NEW RESEARCH

Developmental Differences in a Hippocampal–Cingulate Pathway Involved in Learned Safety Following Interpersonal Trauma Exposure

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Objective: Nearly 65% of youth experience trauma, and up to one-third of youth with trauma exposure face profound mental health sequelae. There remains a need to elucidate factors that contribute to psychopathology following trauma exposure, and to optimize interventions for youth who do not benefit sufficiently from existing treatments. Here, we probe safety signal learning (SSL), which is a mechanism of fear reduction that leverages learned safety to inhibit fear in the presence of threat-associated stimuli and has been shown to attenuate fear via a hippocampal–cingulate—specifically, a dorsal anterior cingulate cortex (dACC)—pathway.

Method: The present study used behavioral and task-based functional magnetic resonance imaging data to examine age-related associations between interpersonal trauma exposure and the behavioral and neural correlates (ie, activation and functional connectivity) of SSL in a group of 102 youth (aged 9-19 years; 46 female, 56 male) with (n = 52) and without (n = 50) interpersonal trauma exposure. Primary analyses examined anterior hippocampal activation and anterior hippocampus–dACC functional connectivity. Exploratory analyses examined centromedial (CMA) and laterobasal (LBA) amygdala activation and anterior hippocampal, CMA, and LBA functional connectivity with additional anterior cingulate subregions (ie, subgenual anterior cingulate cortex [sgACC] and rostral anterior cingulate cortex [rosACC]).

Results: Both youth with and without interpersonal trauma exposure successfully learned conditioned safety, which was determined by using self-report of contingency awareness. Youth with interpersonal trauma exposure (relative to youth in the comparison group) exhibited age-specific patterns of lower hippocampal activation ($F_{2,96} = 3.75$, $p_{FDR} = .049$, $\eta_p^2 = 0.072$), and, in exploratory analyses, showed heightened centromedial amygdala activation ($F_{1,96} = 5.37$, $p_{FDR} = .046$, $\eta_p^2 = 0.053$) and an age-related decrease in hippocampal–sgACC functional connectivity during SSL ($F_{1,94} = 10.68$, $p_{FDR} = .015$, $\eta_p^2 = 0.102$). We also show that hippocampal–sgACC functional connectivity mediated the association between interpersonal trauma exposure and post-traumatic stress disorder symptoms in an age-specific manner in the overall sample.

Conclusion: Together, these findings suggest that although age- and trauma-specific differences in the neural correlates of SSL may relate to the development of psychopathology, youth with interpersonal trauma exposure demonstrate successful learning of conditioned safety over time.

Diversity & Inclusion Statement: We worked to ensure that the study questionnaires were prepared in an inclusive way. We worked to ensure sex and gender balance in the recruitment of human participants. We worked to ensure race, ethnic, and/or other types of diversity in the recruitment of human participants. While citing references scientificall`y relevant for this work, we also actively worked to promote sex and gender balance in our reference list. While citing references scientifically relevant for this work, we also actively worked to promote inclusion of historically underrepresented racial and/or ethnic groups in science in our reference list. We actively worked to promote sex and gender balance in our author group. We actively worked to promote inclusion of historically underrepresented racial and/or ethnic groups in science in our author group. One or more of the authors of this paper self-identifies as a member of one or more historically underrepresented racial and/or ethnic groups in science. One or more of the authors of this paper received support from a program designed to increase minority representation in science.

Key words: safety learning; trauma; fMRI; amygdala; hippocampus

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Approximately two-thirds of all children experience at least 1 traumatic event by age 16 years,[1] and nearly 15% of youth with trauma exposure develop post-traumatic stress disorder (PTSD).[2] Both PTSD and transdiagnostic anxiety disorders are characterized by persistent fear in the absence of an immediate threat and can manifest in symptoms such as intrusive memories, heightened arousal, and avoidance, leading to significant distress and suffering.[3] To address the immense individual and societal suffering that stem from childhood trauma, defined in this study as exposure to interpersonal trauma, it is essential to do the following: (1) to elucidate factors that contribute to the development of mental health conditions such as PTSD

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and anxiety, and (2) to optimize interventions in a developmentally targeted manner.

Exposure-based cognitive–behavioral therapy (CBT) is a component of trauma-focused CBT and the current primary evidence-based intervention for trauma-related conditions, such as anxiety and PTSD,[4] and relies on fear extinction as the primary mechanism of fear reduction. Although exposure-based CBT is indeed effective for many youth with PTSD and anxiety following exposure to trauma,[5] 30% to 50% of youth do not experience sufficient improvement (ie, no longer meet diagnostic criteria for any anxiety disorder) following CBT for PTSD and anxiety disorders.[6] This pattern is in part due to the reliance on mechanisms of fear reduction studied primarily in adults (ie, fear extinction) that undergo developmental[7,8] and trauma-related[9] changes and that require discrimination between overlapping threat and safety representations,[10] in addition to the influence of co-occurring health conditions, cultural factors, and systemic inequities.[11] Thus, there is a critical need to investigate developmental- and trauma-related differences in core features of threat and safety learning and related neural circuitry to optimize processes of fear reduction.

Here, we examine conditioned inhibition of fear via safety signal learning (SSL), which uses conditioned—or learned—safety in the presence of threat-associated stimuli to inhibit and regulate fear responding.[12,13] In SSL, a safety cue is repeatedly conditioned to predict the non-occurrence of an aversive event (ie, the cue becomes a conditioned inhibitor as result of Pavlovian conditioning) and to subsequently inhibit fear in the presence of a threatening stimulus.[12,13] Cross-species evidence has shown that safety signals reliably reduce fear and recruit an anterior hippocampal–dorsal anterior cingulate cortex (dACC) pathway in adults,[14] which is altered among healthy adults with high trait anxiety.[15] Importantly, among adults without psychopathology, neural correlates of SSL are sensitive to trauma exposure even though safety signals reliably reduce fear responding regardless of the degree of trauma exposure.[16] Taken together, extending this research to investigate the neural mechanisms of SSL and its associations with trauma exposure in development could provide key insight into developmental differences in these neural processes and how they might vary following early-life trauma.

SSL may also be a potential mechanism that links trauma exposure and psychopathology, specifically PTSD and anxiety. To inhibit fear using a conditioned safety signal, it is necessary to distinguish between threat and safety, a process that is often challenging for individuals with PTSD and anxiety following trauma.[3,17] For example, adults with higher PTSD symptoms exhibit diminished SSL relative to adults without PTSD or adults with lower PTSD symptoms.[18] Whether this pattern is also present among youth with PTSD and anxiety following trauma exposure remains to be investigated. Critically, even if SSL is altered among individuals with PTSD or anxiety following trauma, it still may be more efficacious than fear extinction because of the type of safety that is learned and the process by which fear is reduced.[14,17] That is, whereas the representation of safety learned in fear extinction overlaps with that of threat, the representation of safety learned in SSL is distinct from that of threat (ie, the "type" of safety learned in SSL is different from that in extinction), and the safety signal has been shown to attenuate fear responding when co-presented with a threat cue (ie, the "process" by which fear is reduced is distinct).[12] Given these representational differences between SSL and fear extinction, it is possible that fear reduction via SSL could still provide benefits to fear reduction over and above extinction despite trauma-related alterations observed in SSL.

Building upon prior research in adults,[14,19] this study uses behavioral and functional magnetic resonance imaging (fMRI) data to examine learned safety in a sample of youth exposed to interpersonal trauma. We hypothesized that youth with interpersonal trauma exposure would exhibit lower accuracy in learning the safety contingency of simultaneously presented threat and safety cues (ie, the condition testing inhibition of fear in the presence of safety).[13] We hypothesized that youth with interpersonal trauma exposure, relative to youth without interpersonal trauma exposure, would exhibit lower hippocampal activation and lower hippocampal–dACC functional connectivity during SSL (ie, the task condition in which the conditioned safety cue is paired with the threat cue relative to the condition in which the threat cue is presented alone) and that this pattern would be more pronounced during adolescence, given nonlinear neurodevelopmental changes in corticolimbic circuitry that supports threat and safety learning.[20] In exploratory analyses, we separately examined amygdala and anterior cingulate subregions, given their distinct involvement in threat and safety learning, and hypothesized that trauma-related differences in activation and functional connectivity but did not specify directionality. Furthermore, we hypothesized that interpersonal Q2 trauma exposure–related reductions in hippocampal activation and hippocampal–anterior cingulate cortical regions (ie, dACC, subgenual anterior cingulate cortex [sgACC], and rostral anterior cingulate cortex [rosACC]) connectivity during SSL would mediate the link between interpersonal trauma exposure and PTSD and anxiety symptoms. Given age-related changes in hippocampal–

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cingulate circuitry,[21] we expected that these effects would be strongest during adolescence.

