For details regarding physiological data preprocessing, quality assurance, PsPM, and statistical analysis, see SI.

2.5. Analysis of fMRI data

fMRI individual-level analyses. For information regarding fMRI acquisition parameters and data preprocessing, please refer to the SI. All fMRI data were analyzed using the FMRIB's Software Library (FSL) version 5.11.0 and the FSL Expert Analysis Tool (FEAT) version 6.00. For the lower-level FEAT analysis, predictors for each task condition (i.e., the full 2 s combining the anticipatory and response periods of the threat cue, safety cue, safety compound, and novel compound conditions; Fig. 1) were convolved with a double-gamma canonical hemodynamic response function (HRF). Temporal derivatives of each predictor were added as a confound term to the GLM to account for slice-timing differences and variability in the HRF delay across regions. Timeseries were high-pass filtered with a cutoff of 90 s (estimated for our specific task design using FSL's *cutoffcalc* function) to remove low frequency artifacts and prewhitened within FILM to correct for autocorrelations in the timeseries. See SI for details regarding motion correction.

Activation analyses. Mean percent signal change for each subject was extracted for each condition and each region of interest (ROI) using anatomical masks for the right and left anterior hippocampus (Hindy and Turk-Browne, 2016, Fig. 3A) and right and left whole amygdala (Amunts et al., 2005, Fig. 3D). The extracted values (i.e., percent signal change) for each task condition (i.e., threat cue, safety cue, safety compound, and novel compound) were then entered into separate repeated-measures ANCOVAs for each ROI, in which the within-subjects factor was the task condition, and the between-subjects factor was the total number of traumatic events (entered as a continuous variable). The Greenhouse-Geisser adjustment was used to address sphericity assumption violations in the ANCOVA models. All models with significant main effects or interactions were corrected for multiple comparisons using false discovery rate correction at the level of the hypothesis (i.e., 4 total comparisons pertaining to the 4 ROIs). Post-hoc *t*-tests for *a priori* contrasts of interests (i.e., threat cue versus safety compound and novel compound versus safety compound) were conducted following significant main effects or interactions.

Functional connectivity analyses. To analyze task-evoked functional connectivity between the hippocampus and dACC, a general psychophysiological interaction (gPPI) model was employed (McLaren et al.,

2012) using FEAT version 6.00 (FSL version 5.11.0) with FILM autocorrelation correction. First, mean timeseries were extracted for right and left hippocampal (Hindy and Turk-Browne, 2016) seed regions using the FSL *meants* function and entered into separate models as the physiological regressor. Next, individual psychological regressors for each condition (i.e., threat cue, safety cue, safety compound, and novel compound) were entered into the models. Finally, psychophysiological interaction terms between each condition and the mean timeseries were included in the design matrices as separate regressors. Consistent with the lower-level activation analyses, psychological predictors (i.e., task condition) were convolved with a double-gamma canonical HRF and temporal derivatives of each psychological predictor were added as confound variables to the design matrix. Timeseries were high-pass filtered with a cutoff of 90 s (estimated for our specific task design using FSL's *cutoffcalc* function) and prewhitened within FILM to correct for autocorrelations in the timeseries. Functional connectivity parameter estimates for the bilateral dACC (Rolls et al., 2020; Fig S2) were extracted using FSL's featquery tool. Out of the 64 total participants, one participant was excluded from the gPPI analysis due to technical errors in the FSL gPPI processing pipeline. This resulted in a final subsample of 63 participants for the gPPI analysis. Paralleling the activation statistical analyses, extracted functional connectivity estimates for each task condition were entered into a repeated-measures ANCOVA, in which the task condition was included as a within-subjects factor and the total number of traumatic events (entered as a continuous variable) was included as the between-subjects factor. The Greenhouse-Geisser adjustment was used to address sphericity assumption violations in the ANCOVA models.

Whole-brain activation analysis. To examine brain regions that may be involved in SSL in a trauma-dependent manner, we conducted an exploratory group-level whole-brain analysis for our contrasts of interest that index SSL between the safety compound and novel compound and between the safety compound and threat cue. First, we conducted a mid-level analysis (i.e., combining across the first and second testing runs of the task) using FEAT fixed-effects higher-level modeling, which was then fed into a second higher-level group analysis (i.e., combining across subjects). For this higher-level group analysis, the total number of traumatic events–paralleling the ROI analyses–was entered continuously as an explanatory variable into the GLM. Cluster-level correction was applied ($z > 3.1$, $p < 0.001$) with a cluster p-threshold of $p < 0.05$ (Woo et al., 2014). This analysis was carried out using FMRIB's Local Analysis of Mixed Effects (FLAME) 1 + 2. For additional details regarding whole-brain analysis, see SI.