METHOD

Participants and Study Procedures

The present study is a cross-sectional analysis from the follow-up time point of a larger study that aimed to examine how physical abuse, sexual abuse, and domestic violence affect structural and functional neurodevelopment in ways that might increase risk for psychopathology.[22] Participants were originally enrolled in the study based on exposure or non-exposure to interpersonal trauma, and *a priori* followed up 2 years later (the present study), with no interventions. A sample of 121 participants aged 9 to 19 years (mean = 14.17, SD = 2.72) completed the follow-up time point of the study during which the conditioned inhibition task was first administered. Inclusion criteria for youth in the group with interpersonal trauma exposure included exposure to physical or sexual abuse or direct witnessing of domestic violence, whereas youth in the comparison group had no history of exposure to interpersonal trauma (endorsed at either the baseline or follow-up assessment). The 2 groups were matched on age, sex, and handedness. Written informed consent in accordance with the University of Washington Institutional Review Board was obtained from legal guardians; children provided written assent.

Of the 121 participants with neuroimaging data who returned for the follow-up assessments, 117 started a conditioned inhibition task in the fMRI scanner. Of these 117 participants, 15 participants were excluded because of excessive motion (n = 7), incomplete scans (n = 7), and technical issues (n = 1), resulting in a final analytic sample size of N = 102 (46 female and 56 male partipants). Supplement 1 available online, provides exclusion criteria and recruitment details, and Table 1[23-27] lists sociodemographic characteristics.

Assessment of Trauma Exposure

The present study focuses on interpersonal traumatic events in the form of maltreatment in childhood and adolescence (ie, physical abuse, sexual abuse, and domestic violence). Consistent with prior work on threat and safety learning in a subset of the present sample,[22] exposure to physical or sexual abuse was determined using youth report on the Childhood Experiences of Care and Abuse (CECA) Interview,[28] the UCLA PTSD Reaction Index (PTSD-RI),[24] and the Childhood Trauma Questionnaire[25]; and caregiver report on the Juvenile Victimization Questionnaire (JVQ)[26] or PTSD-RI. Specifically, youth were included in the group with interpersonal trauma exposure if physical or sexual abuse was endorsed on any one of these measures (ie, response of "yes" to physical or sexual abuse screener questions on the CECA, PTSD-RI, or JVQ, or if the physical abuse or sexual abuse subscale score was above the validated threshold of 8 for the CTQ). Exposure to domestic violence (ie, violence toward caregiver) was assessed using youth report on the CECA, PTSD-RI, and Violence Exposure Scale for Children—Revised (VEX-R)[27]; and caregiver report on the JVQ and PTSD-RI. Specifically, youth were included in the group with interpersonal trauma exposure if domestic violence was endorsed on any measure (ie, response of "yes" to domestic violence screener questions on the CECA, PTSD-RI, or JVQ, or response of greater than "once" to domestic violence screener questions on the VEX-R). Youth with exposure to physical abuse, sexual abuse, or domestic violence are hereafter referred to as youth with interpersonal trauma exposure, and youth who never experienced these forms of trauma are hereafter referred to as youth without interpersonal trauma exposure (Table S1, available online, reports frequency of exposure to traumatic events). Of the final sample of 102 participants, 52 youth were exposed to interpersonal trauma exposure, and 50 youth were never exposed to interpersonal trauma exposure. Youth reported exposure to interpersonal trauma at a range of ages, from age 2 to age 19 years (Supplement 1 available online, includes additional details).

Assessment of PTSD and Anxiety

Given that multi-informant discrepancies in the assessment of youth psychopathology have been shown to differentially relate to behavioral and biological constructs,[29] PTSD symptom severity was operationalized using youth report on the UCLA PTSD-RI.[24] Anxiety symptoms were assessed using the Screen for Child Anxiety Related Emotional Disorders (SCARED),[30] which was administered to youth. Table 1 provides diagnostic information and Figure S1, available online, gives PTSD and anxiety symptom distributions.

Task Design

The SSL task used in the present study (Figure 1) is largely consistent with the task employed in prior studies,[14,15,19] which was adapted from the AX+/BX- task of conditioned inhibition[31,32] to be used with children and adolescents in related studies. Conditioned stimuli (CS) were neutral geometric shapes of different colors; the unconditioned stimulus (US) was an aversive metallic noise[33] delivered at 95 to 100 dB through MRI-safe noise-canceling headphones (www.optoacoustics.com).

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TABLE 1 Demographic Variables for Full Sample (N = 102)

Characteristics	Interpersonal trauma exposure[a] (n = 52) Mean (SD) or n (%)	No interpersonal trauma exposure (n = 50) Mean (SD) or n (%)
Age, y	14.32 (2.93)	14.02 (2.50)
Sex assigned at birth, female	24 (46.2)	22 (44.0)
Any anxiety disorder[b]		
Lifetime	20 (38.5)	7 (14.0)
Current	18 (34.6)	7 (14.0)
Anxiety symptoms[c]	23.60 (15.99)	17.26 (9.36)
PTSD diagnosis[d]	12 (36.5)	1 (2.0)
PTSD symptoms[d]	18.17 (14.42)	1.36 (5.94)
Race/ethnicity		
Asian	5 (9.6)	7 (14.0)
Black or African American	21 (40.4)	3 (6.0)
Hispanic/Latino	8 (15.4)	2 (4.0)
Non-Hispanic White	10 (19.2)	36 (72.0)
Other/unknown	8 (15.4)	2 (4.0)

Note: Continuous variables are presented as mean with SD; categorical variables are presented as n with percentage. Groups were matched on age ($t_{100} = 0.56$, $p = .58$) and sex ($\chi^2 = 0.05$, $p = .827$).
[a]Determined using the Childhood Experiences of Care and Abuse Interview,[23] UCLA PTSD Reaction Index (PTSD-RI),[24] Childhood Trauma Questionnaire,[25] Juvenile Victimization Questionnaire,[26] and Violence Exposure Scale for Children-Revised.[27]
[b]Determined using parent and child report on the Kiddie Scale for Affective Disorders and Schizophrenia. Any anxiety disorder = separation anxiety disorder, social phobia, panic disorder, specific phobia, generalized anxiety disorder.
[c]Determined using child report on the Screen for Child Anxiety Related Emotional Disorder.
[d]Determined using child report on the PTSD-RI.[24]

Supplement 1, available online, provides a full description and details of the task.

Behavioral Data and Analyses

During each testing run of the task, participants were asked 3 US expectancy questions (ie, "Do you think you will hear the sound?") pertaining to the safety compound condition. We examined participants' dichotomous responses (ie, "Yes" or "No," with the correct answer being "No") to assess accuracy in learning the safety compound contingency, a measure that has been shown to track with anxiety and PTSD symptomatology.[34] We used a binomial generalized linear mixed model in R to test for interpersonal trauma exposure–related differences in learning, as well as the interaction between interpersonal trauma exposure and age, within each of the first and second testing runs. In the presence of significant main effects and interactions, we report significant beta values and corresponding *p* values from the models. In addition to US expectancy responses to the safety compound condition, participants' reaction times to each of the 4 conditions (ie, time to press the button in response to the presentation of a white dot at the center of each shape) were also examined as a behavioral measure. Supplement 1, available online, includes additional details about behavioral data and analyses.

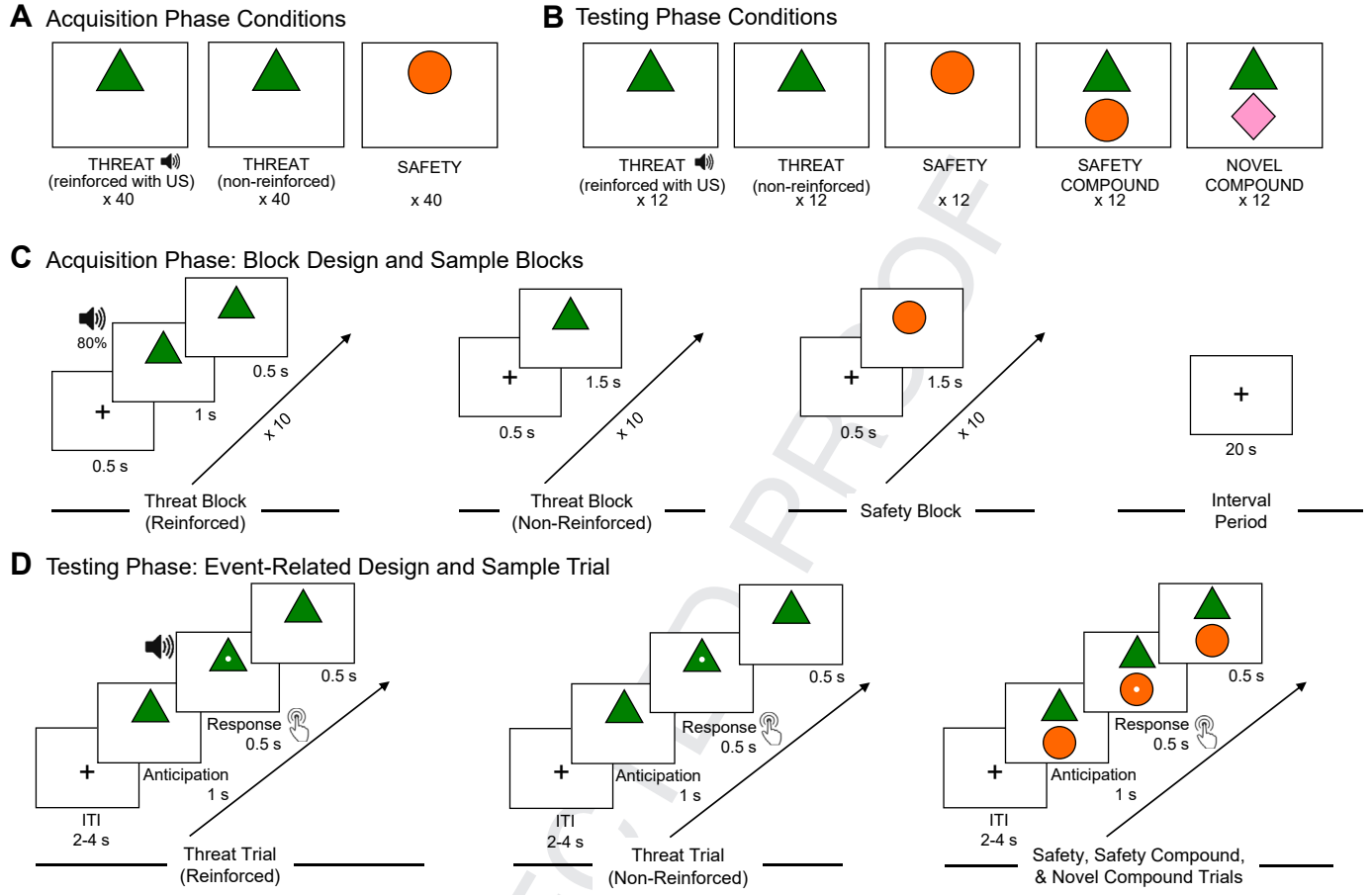
Analysis of fMRI Data

Region-of-Interest Activation Analysis. Supplement 1, available online, provides details regarding fMRI acquisition parameters, processing, and motion correction.

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. In the individual-level FEAT analysis, predictors for each task condition were convolved with a double-gamma canonical hemodynamic response function (HRF). The regressor included the full 2 seconds of each trial, which included the anticipation (1 second), response (0.5 second), and post-response (0.5 second) periods. To account for possible confounding activity associated with the button press, we included a regressor for the response period to remove any correlative influence of the button press.

Activation Analyses Included Primary and Exploratory Analyses. Primary analyses included right and left anterior hippocampal activation, building on prior research examining neural correlates of SSL,[14,15,19] and exploratory analyses included bilateral centromedial (CMA) and laterobasal (LBA) amygdala activation. The CMA and LBA were specifically selected given the central involvement of the amygdala in threat and safety learning[35] and the functional

FIGURE 1 Safety Signal Learning Task



Note: (A) Conditions for the acquisition phase included the reinforced and non-reinforced threat cues and the safety cue, which was never reinforced. There was a total of 40 trials of each condition across the acquisition phase. (B) Conditions for the testing phase included the same threat and safety cues from the acquisition phase in addition to the safety compound (pairing of the threat cue and safety cue) and the novel compound (pairing of the threat cue and a novel cue to control for the compound nature of the stimulus and to rule out the reduction of fear via novelty [ie, external inhibition]). There was a total of 12 trials of each condition across 2 functional magnetic resonance imaging runs. (C) Acquisition phase: block design and sample blocks. The acquisition phase comprised a block design, with each block consisting of 10 trials of each condition (ie, threat cue reinforced, threat cue non-reinforced, safety cue) and a total of 4 blocks of each of the 3 conditions. There was also a total of 4 inter-block interval periods, the first of which was first presented after a sequence of a safety cue, threat cue reinforced, and threat cue non-reinforced block (in this order), after which the remaining 3 were presented in a pseudorandomized order along with the rest of the stimulus blocks. (D) Testing phase: event-related design and sample trial. The phase that tested conditioned inhibition (ie, "testing phase") followed an event-related design. Each trial started with a variable 2- to 4-second inter-trial interval (ITI), followed by a 1-second anticipation period, followed by a 0.5-second response or attention check period during which participants were instructed to make a button press, and a final 0.5-second period during which the shape remained on the screen. Supplement 1, available online, provides a full description and details of the task.

heterogeneity of the amygdala subregions in the context of threat and safety learning.[36] Bilateral masks were used for both the CMA and LBA to constrain the number of tests for exploratory analyses. Mean percent signal change values (ie, mean blood oxygen level–dependent [BOLD] signal during the anticipation and response periods of the trial relative to the intertrial interval) for each participant and for each condition from the first and second runs of the testing phase were extracted from the individual-level FEAT results using FSL's featquery tool, with anatomical masks for the right and left anterior hippocampus derived from manual segmentations using anatomical landmarks[37] (details in Supplement 1, available online) and anatomical masks from the Juelich Atlas[38] for the bilateral CMA and LBA subregions. All anatomical regions of interest (ROI) masks were thresholded at 50% and registered to native space for each participant using Advanced Normalization Tools.[39] Figure S2, available online, depicts all anatomical masks.

Task-Based Functional Connectivity Analysis. Functional connectivity analyses included primary and exploratory analyses. Primary analyses included functional connectivity between each the right and left anterior hippocampus as the seed regions and the bilateral dACC as the target region.

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Exploratory analyses included functional connectivity between each of the right and left anterior hippocampus (seed regions) and bilateral sgACC and rosACC (target regions) and between each of the bilateral CMA and LBA (seed regions) and the dACC, sgACC, and rosACC (target regions). The sgACC and rosACC were specifically selected as exploratory target regions for functional connectivity analyses, given the broader neural circuit implicated in threat and safety learning[40] and functional heterogeneity of the prefrontal cortex.[41] Figure S2, available online, depicts all anatomical masks. All functional connectivity analyses were carried out using a generalized psychophysiological interaction (gPPI) analysis.[42]

Individual-level gPPI FEAT analysis was conducted similarly to the above models, additionally including the timeseries for each seed region (extracted using FSL's meants command) as an explanatory variable in each model. Interactions between the physiological variable (ie, the seed region timeseries) and each of the psychological variables (ie, each task condition) were computed and included in the design matrix as the variables of interest. Functional connectivity estimates were extracted using FSL's featquery tool for the dACC, sgACC, and rosACC (with the anterior hippocampus, CMA, and LBA as the seed regions).