3. Results

3.1. Behavior and psychophysiology

To determine whether participants successfully learned the task contingencies, we examined US expectancy responses using a binomial generalized linear mixed model (see SI for details regarding US expectancy data, statistical analyses, and results). There was no main effect of condition on overall expectancy accuracy ($\chi^2 = 5.89$, $p = 0.117$). That is, there was no difference in expectancy performance between the four task conditions, with more than 85% of all participants correctly learning contingencies for all four conditions (Fig S3).

SCR was measured to index changes in physiological reactivity during the conditioned inhibition task. A subsample of 27 participants were included in SCR analyses; there was no difference in trauma exposure between the subsample of participants included in (n = 27) and excluded from (n = 37) SCR analyses ($t(62) = 0.04$, $p = 0.970$; Fig S5; see Table S2 for subsample demographic information). A repeated-measures ANCOVA used to test the association between the total number of traumatic events and SCR during the task revealed a significant main effect of trauma exposure on SCR, $F(1, 25) = 5.00$, $p = 0.034$, $\eta_p = 0.17$. Specifically, more exposure to trauma was associated with higher physiological reactivity throughout all conditions of the task (Fig. 2). The degree of trauma exposure was not associated with reactivity during a specific task condition or during specific trials of each condition (i.e., the first three (early) versus last three (late) trials of each condition). That is, there was no interaction between trauma exposure and condition, trauma exposure and timing (i.e., early versus late trials), or trauma exposure, condition, and timing. Safety signals did, however, effectively reduce SCR from early to late trials of the task in the overall sample, ($t(26) = -3.14$, $p = 0.002$), whereas there was no difference in SCR from early to late trials in response to the threat cue alone ($t(26) = 0.34$, $p = 0.736$; Fig. 2).

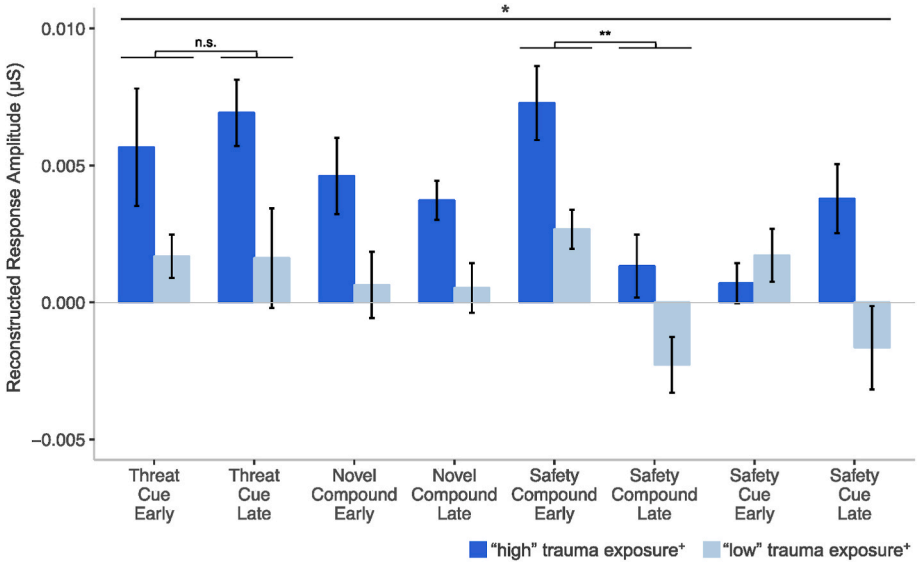

Fig. 2. Trauma exposure and task-related physiological reactivity (SCR). Mean SCR was elevated among individuals with exposure to a greater number of traumatic events across all conditions of the conditioned inhibition task, n = 27, $F(1, 25) = 5.00$, $p = 0.034$, $\eta_p = 0.17$. All error bars show ±1 SEM. *$p < 0.05$, **$p < 0.01$. +Total number of traumatic events modeled as continuous variable; median split (13.5 events) used here for data visualization.