Statistical Analyses. Primary analyses included left and right anterior hippocampal activation and left and right anterior hippocampal–bilateral dACC functional connectivity within the first and within the second testing run. For each of these ROIs (for activation analyses) or for each of these pairs of ROIs (for functional connectivity analyses), 1 repeated-measures analysis of covariance (ANCOVA) was conducted. Extracted beta parameter estimates (ie, percent signal change or functional connectivity) for each task condition (ie, threat cue, safety cue, safety compound, and novel compound) were entered into each repeated-measures ANCOVA. The within-subjects factor for each model was the task condition, and the between-subjects factors were interpersonal trauma exposure (dichotomous variable) and age at the scan (continuous variable; mean centered). Given our specific hypothesis that interpersonal trauma exposure–related differences for neural mechanisms involving the anterior hippocampus would be heightened during adolescence, age-squared was also included as a between-subjects factor to test for possible non-linear effects of age. We examined 3 key interactions in our models: task condition × interpersonal trauma exposure; task condition × interpersonal trauma exposure × age; and task condition × interpersonal trauma exposure × age-squared. Significant linear, quadratic, or cubic effects resulting from the repeated-measures ANCOVA were interpreted. The Greenhouse–Geisser adjustment was used to address sphericity assumption violations in the ANCOVA models. Post hoc *t* tests for planned contrasts of interest (ie, safety compound vs threat cue, and safety compound vs novel compound) were conducted following significant main effects or interactions. More specifically, 3-way interactions between task condition, interpersonal trauma exposure, and age were probed accordingly using post hoc pairwise *t* tests for the same planned contrasts of interest within 2 age bins (defined using a median split of 13.6 years) for each group (ie, youth with and without interpersonal trauma exposure). Post hoc pairwise tests were corrected for multiple comparisons using false discovery rate (FDR) correction.

Exploratory analyses included bilateral CMA and LBA activation, left and right anterior hippocampal–bilateral sgACC and –bilateral rosACC functional connectivity, and bilateral amygdala subregion–bilateral cingulate subregion functional connectivity within the first and within the second testing run. For each of these ROIs (for activation analyses) or for each of these pairs of ROIs (for functional connectivity analyses), we carried out 2 separate univariate analyses that focused on 2 planned contrasts of interest: safety compound vs threat cue and safety compound vs novel compound. For activation analyses, parameter estimates (ie, CMA and LBA percent signal change) for planned contrasts of interest were entered as the dependent variable, interpersonal trauma exposure as the fixed factor, and age as the covariate of interest. For functional connectivity, parameter estimates (ie, CMA and LBA functional connectivity with dACC, sgACC, rosACC; hippocampal functional connectivity with sgACC and rosACC) for planned contrasts of interest were entered as the dependent variable, interpersonal trauma exposure as the fixed factor, and age as the covariate of interest. Age-squared was included as a between-subjects factor to test for possible non-linear effects of age in models for anterior hippocampal functional connectivity with the sgACC and rosACC. The main effect of interpersonal trauma exposure and the interaction between interpersonal trauma exposure and age (and interpersonal trauma exposure and age-squared for relevant models) were examined in all models.

For both primary and exploratory analyses, models were corrected for multiple comparisons using FDR adjustment at the level of the hypothesis (ie, ROI) within primary and within exploratory analyses. This leads to the correction for 2 models for primary activation analyses (right and left anterior hippocampus), 2 models for exploratory activation analyses (CMA and LBA), 2 models for primary functional connectivity analyses (right and left anterior hippocampus–dACC functional connectivity), and 10 models for exploratory functional connectivity analyses (right and left

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hippocampal–sgACC and –rosACC functional connectivity [4 models]; CMA and LBA-dACC, –sgACC, and –rosACC functional connectivity [6 models]). Finally, given that this study is the first to examine neural mechanisms of SSL in youth and, in addition, to examine associations between SSL and trauma exposure in youth, the balance between type 1 and type 2 errors was carefully weighed, and multiple comparisons adjustments were made at the level of the hypothesis (ie, ROI) and did not account for the 2 testing runs and the 2 planned contrasts that were used for exploratory analyses.

For significant models from primary and exploratory analyses (ie, models for which there were significant interpersonal trauma exposure–related effects), additional analyses were conducted to determine whether interpersonal trauma exposure interacted with sex assigned at birth or with pubertal stage for these specific neural variables.

Psychopathology. We investigated whether neural activation and functional connectivity during SSL were associated with PTSD and anxiety symptoms. Primary neural variables included right and left anterior hippocampal activation and right and left hippocampal–dACC functional connectivity from both testing runs. Exploratory neural variables were selected from exploratory ROIs stated previously based on the presence of significant interpersonal trauma exposure–related differences in activation and functional connectivity. Activation and functional connectivity parameter estimates for each of the 2 planned contrasts of interest (ie, safety compound vs threat cue, and safety compound vs novel compound) were entered as independent variables, and PTSD and anxiety symptoms were entered as dependent variables into separate linear models in R using the lmer4 package.[23]

To determine whether the association between interpersonal trauma exposure and psychopathology was mediated by neural activation and functional connectivity during SSL, we performed nonparametric mediation models with 10,000 simulations using the mediation package in R.[43] For both primary and exploratory neural variables, mediators were selected to be tested if arm a of the model was significant (ie, significant association between interpersonal trauma exposure and the neural measure) or arm b of the model was $p < .1$. This approach is consistent with current approaches to mediation analyses that do not require significant direct effects for arms a and b in order to estimate the indirect effect of the mediator.[44]

Finally, we tested whether age moderated the indirect effect of potential neural mediators on the association between interpersonal trauma exposure and psychopathology (ie, PTSD and anxiety symptoms). Neural measures were examined for moderated mediation analyses if they were selected as potential mediators from the primary neural variables or if there was a significant interaction with interpersonal trauma exposure and age. We used PROCESS macro version 4.1 for R version 4.1.141, model 7 (ie, conditional indirect effects), with bias-corrected 95% confidence intervals (n = 10,000). This model examined the moderating effect of age on path a (ie, predictor to mediator path) and the index of moderated mediation tested the differences in the indirect effects across age. Mediation and moderated mediation models were corrected for multiple comparisons using Bonferroni-adjusted confidence intervals for the total number of models run for each form of psychopathology (ie, PTSD and anxiety symptoms).

Supplement 1, available online, provides additional information about mediation and moderated mediation analyses.

RESULTS

Behavioral Findings

In the first testing run, 13 (25%), 34 (65.38%), and 45 (86.54%) of 52 youth with interpersonal trauma exposure responded to the first, second, and third expectancy questions, respectively. Of 50 youth without interpersonal trauma exposure, 4 (8%), 34 (68%), and 43 (86%) responded to the first, second, and third expectancy questions, respectively. The first expectancy question was excluded from subsequent analyses because of the low response rates. In the second testing run, 45 (86.54%), 47 (90.38%), and 47 (90.38%) of 52 youth with interpersonal trauma exposure responded to the first, second, and third expectancy questions, respectively. Of 50 youth without interpersonal trauma exposure, 42 (84%), 46 (92%), and 42 (84%) responded to the first, second, and third expectancy questions, respectively.

By the end of the second testing run, 78.72% of youth with interpersonal trauma exposure and 83.33% of youth without interpersonal trauma exposure who responded to the safety compound expectancy questions correctly responded to the questions (ie, a response of "No" when presented with the safety compound condition and asked, "Do you think you will hear the sound?"), demonstrating successful learning of the safety compound contingency. In the overall sample and across both testing runs, binomial generalized linear mixed models revealed a main effect of time ($\chi^2 = 10.34$, $p = .035$, Cohen $\omega = 0.32$), such that there was an increase in accuracy among youth with and without interpersonal trauma exposure. Specifically, there was a significant increase in accuracy from the first to the third (b = 1.49, SE = 0.63, $p = .018$) and the first to the fourth (b = 1.71, SE = 0.63, $p = .007$) safety compound US expectancy questions

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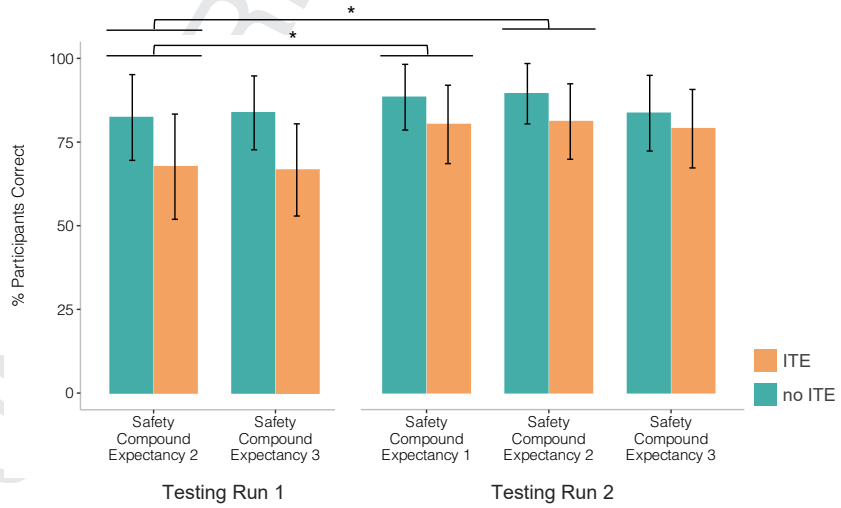
included in the analyses. There was no main effect of interpersonal trauma exposure or interaction between time, interpersonal trauma exposure, and age across both testing runs (all $p > .05$) (Figure 2). Within each of the first and second testing runs, there were no significant main effects of time or interpersonal trauma exposure, and no significant interactions among time, interpersonal trauma exposure, and age (all $p > .05$) (Figure 2). There were no interpersonal trauma–related differences in reaction time between conditions (ie, no condition by interpersonal trauma exposure interaction) in either of the 2 testing runs or across both testing runs (Figure S3 available online).

Age- and Interpersonal Trauma–Related Differences in Neural Activation During SSL

Primary activation analyses examined the left and right anterior hippocampus. Across both testing runs (ie, averaging across the first and second testing runs), there was no significant main effect of interpersonal trauma exposure and no significant interactions of interpersonal trauma exposure with condition, age, or age-squared for right or left anterior hippocampal activation (all $p > .05$). In the first testing run, there was a 3-way interaction between task condition, interpersonal trauma exposure, and age (left anterior hippocampus; linear contrast, $F_{2,96} = 3.75$, $p_{FDR} = .049$, $\eta_p^2 = 0.072$) (Figure 3). Specifically, among older youth (determined using median split of age), youth with interpersonal trauma exposure, compared to youth without interpersonal trauma exposure, showed diminished left hippocampal recruitment in response to the safety compound relative to the threat cue ($t_{26} = -3.79$, $p_{FDR} = .007$) (Figure S4, available online, provides an alternative visualization of age bins). In the second testing run, there was a significant 3-way interaction between task condition, interpersonal trauma exposure, and age for the right hippocampus (quadratic contrast, $F_{2,96} = 3.12$, $p_{FDR} = .049$, $\eta_p^2 = 0.061$), but post hoc pairwise tests did not survive correction for multiple comparisons (Figure S5, available online). The remaining primary activation analyses revealed no significant main effects of interpersonal trauma exposure or interactions between interpersonal trauma exposure and age in either testing run.

Exploratory activation analyses examined amygdala subregions (ie, bilateral CMA and LBA). To focus our analyses, we examined 2 planned contrasts of interest: safety compound vs novel compound, and safety compound vs threat cue. Across both testing runs, there was a significant main effect of interpersonal trauma exposure for CMA activation ($F_{1,96} = 5.37$, $p_{FDR} = .046$, $\eta_p^2 = 0.053$), such that youth with interpersonal trauma exposure, relative to youth without interpersonal trauma exposure, exhibited elevated CMA activation to the safety compound compared to the threat cue. There was no significant interaction between interpersonal trauma exposure and age for CMA activation. There was no

FIGURE 2 Unconditioned Stimulus Expectancy Responses for the Safety Compound Condition



Note: *During each of the 2 testing runs, participants were asked "Do you think you will hear the sound?" 3 times while viewing the safety compound condition. The y-axis shows the percentage of participants who correctly answered the question (ie, "No") among the total number of participants who responded to each question. Across both testing runs, there was a main effect of time ($\chi^2 = 10.34$, p = .035, Cohen $\omega = 0.32$), such that there was an increase in accuracy among youth with and without interpersonal trauma exposure (ITE). Specifically, there was a significant increase in accuracy from the first to the third (b = 1.49, SE = 0.63, p = .018) and the first to the fourth (b = 1.71, SE = 0.63, p = .007) safety compound unconditioned stimulus (US) expectancy questions included in the analyses. Within each of the first and second testing runs, there were no significant main effects of time or ITE, and no significant interactions among time, ITE, and age (all p > .05). All error bars show 95% binomial proportion confidence intervals.*

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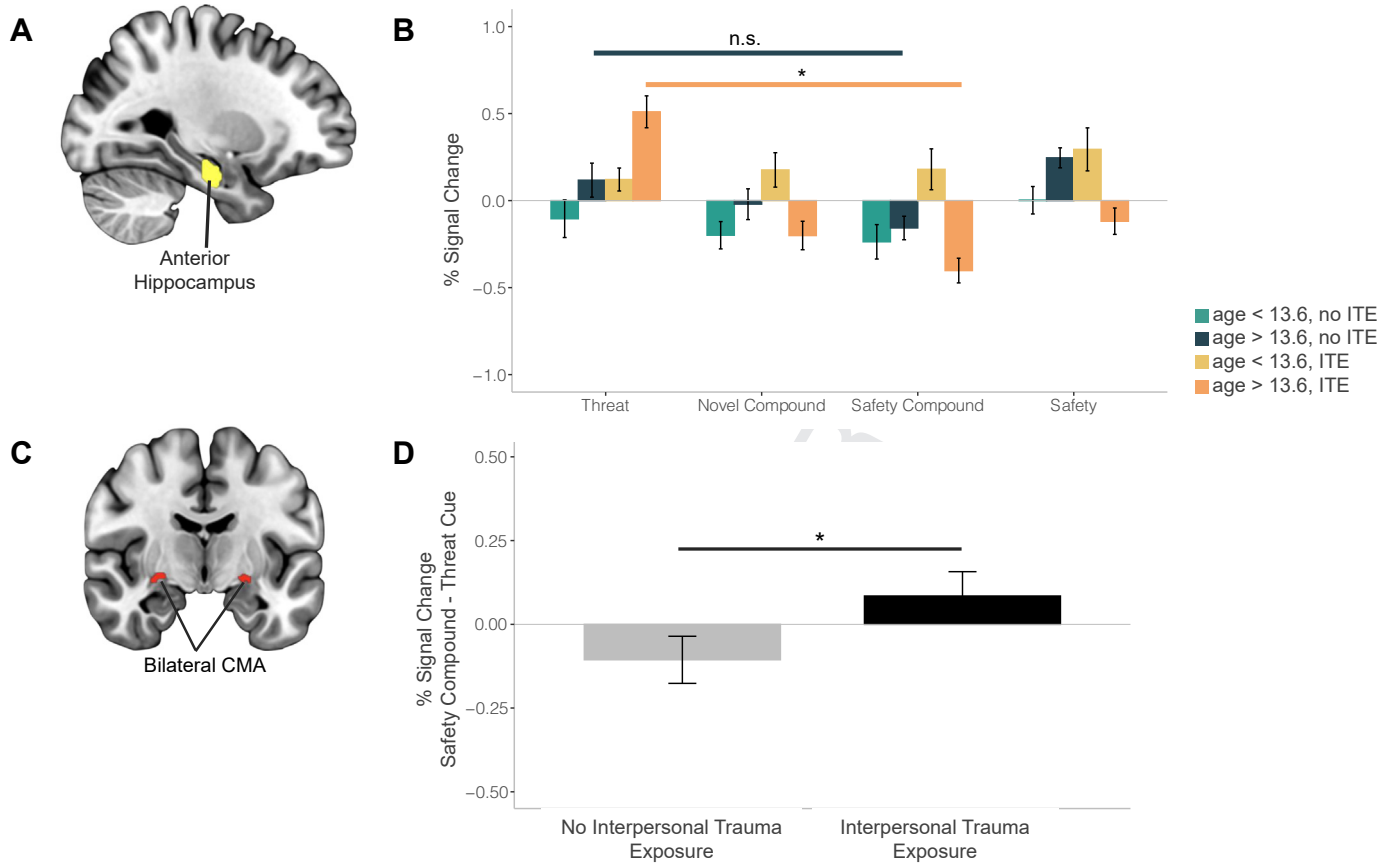
FIGURE 3 Anterior Hippocampal Activation During Safety Signal Learning Differs by Interpersonal Trauma Exposure and Age



Note: *(A) Anterior hippocampus region of interest (ROI).*[37] *(B) A repeated-measures analysis of covariance revealed a significant 3-way condition × interpersonal trauma exposure (ITE) × age interaction linear contrast ($F_{2,96} = 3.75$, $p_{FDR} = .049$, $\eta_p^2 = 0.072$), such that among older youth, those with ITE, relative to those without ITE, showed diminished left anterior hippocampal activation in response to the safety compound relative to the threat cue ($t_{26} = -3.79$, $p_{FDR} = .007$) during the first testing run. Median split of age (13.6 years) used here for data visualization and post hoc tests. (C) Bilateral CMA mask.*[38] *(D) Youth with ITE exhibited more CMA activation during SSL (ie, safety compound vs threat cue) relative to youth without ITE across both testing runs ($F_{1,96} = 5.37$, $p_{FDR} = .046$, $\eta_p^2 = 0.053$). All error bars show ± 1 SEM.*
*p < .05.