3.2. Trauma-related differences in hippocampal and amygdala activation

A repeated-measures ANCOVA was used to test the association between trauma exposure and hippocampal activation during the first and second testing runs of the task. Given that significant habituation was observed in SCR during the second testing run of the task (Fig S6), all activation and functional connectivity results presented hereafter will focus on the first testing run. The model revealed a significant interaction contrast between task condition and trauma exposure in the right hippocampus (linear contrast, $F(1,62) = 4.57$, $p = 0.048$, $\eta_p = 0.07$, corrected for multiple comparisons; Fig. 3C). There was also a trend-level interaction contrast between task condition and trauma exposure in the left hippocampus (linear contrast; $F(1,62) = 3.22$, $p = 0.078$, $\eta_p = 0.05$; Fig. 3B). Specifically, and consistent with our hypotheses, higher levels of trauma exposure (i.e., a greater number of total traumatic events) appear to be associated with diminished hippocampal engagement to the safety compound relative to the novel compound (i.e., one of two *a priori* contrasts of interest to index SSL; $t(31) = -2.12$, $p = 0.021$). By contrast, lower levels of trauma exposure (i.e., fewer total traumatic events) were associated with more hippocampal involvement during the safety compound condition compared to the threat cue alone (i.e., one of two *a priori* contrasts of interest to index SSL; right hippocampus, $t(31) = 2.10$, $p = 0.022$; left hippocampus $t(31) = 3.00$, $p = 0.003$). Finally, within only the safety compound condition, left hippocampal recruitment was lower among individuals with higher levels of trauma exposure relative to individuals with lower levels of trauma exposure ($t(62) = -2.21$, $p = 0.015$).

Given that threat and safety learning is supported by a broader neural circuit and prior studies have shown evidence for safety encoding in the amygdala (Sangha et al., 2013), we also examined amygdala activation during the conditioned inhibition task. A repeated-measures ANCOVA exhibited a significant interaction contrast between trauma exposure and task condition in both the left (linear, $F(1,62) = 8.03$, $p = 0.024$, $\eta_p = 0.12$, corrected for multiple comparisons; Fig. 3E) and right (linear, $F(1,62) = 5.69$, $p = 0.040$, $\eta_p = 0.08$; corrected for multiple comparisons; Fig. 3F) amygdala. Specifically, and contrary to our hypothesis, individuals with a greater degree of trauma exposure exhibited less amygdala recruitment to the safety compound compared to the novel compound ($t(31) = -2.18$, $p = 0.018$). By contrast, individuals with exposure to a lower number of traumatic events exhibited greater amygdala activation during the safety compound compared to the threat cue condition (right amygdala, $t(31) = 2.08$, $p = 0.023$; left amygdala, $t(31) = 2.62$, $p = 0.007$). In addition, higher, relative to lower, levels of trauma exposure were associated with more amygdala activation within the threat cue condition (right amygdala, $t(62) = 2.00$, $p = 0.025$; left amygdala, $t(62) = 2.64$, $p = 0.005$), but not within the safety compound condition (right amygdala, $t(62) = 0.74$, $p = 0.231$; left amygdala, $t(62) = 0.98$, $p = 0.166$).

Finally, given that 37 out of 64 participants included in the neural analyses were excluded from SCR analyses, we tested whether there were any differences in hippocampal or amygdala activation in response to the threat cue, safety compound, or novel compound between the two groups (i.e., 27 participants with versus 37 participants without useable SCR data). There were no significant differences in neural activation