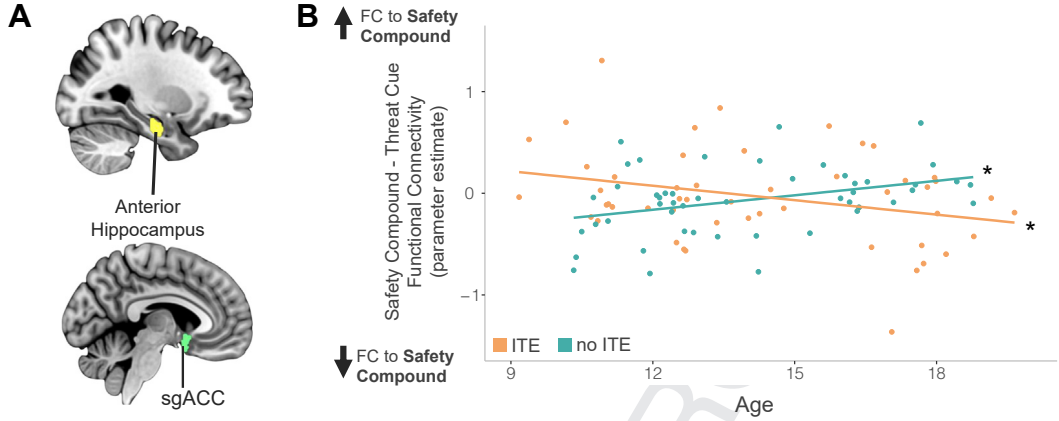
significant main effect of interpersonal trauma exposure or interaction with age for LBA activation (all $p > .05$). A similar pattern was observed in the first testing run, in which there was a main effect of interpersonal trauma exposure on bilateral CMA activation in response to the safety compound relative to the threat cue, such that youth with interpersonal trauma exposure exhibited heightened CMA activation to the safety compound relative to the threat cue; however, this finding within the first testing run did not survive correction for multiple comparisons ($p_{FDR} = .082$) (Figure S6, available online). The remaining exploratory activation analyses revealed no significant main effects of interpersonal trauma exposure or interactions between interpersonal trauma exposure and age in either testing run.

Sex and pubertal stage did not interact with interpersonal trauma exposure for anterior hippocampal activation.

Age- and Interpersonal Trauma–Related Differences in Functional Connectivity During SSL

Primary analyses examined left and right anterior hippocampal–bilateral dACC functional connectivity. Across both testing runs (ie, averaging across the first and second testing runs), there was no significant main effect of interpersonal trauma exposure and no significant interaction of interpersonal trauma exposure with condition, age, or age-squared for right or left anterior hippocampal–dACC functional connectivity (all $p > .05$). In the first testing run, there was a significant interaction between task condition, interpersonal trauma exposure, and age for left hippocampal–bilateral dACC functional connectivity; however, it did not survive correction for multiple comparisons (Figure S7, available online). The remaining primary analyses revealed no significant main effects of interpersonal trauma exposure or interactions between

FIGURE 4 Hippocampal–Cingulate Functional Connectivity During Safety Signal Learning Varies by Interpersonal Trauma Exposure and Age



Note: *(A) Anterior hippocampus seed region of interest (ROI)[37] and subgenual anterior cingulate cortex (sgACC) target ROI[45] used for generalized psychophysiological interaction (gPPI) analyses. (B) There was a significant interaction between interpersonal trauma exposure (ITE) and age for right hippocampal–sgACC functional connectivity (FC) during safety signal learning (SSL) (ie, safety compound vs threat cue; second testing run; $F_{1,94} = 10.68$, $p_{FDR} = .015$, $\eta_p^2 = 0.102$). Among youth with ITE, hippocampal–sgACC FC during SSL decreased with age. By contrast, youth without ITE exhibited elevated hippocampal–sgACC FC during SSL with age.*
*p < .05.

interpersonal trauma exposure and age in either testing run.

Exploratory analyses examined the associations between interpersonal trauma exposure and the following: (1) left and right anterior hippocampal functional connectivity with sgACC and rosACC during SSL (ie, safety compound vs threat cue contrast and safety compound vs novel compound); and (2) CMA and LBA functional connectivity with the dACC, sgACC, and rosACC during SSL. Across both testing runs, there was no significant main effect of interpersonal trauma exposure, and no significant interaction of interpersonal trauma exposure with condition or age for exploratory analyses examining amygdala subregions or with condition, age, or age-squared for exploratory analyses examining the anterior hippocampus (all $p > .05$). In the second testing run, there was a significant interaction between interpersonal trauma exposure and age for right hippocampal–bilateral sgACC functional connectivity for the safety compound vs threat cue contrast ($F_{1,94} = 10.68$, $p_{FDR} = .015$, $\eta_p^2 = 0.102$) (Figure 4[45]). Specifically, whereas age was positively associated with right anterior hippocampal–sgACC functional connectivity during SSL among youth without interpersonal trauma exposure, age was negatively associated with right anterior hippocampal–sgACC functional connectivity among youth with interpersonal trauma exposure. Sex and pubertal stage did not interact with interpersonal trauma exposure for right anterior hippocampal–sgACC functional connectivity. The remaining exploratory analyses revealed no significant main effects of interpersonal trauma exposure or interactions between interpersonal trauma exposure and age in either testing run.

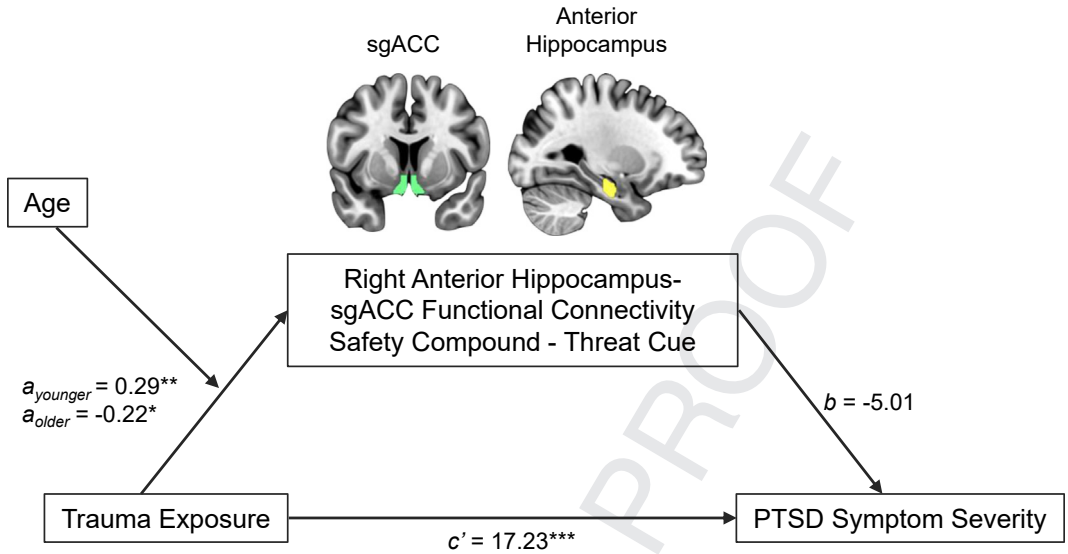
Associations Between Neural Processes During SSL and Psychopathology

Interpersonal trauma exposure was associated with higher PTSD symptoms (b = 2.59, SE = 0.34, $p < .001$) and anxiety symptoms (b = 0.31, SE = 0.13, $p = .019$). There were no associations between anterior hippocampal activation, anterior hippocampal–dACC functional connectivity, or hippocampal–sgACC functional connectivity during SSL and PTSD symptom severity. There were no significant associations between any of the neural processes during SSL and anxiety symptoms.

Neural Correlates of SSL as Mediators Linking Interpersonal Trauma Exposure and Psychopathology

The following neural measures were identified and tested as potential mediators of the association between interpersonal trauma exposure and psychopathology: left hippocampal activation, bilateral CMA activation, left hippocampal–dACC functional connectivity, and right hippocampal–sgACC functional connectivity during SSL for PTSD symptoms and left hippocampal–dACC functional connectivity, right hippocampal–dACC functional connectivity, right hippocampal activation, and right hippocampal–sgACC functional connectivity during SSL for anxiety symptoms. Neither the association between interpersonal trauma exposure and PTSD symptoms nor the association between interpersonal trauma exposure and anxiety symptoms was

FIGURE 5 Right Hippocampal–Subgenual Anterior Cingulate Cortex Functional Connectivity Mediates the Association Between Interpersonal Trauma Exposure and Post-Traumatic Stress Disorder Symptoms in an Age-Specific Manner



Note: *The moderated mediation model was supported by a significant index of moderated mediation (index = 0.475, 98.3% CI_{FWE} = 0.017, 5.146), such that among younger and older youth (<11.45 years and >16.89 years, respectively) but not among youth between 11.45 and 16.89 years, right hippocampal–subgenual anterior cingulate cortex (sgACC) functional connectivity (FC) during safety signal learning (SSL) mediated the association between interpersonal trauma exposure (ITE) and post-traumatic stress disorder (PTSD) symptom severity. ITE was associated with more PTSD symptoms (c' = 17.23, SE = 2.20, p < .001). Whereas ITE was associated with more hippocampal–sgACC FC among younger youth (direct effect, a = 0.29, SE = 0.11, p = .009), the opposite pattern was observed among older youth (direct effect, a = −0.22, SE = 0.11, p = .043). Hippocampal–sgACC FC was negatively associated with PTSD symptoms in older youth (b = −21.81, SE = 7.64, p = .010) but was not associated with PTSD symptoms in younger youth (b = 5.49, SE = 3.73, p = .158) or in the overall sample (b = −5.01, SE = 2.77, p = .074).*
*p < .05, **p < .01, ***p < .001.

mediated by any of the identified neural measures (ie, all indirect $p > .05$) (Table S2, available online).

Neural Correlates of SSL as Mediators Linking Interpersonal Trauma Exposure and Psychopathology in an Age-Specific Manner

The same neural measures identified for mediation analyses were examined for moderated mediation analyses. For both PTSD and anxiety symptoms, there were no significant indices of moderated mediation for neural measures of hippocampal activation or hippocampal–dACC functional connectivity (Table S3, available online). For hippocampal–sgACC functional connectivity, however, the moderated mediation model for PTSD symptoms was supported by a significant index of moderated mediation (index = 0.475, 98.3% CI_{FWE} = 0.017, 5.146), such that among younger youth (ie, 1 SD below the mean age, <11.45 years; indirect effect = −1.46, 95% CI = −3.33, −0.08) and older youth (ie, 1 SD above the mean age, >16.89 years; indirect effect = 1.13, 95% CI = 0.01, 2.97), but not youth at the mean age (>11.45 and <16.89 years; indirect effect = −0.17, 95% CI = −0.98, 0.712), hippocampal–sgACC functional connectivity during SSL mediated the association between interpersonal trauma exposure and PTSD symptom severity. Interpersonal trauma exposure was associated with more PTSD symptoms (c' = 17.23, SE = 2.20, $p < .001$), and interpersonal trauma exposure was associated with hippocampal–sgACC functional connectivity in an age-specific manner (b = −0.09, SE = 0.03, $p = .001$, R^2_{adj} = 0.10). Specifically, interpersonal trauma exposure was associated with more hippocampal–sgACC functional connectivity among younger youth (direct effect, a = 0.29, SE = 0.11, $p = .009$) and less hippocampal–sgACC functional connectivity among older youth (direct effect, a = −0.22, SE = 0.11, $p = .043$). Finally, hippocampal–sgACC functional connectivity was negatively associated with PTSD symptoms in older youth (b = −21.81, SE = 7.64, p = .010), but was not associated with PTSD symptoms in younger youth (b = 5.49, SE = 3.73, $p = .158$) or in the overall sample (b = −5.01, SE = 2.77, $p = .074$) (Figure 5). There was no significant index of moderated mediation for hippocampal–sgACC functional connectivity for the model for anxiety symptoms (Table S3, available online).

DISCUSSION

Interpersonal trauma exposure in youth is associated with key neural differences—but intact behavior—during

conditioned inhibition via SSL. On average, the overall sample of youth successfully learned the safety compound contingency, and there was no difference in the rate of learning between youth with and without interpersonal trauma exposure. Despite similar behavior, findings from primary analyses revealed that youth with interpersonal trauma exposure—specifically older adolescents—show diminished hippocampal activation during SSL. In addition, results from exploratory analyses demonstrated that interpersonal trauma exposure was associated with more CMA activation and less hippocampal–sgACC functional connectivity during SSL with increasing age. Furthermore, hippocampal–sgACC functional connectivity mediated the association between interpersonal trauma exposure and PTSD symptoms in an age-specific manner (ie, only among younger, but not older, participants). Collectively, these findings suggest that alterations in the hippocampal–cingulate circuit during SSL among youth with interpersonal trauma exposure in part link trauma and psychopathology.

Intact Behavior During SSL Despite Neural Alterations Following Interpersonal Trauma Exposure

Both youth with and without interpersonal trauma exposure demonstrated behavioral evidence of learned safety, with no behavioral group differences. Critically, fear extinction has been shown to be disrupted following exposure to trauma in youth,[9] suggesting that fear reduction via fear extinction, but not via conditioned inhibition, may be particularly susceptible to stress. This pattern is consistent with evidence in rodents in which conditioned inhibition via SSL was intact—specifically in the adolescent period—following pre-adolescent chronic unpredictable stress.[46] It is also important to consider that the lack of behavioral group differences may be related to the way in which the 2 groups were constructed. Specifically, given that some youth in the comparison group had still been exposed to some non-interpersonal trauma, SSL may be intact following different types of stressors. Taken together, this present finding highlights that SSL could provide a promising approach to enhance fear reduction in the context of trauma exposure that relies on a different type of learned safety.[47] That is, the inhibition of fear through a conditioned safety signal may be particularly effective, given the distinct representations of threat and safety that are formed. It is also important to note, however, that evidence from clinical science has underscored the potential deleterious influence of safety behaviors on sustaining fear,[48,49] particularly if they are used to prevent threat confrontation altogether.[50] Accordingly, the judicious use of safety signals—carefully weighing the manner in which safety signals are implemented and the conditions under which they may or may not be helpful—is of critical importance.[47,51,52] Future studies that directly compare the efficacy of SSL in reducing fear compared with traditional extinction in youth with trauma exposure have the potential to further inform the application of safety signals in a clinical context to enhance fear reduction.

Although youth with interpersonal trauma exposure displayed intact behavior during SSL, we observed interpersonal trauma exposure–related differences in neural function. We interpret these differences in neural function in the absence of behavioral effects, given the important need for increased mechanistic understanding at the neurobiological level to optimize learning-based approaches to early intervention for youth with history of trauma exposure,[53] particularly in the context of prior studies demonstrating that neural mechanisms of learning mediate the association between interpersonal trauma exposure and psychopathology independent of behavioral effects[22,54] and the difficulties of assessing behavior in youth in the context of threat and safety learning.[55] Starting with the anterior portion of the hippocampus, this region plays a critical role in threat and safety learning by processing and relaying contextual information from environmental inputs to the amygdala and prefrontal cortical regions.[56] Consistent with our hypothesis, we found that hippocampal involvement during SSL (ie, safety compound compared to threat cue) is diminished among youth with exposure to trauma—specifically among older adolescents; the same pattern was not observed among children and younger adolescents with interpersonal trauma exposure or among youth without interpersonal trauma exposure. In other words, hippocampal activation was elevated to the threat cue compared to the safety compound only among older adolescents with interpersonal trauma exposure. This age-related association is consistent with recent research in youth with and without interpersonal trauma exposure in which hippocampal activation to fearful faces (vs scrambled faces) was positively associated with age (ie, older youth exhibited more hippocampal recruitment in response to a threat-related stimulus).[54] Furthermore, prior research in youth has demonstrated that exposure to trauma (in particular, to interpersonal violence) is associated with elevated hippocampal activation during the processing of threat or fear-related information.[57] Our findings may suggest that exposure to trauma may not only potentially disrupt hippocampal involvement during conditioned inhibition of fear, but may also lead to heightened hippocampal responding in response to threat-related cues.