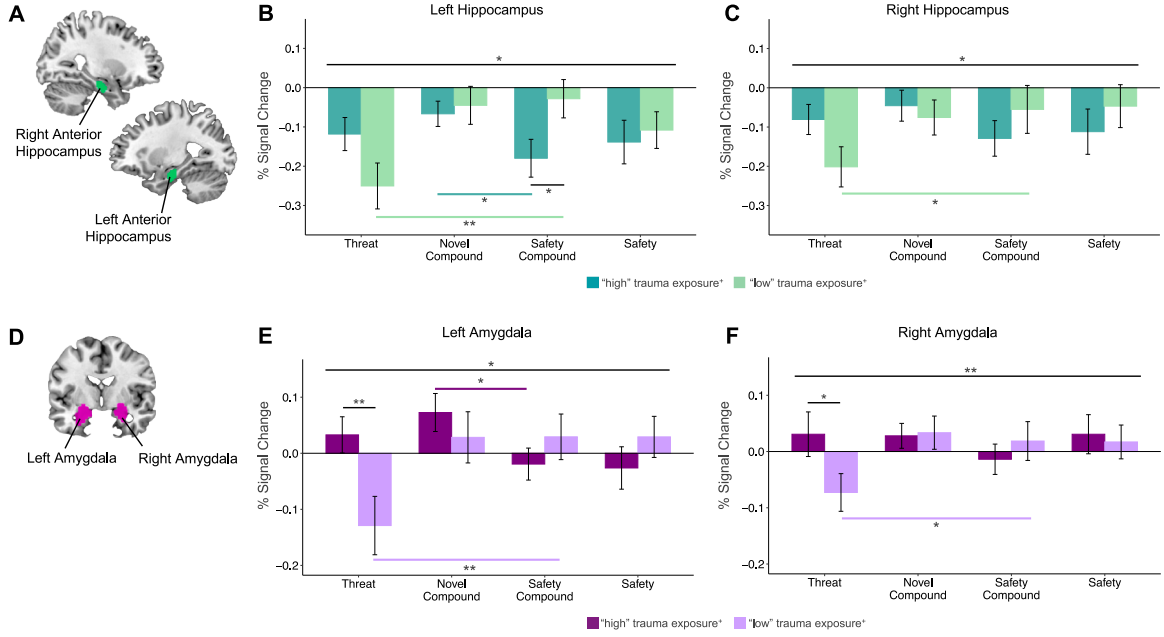

Fig. 3. Trauma exposure and hippocampal and amygdala involvement during the conditioned inhibition task. **(A)** Anterior hippocampus ROI (Hindy and Turk-Browne, 2016). **(B)** Left anterior hippocampus involvement by trauma exposure and task condition. A trend-level linear contrast for the interaction between trauma exposure and condition ($F(1,62) = 3.22$, $p = 0.078$, $\eta_p = 0.05$) suggested that whereas exposure to a greater number of traumatic events may be associated with diminished left hippocampal involvement during the safety compound condition compared to the novel compound, lower levels of trauma exposure may be associated with elevated hippocampal recruitment to the safety compound compared to the threat cue. **(C)** Right anterior hippocampus involvement by trauma exposure and task condition. A significant linear contrast for the interaction between trauma exposure and condition ($F(1,62) = 4.57$, $p = 0.048$, $\eta_p = 0.07$, corrected) revealed that exposure to lower, but not higher, levels of trauma exposure was associated with elevated left hippocampal involvement during the safety compound condition compared to the threat cue. **(D)** Amygdala ROI (Amunts et al., 2005). **(E)** Left amygdala activation by trauma exposure and task condition. A significant linear contrast for the interaction between trauma exposure and condition ($F(1,62) = 8.03$, $p = 0.024$, $\eta_p = 0.12$, corrected) revealed that higher levels of trauma exposure were associated with less amygdala recruitment to the safety compound compared to the novel compound. By contrast, exposure to fewer traumatic events was associated with higher right amygdala activation during the safety compound condition than during the threat cue condition. **(F)** Right amygdala activation by trauma exposure and task condition. A significant linear contrast for the interaction between trauma exposure and condition ($F(1,62) = 5.69$, $p = 0.040$, $\eta_p = 0.08$; corrected) showed that lower, but not higher, levels of trauma exposure were associated with elevated left amygdala activation during the safety compound condition compared to the threat cue. All error bars show ±1 SEM. *$p < 0.05$, **$p < 0.01$. $^{+}$Total number of traumatic events modeled as continuous variable; median split (13.5 events) used here for data visualization and post-hoc tests.

between the two groups for the left or right hippocampus or left or right amygdala (i.e., $p > 0.05$ for all independent samples t-tests).

3.3. No trauma-related differences in functional connectivity

A repeated-measures ANCOVA revealed no significant main effect of trauma exposure or interaction between trauma exposure and condition for functional connectivity between the right ($N = 63$, $F(3,183) = 1.05$, $p = 0.371$, $\eta_p = 0.02$) or left ($N = 63$, $F(2.67,163.03) = 0.80$, $p = 0.481$, $\eta_p = 0.01$; corrected for sphericity violation) anterior hippocampus and dACC during the conditioned inhibition task.

3.4. Trauma-Related Differences in Whole-Brain Neural Activation

A whole-brain analysis showed that higher levels of trauma exposure were associated with less activation to the safety compound compared to the threat cue in the left middle frontal gyrus (MFG) in a cluster that included voxels in the dorsolateral prefrontal cortex (dlPFC; i.e., left MFG cluster partially overlapped with dlPFC reference image from NeuroSynth, Yarkoni et al., 2011; see SI for details) and the left inferior frontal gyrus (Fig. 4A and B, Table 1). When examining the contrast between the safety compound and novel compound, individuals with more exposure to trauma exhibited less activation to the safety compound relative to the novel compound in the left MFG, which also included voxels in the dlPFC, as well as the left frontal pole, right putamen, and left lateral occipital cortex (Fig. 4C and D, Table 1).

4. Discussion

There is a significant need to investigate mechanisms of fear reduction and understand the neural processes supporting these mechanisms in the context of trauma exposure. The present study is the first to our knowledge to examine associations between trauma exposure and the neural correlates of conditioned inhibition via SSL in humans. Our findings—from a group of 64 young adults with varied trauma exposure across their lifespan and no mental health conditions—demonstrate that, while fear reduction via SSL (indexed using psychophysiological reactivity) does not differ by the degree of trauma exposure (i.e., total number of traumatic events), the neural correlates of SSL are indeed sensitive to trauma exposure. In particular, we show that the anterior hippocampus and amygdala—both nodes of the putative neural circuit supporting SSL—as well as the dlPFC are less engaged during SSL among individuals who have experienced a greater degree of trauma. These findings not only identify neural processes that may be unique to SSL in the context of trauma (i.e., dlPFC involvement), but also extend previous research by highlighting trauma-related differences in hippocampal and amygdala involvement during SSL specifically and threat and safety learning more broadly.

Prior research has examined fear reduction via SSL in individuals with various degrees of trauma exposure and PTSD symptoms (Jovanovic et al., 2009a, 2009b, 2010a), and here, we build on the existing literature to examine psychophysiological reactivity in conjunction with

Table 1
Brain regions with significant trauma-related differences in activation during conditioned inhibition.

Voxels	Peak (x, y, z)	Cluster Region(s)	Peak Voxel z-Score
Safety Compound > Threat Cue			
186	−46, 16, 34	Left MFG/dlPFC	4.93
128	−48, −56, −8	Left inferior temporal gyrus	5.16
Safety Compound > Novel Compound			
288	−38, −60, 50	Left lateral occipital cortex	4.00
185	−32, 4, 38	Left MFG/dlPFC	4.16
159	−38, 46, 4	Left frontal pole	4.31
93	28, 12, −2	Right putamen	4.69

Peak (x, y, z) = Montreal Neurological Institute (MNI) coordinates for maximum intensity (i.e., z-statistic) voxel within each cluster; MFG = middle frontal gyrus; dlPFC = dorsolateral prefrontal cortex.