Contrasting this pattern of neural activity in the anterior hippocampus, we found higher CMA activation among

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youth with interpersonal trauma exposure compared with youth without interpersonal trauma exposure during SSL (ie, contrast between the safety compound and threat cue). Cross-species research has delineated the functional and structural heterogeneity of the amygdala. In particular, the LBA receives and integrates sensory, contextual, and regulatory information from various brain regions and relays these inputs via inhibitory and excitatory connections to the CMA, which then coordinates downstream threat or fear responses by way of connections with the hypothalamus, basal forebrain, and brainstem.[58] The finding of possible heightened CMA activation during SSL in youth with interpersonal trauma exposure compared to youth without interpersonal trauma exposure may suggest that among youth with interpersonal trauma exposure, there may be weaker or insufficient inhibition or regulation of CMA output, potentially contributing to an elevated fear response during SSL.

Age-Specific Deviations in Hippocampal–Cingulate Functional Connectivity Link Interpersonal Trauma Exposure and PTSD Symptomatology

Turning to the hippocampal–sgACC pathway, functional connectivity between these regions was diminished among youth with interpersonal trauma exposure relative to youth without interpersonal trauma exposure in an age-related manner. Whereas there was a negative association between age and functional connectivity among youth with interpersonal trauma exposure, the opposite pattern was observed in youth without interpersonal trauma exposure (ie, hippocampal–sgACC functional connectivity was positively associated with age). This finding suggests that the sgACC and its functional coupling with the anterior hippocampus may play an increasingly important role in SSL across development, which is disrupted among youth with interpersonal trauma exposure. This pattern among youth with interpersonal trauma exposure could also, however, represent a more mature pattern of connectivity, or could suggest that this pathway serves a different function during SSL at an earlier developmental stage in the context of trauma. Evidence from human neuroimaging studies in adults indicates that the sgACC is activated during extinction recall,[59] suggesting that the sgACC may be involved in threat regulation more broadly, with increasing importance across development. Future research integrating psychophysiological measures and subjective ratings of fear would be well positioned to discern whether these trauma- and age-specific differences in hippocampal–sgACC functional connectivity among youth with interpersonal trauma exposure are indeed related to fear reduction via conditioned inhibition.

Critically, we found that hippocampal–sgACC functional connectivity mediated the association between interpersonal trauma exposure and PTSD symptoms only among younger and older youth (ie, <11.45 and >16.89 years, respectively), suggesting that age-specific aberrations in this pathway during SSL in youth with interpersonal trauma exposure may contribute to the development of PTSD. This pathway between the anterior hippocampus and sgACC is not only involved in SSL to a greater extent with increasing age, but it also may be particularly sensitive to exposure to maltreatment-related interpersonal trauma during late childhood and late adolescence, serving as a mechanism linking interpersonal trauma and PTSD. In particular, whereas greater hippocampal–sgACC functional connectivity may be beneficial in adolescence in the context of fear inhibition, the same pattern in younger youth with interpersonal trauma exposure appears to be associated with risk for psychopathology. Prior studies have demonstrated alterations in the timing of corticolimbic development among youth exposed to trauma; however, evidence of these effects has been mixed and has varied depending on factors such as the nature of trauma and the neural circuit being examined.[60] In the case of sgACC–hippocampal functional connectivity, it is possible that a more mature pattern of positive hippocampal–sgACC coupling during SSL emerges among youth with interpersonal trauma exposure during the transitional period to adolescence and that this particular divergence in the developmental trajectory of this pathway, in part, gives rise to more severe PTSD symptoms. By contrast, among youth later in the adolescent period, heightened hippocampal–sgACC coupling may be needed to sufficiently inhibit fear through learned safety, and the pattern of diminished coupling among youth with interpersonal trauma exposure may contribute to more PTSD symptoms. Future examination in studies with longitudinal assessments of neural function during SSL will be important to clarify the interpretation of these results.

There are some key limitations to this research. Because of the brief inter-trial intervals used in the design of this task, physiological (ie, skin conductance response [SCR]) data were not obtained. Although we assessed contingency awareness, the response rate to the first expectancy question was low in the overall sample, possibly because youth were not anticipating an expectancy question during the testing run; future studies may aim to improve the response rate by including an instruction before the first testing run that participants will receive questions during the runs.[61] Furthermore, future studies in youth that examine SSL and collect SCR data or other physiological measures (eg, fear-potentiated startle)[17] would be well positioned to additionally complement the behavioral findings presented

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here to address outstanding empirical questions on SSL-related fear reduction in the context of early-life trauma. Age was operationalized in our analyses as the age at assessment (ie, when the SSL task was completed), given that we were well positioned to examine variability in neural activation and functional connectivity as a function of age at assessment because of the broad age range of the sample in the present study. This approach also builds on prior research suggesting that early-life stress can lead to age-specific biological and behavioral differences.[62,63] Critically, however, given considerable evidence that the age as well as type of trauma exposure may uniquely contribute to differences in neurobiological development and psychopathology,[64-67] it will be important for future studies to examine the age of trauma exposure in the context of safety signal learning. Next, the effect sizes of the neural findings were in the low-to-moderate range and should therefore be interpreted with caution and be replicated in future studies. Finally, given that the SSL task was completed at a follow-up assessment and the strong theoretical and empirical precedent for examining neural mechanisms of threat and safety learning as mediators of the link between trauma exposure and psychopathology,[53] this study used a cross-sectional mediation design. Future studies that leverage a longitudinal design would be ideally suited to build on the contributions of this study to further examine neural mechanisms of SSL as mediators of the association between trauma exposure and SSL. Strengths of this study include a large, well-characterized sample of children with interpersonal trauma exposure, the investigation of amygdala and cingulate subregions, and, to our knowledge, the first examination of neural correlates of SSL in youth.

Investigating mechanisms of fear reduction and associated neural processes in youth is critical to the generation and optimization of developmentally targeted interventions for youth who are experiencing trauma-related psychopathology. In the present study, we examined associations between interpersonal trauma exposure and conditioned inhibition via SSL in youth, and found comparable behavior following interpersonal trauma exposure but interpersonal trauma-related differences in the neural circuitry supporting SSL that varied with age. Specifically, youth with interpersonal trauma exposure showed diminished hippocampal activation and diminished hippocampal functional connectivity with the sgACC during SSL, relative to youth without interpersonal trauma exposure. Importantly, the interpersonal trauma–associated differences in hippocampal activation and functional connectivity with the sgACC were developmentally specific. Namely, hippocampal–sgACC functional connectivity was elevated during SSL among children and young adolescents, relative to older adolescents, with interpersonal trauma exposure, highlighting a possibility that hippocampal–sgACC functional connectivity serves a unique role during SSL among youth with interpersonal trauma exposure during the transitional period to adolescence. Taken together, SSL may hold promise as a mechanism of fear reduction that could be beneficial for youth with mental health conditions following interpersonal trauma exposure. Future research will be important to further examine the efficacy of SSL in reducing fear among youth with interpersonal trauma exposure and to elucidate whether aberrations in SSL may mediate or moderate the association between interpersonal trauma exposure and mental health conditions in youth. We conclude by underscoring that although it is vital to optimize developmentally focused interventions for youth, it must also remain a key focus of researchers and clinicians alike to transform the social and material conditions that contribute to—and are often the source of—traumatic experiences that are so prevalent in the lives of youth.

CRediT authorship contribution statement

Sahana Kribakaran: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Stephanie N. DeCross:** Writing – review & editing, Resources, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation. **Paola Odriozola:** Writing – review & editing, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization. **Katie A. McLaughlin:** Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization. **Dylan G. Gee:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization.

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The research was performed with permission from the University of Washington Institutional Review Board.

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Disclosure: Drs. Kribakaran, Odriozola, McLaughlin, and Gee and Ms. DeCross have reported no biomedical financial interests or potential conflicts of interest.

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