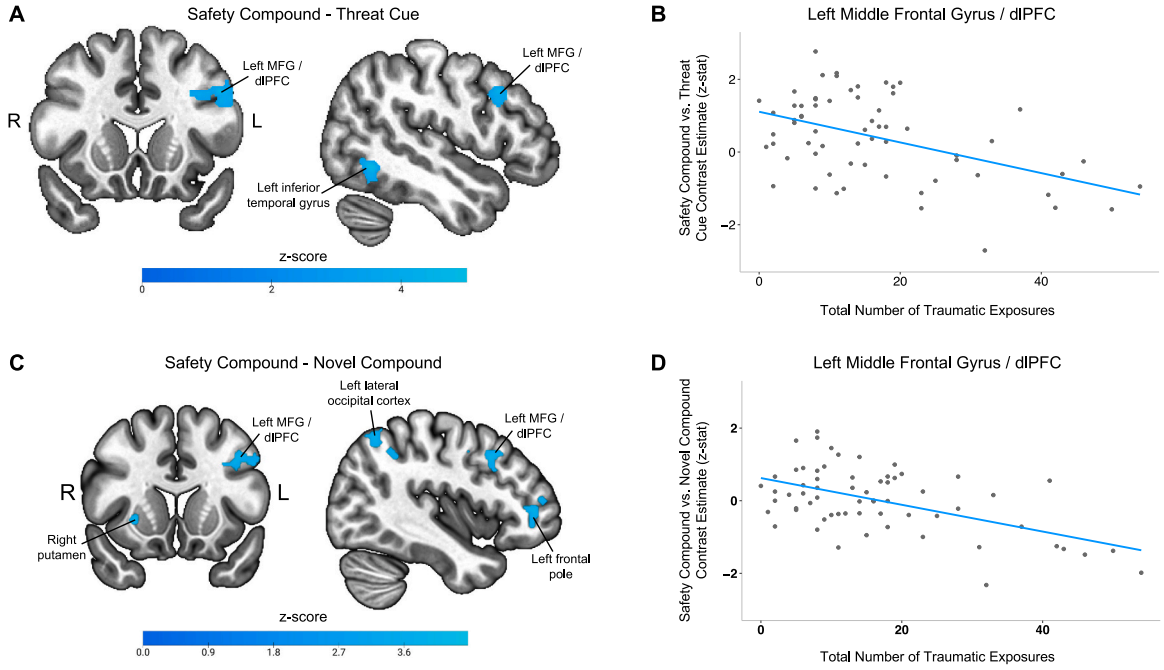

Fig. 4. Trauma-Related Differences in Whole-Brain Neural Activation. **(A)** Individuals with more trauma exposure showed less activation to the safety compound relative to the threat cue in the left MFG (overlapping with the dlPFC) and left inferior temporal gyrus. **(B)** Scatter plot visualizing average contrast estimates for the left MFG/dlPFC cluster by trauma exposure across subjects. **(C)** Individuals with more trauma exposure exhibited less activation to the safety compound relative to the novel compound in the left MFG (overlapping with the dlPFC), left frontal pole, right putamen, and left lateral occipital cortex. **(D)** Scatter plot to visualize average contrast estimates for the left MFG/dlPFC cluster by trauma exposure across subjects. Cluster detection threshold $z > 3.1$ ($p < 0.001$); Cluster p-threshold $p < 0.05$.

functional neuroimaging during conditioned inhibition. Although higher levels of trauma exposure were associated with overall elevated SCR across all task conditions, there was no interaction between trauma exposure and task condition. This pattern may be due to the fact that participants in this study did not have any mental health conditions, given that prior work has shown diminished SSL (assessed using fear-potentiated startle) only among individuals with high symptoms of PTSD, relative to those with no trauma exposure or low symptoms of PTSD, across several community samples (Jovanovic et al., 2009b, 2010a, 2010b). Further evidence in rodents suggests that conditioned inhibition may be a robust approach to fear reduction following stress. Specifically, conditioned inhibition, but not fear extinction, remained intact following stress experienced during adulthood (Woon et al., 2020). Moreover, stress experienced during the juvenile period disrupted SSL in adulthood, but not in adolescence (Meyer et al., 2021). Taken together, our results suggest that SSL may not only be a useful mechanism of fear reduction, but may also be a process that moderates or mediates an association between trauma exposure and mental health later in life (Jovanovic et al., 2012; McLaughlin et al., 2019), along with additional neural, behavioral, or psychosocial factors (Fazel et al., 2012; McLaughlin and Lambert, 2017) to be probed in future research.

Although there were no trauma-related differences at the psychophysiological level, several differences emerged at the level of neural activation. Before discussing specific trauma-related patterns in hippocampal and amygdala activation, we note the overall pattern of hippocampal deactivation across all conditions of the task. Given that our individual-level fMRI analyses modeled the combined 2-s anticipatory and response epochs relative to implicit rest epochs (i.e., the 10-s intertrial interval), we may be observing anterior hippocampal deactivation consistent with overall task-related deactivation of the default mode network (DMN; Greicius and Menon, 2004). Specifically, hippocampal activation may be elevated during implicit rest given its role in self-referential processing as part of the DMN, especially during episodic and associative memory processing (Reas et al., 2011). Here, less hippocampal deactivation in condition X relative to condition Y is therefore interpreted as greater hippocampal engagement or involvement during the anticipatory and response epochs of condition X relative to condition Y.

We turn now to examine trauma-related differences in hippocampal and amygdala activation. First, higher levels of trauma exposure were associated with diminished hippocampal recruitment during the safety compound condition–during which we test the active inhibition of fear in the presence of safety–and more amygdala activation to the threat cue. This overarching pattern builds on the canonical roles of the amygdala and hippocampal nodes in circuitry involved in threat and safety learning (Fullana et al., 2016). Specifically, the amygdala is centrally involved during threat detection (Phelps and LeDoux, 2005) and this functional pattern is often augmented (i.e., amygdala hyperreactivity) following trauma exposure in adults and youth (Hein and Monk, 2017; McCrory et al., 2011; Suarez-Jimenez et al., 2020). Hippocampal activity, however, is central to encoding and processing safety and contextual information (Maren et al., 2013; Sotres-Bayon et al., 2012), and the anterior hippocampus, in particular, is engaged during SSL (i.e., elevated activation in response to the safety compound relative to a threat cue alone; Meyer et al., 2019). Collectively, these findings highlight that trauma exposure may distinctly affect parts of the neural circuitry supporting SSL in an input (i.e., threat versus safety)-specific manner.

Second, we show that individuals with a greater degree of trauma exposure showed diminished amygdala and hippocampal activity in response to the safety compound relative to the novel compound, which is a contrast used to index SSL. By contrast, only among individuals with lower levels of trauma exposure, both hippocampal and amygdala involvement were elevated to the safety compound relative to the threat cue. Interestingly, this may suggest that the amygdala is involved in coding safety-related information, but only in the context of low trauma exposure. This finding parallels past findings in rodents where cells in the basolateral amygdala were found to selectively respond to a combination of a threat and safety cue (Sangha et al., 2013). In addition, recent evidence from mega-analytic studies in humans demonstrated heightened amygdala activation in response to learned safety relative to threat (Visser et al., 2021) and differential involvement of amygdala subregions (i.e., centromedial amygdala and basolateral amygdala) in response to safety in a temporally-specific manner (Wen et al., 2022), underscoring important anatomical and temporal heterogeneity in amygdala involvement in the context of threat and safety. Given that both hippocampal and amygdala engagement are elevated to the safety compound relative to the threat cue among individuals with lower, but not higher, levels of trauma exposure, it is possible that exposure to trauma alters the degree to which or the ways in which these regions are detecting safety or processing the inhibition of fear inherent to the safety compound condition.

Interestingly, this neural pattern does not parallel fear reduction at the psychophysiological level in this group of adults (i.e., individuals with lower, relative to higher, levels of trauma exposure did not exhibit enhanced fear reduction via SSL**,** and vice versa). Given that several studies in adults have demonstrated diminished fear reduction and altered neural processing among individuals with trauma exposure and related mental health conditions (e.g., Jovanovic et al., 2012) and that the adults in this study did not have any psychopathology, it is possible that additional factors (e.g., neural, behavioral, or psychosocial) are potentially being recruited during the learning of conditioned safety to sufficiently inhibit fear.

Although amygdala and hippocampal engagement were elevated in response to the safety compound compared to the threat cue among individuals with lower, but not higher levels of trauma exposure, it is important to note that a similar pattern emerged in response to the novel compound and safety cue relative to the threat cue, indicating that this trauma-related difference in hippocampal and amygdala activation is not specific to the safety compound condition of the task. These nonspecific effects may be occurring for multiple reasons. First, both the safety compound and the safety cue conditions possess safety-related information; if both the amygdala and hippocampus are detecting these elements of safety, we would expect to see similar levels of neural engagement to both task conditions relative to the threat cue. Second, prior evidence indicates that novelty may hold threat-related properties (Balderston et al., 2011) in addition to safety-related properties (e.g., novelty-facilitated extinction; Dunsmoor et al., 2015; Lucas et al., 2018). Thus, it is possible that the results in the present study are consistent with hippocampal and amygdala activation to safety information that may be represented by the novel compound. Future research delineating the unique and overlapping neural mechanisms of novelty and conditioned safety in the context of fear reduction following trauma exposure may shed light on differential neurobiological targets for fear reduction.

Contrary to our hypotheses, we did not find any trauma-related differences in hippocampal-dACC functional connectivity during SSL. Given that we probed a specific *a priori* neural pathway implicated in SSL, this finding may suggest that additional functional pathways may be recruited during SSL in the context of trauma exposure and must be explored further. For example, increased amygdala functional connectivity with the hippocampus and prefrontal cortex in response to negative affective stimuli has been observed in adults with histories of trauma (Jedd et al., 2015). Further, recent evidence in youth demonstrates differences in functional connectivity between the amygdala and several brain regions in response to threat, including reduced connectivity with the hippocampus and posterior cingulate cortex and increased connectivity with the anterior cingulate cortex among youth with trauma exposure compared to youth without trauma exposure (DeCross et al., 2021). These findings suggest that functional connectivity with the amygdala during SSL may vary as a function of trauma exposure and that future research investigating pathways involving the amygdala hub could provide important insight into the neural

mechanisms supporting SSL following trauma exposure.

Finally, using a whole-brain analytic approach, we show that participants with higher, relative to those with lower, levels of trauma exposure exhibited less activation in the MFG/dlPFC in response to the safety compound relative to the threat cue and to the novel compound, suggesting that a pathway involving the dlPFC may be important for the process of conditioned inhibition as a function of trauma exposure. Higher levels of trauma exposure were also associated with less activation in the frontal pole and putamen in response to the safety compound relative to the novel cue, and less activation in the inferior temporal gyrus in response to the safety compound compared to the threat cue. The dlPFC is involved in cognitive regulation of subjective fear (Kroes et al., 2019) and responds to uncertainty during aversive learning (Dunsmoor et al., 2007). Recent research on the neural mechanisms of conditioned inhibition using human neuroimaging demonstrates involvement of the dlPFC during conditioned inhibition of threat via safety learning (Laing et al., 2022). Furthermore, evidence from non-human primates indicates that the dlPFC sends projections to the pregenual anterior cingulate cortex, which then targets inhibitory neurons in the subgenual cingulate, with regulatory effects on emotional states (Joyce et al., 2020). Taking these findings together, results from the present study suggest that the dlPFC may be involved in top-down regulation during conditioned inhibition via SSL (i.e., engagement to the safety compound versus the threat cue or novel compound), which is altered among individuals with a greater degree of trauma exposure.

Less is known about the role of the frontal pole and putamen in the context of threat and safety learning and trauma exposure. Recent developmental studies have shown trauma-related structural and functional differences in both the frontal pole and putamen (Jeong et al., 2021; Weissman et al., 2019). For example, trauma exposure in youth was associated with reduced frontal pole activation in response to fearful and neutral faces (relative to scrambled faces; Weissman et al., 2019). Here, we find that adults with more traumatic exposure, compared to those with lower levels of exposure, exhibit less activation in the frontal pole and putamen to the safety compound relative to the novel compound. Although the present study differs from prior studies (i.e., examines conditioned inhibition using a task with geometric stimuli in an adult sample), this finding suggests that the frontal pole, in particular, may have a role in responding to threat as well as safety in a trauma-sensitive manner during development and early adulthood.

Of note, one limitation of this study is that only a subsample of participants could be included in the psychophysiological analyses ($n = 27$) due to low SCR levels, lack of sustained learning, missing data due to technical issues, and an outlier. Although having only a subsample of data for SCR analyses is not uncommon in studies where psychophysiological data are simultaneously collected with fMRI data (Laing et al., 2022; Lonsdorf et al., 2017; Meyer et al., 2019), it is important to interpret the present findings with this limitation in mind. Specifically, while the divergent psychophysiological and neural findings (i.e., no trauma-related differences in SCR and distinct trauma-related differences in neural activation during SSL) suggest the involvement of alternate neural, behavioral, or psychosocial factors that may serve as compensatory processes, it is possible these divergent findings are, in part, due to only a subsample of participants having been included in the SCR analyses. However, there were no differences in trauma exposure or in hippocampal or amygdala activation for key conditions of interest between the two subsamples. Future studies leveraging larger samples and multimodal approaches would be well-positioned to address these outstanding possibilities.

Understanding mechanisms of fear reduction and the supporting neural processes is a key priority in the effort to develop interventions for trauma-related mental health conditions. Here, we probed conditioned inhibition via SSL and found no association between trauma exposure and SSL task condition, suggesting that conditioned safety signals may be able to reduce fear in the presence of threat regardless of the degree of trauma individuals have experienced. Interestingly, however, our results also revealed that higher levels of trauma exposure were associated with lower hippocampal, amygdala, and dlPFC involvement during SSL, foreshadowing a possibility that these neurobiological sensitivities may be heightened among individuals with trauma-related mental health conditions. Taken together, SSL remains an important target for future research that has the potential to not only shed light on conditioned inhibition as an approach to fear reduction in the context of anxiety and PTSD following trauma exposure, but also examine whether SSL and its neural correlates may moderate or mediate the association between trauma exposure and mental health conditions.

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CRediT authorship contribution statement

Sahana Kribakaran: Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Funding acquisition. **Paola Odriozola:** Conceptualization, Methodology, Software, Formal analysis, Investigation, Data curation, Writing – review & editing, Supervision. **Emily M. Cohodes:** Conceptualization, Methodology, Investigation, Data curation, Supervision. **Sarah McCauley:** Investigation, Data curation. **Sadie J. Zacharek:** Software, Formal analysis, Investigation. **H.R. Hodges:** Investigation. **Jason T. Haberman:** Conceptualization, Methodology, Investigation. **Jasmyne C. Pierre:** Investigation, Data curation. **Dylan G. Gee:** Conceptualization, Methodology, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors have no competing interests to declare.

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Appendix A. Supplementary data

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